

## Synthesis and Magnetic Relaxation Properties of Paramagnetic Gd-complexes of New DTPA-bis-amides. The X-ray Crystal Structure of [Gd(L)(H<sub>2</sub>O)]·3H<sub>2</sub>O (L = DTPA-bis(4-carboxylicphenyl)amide)

Sujit Dutta, Suk-Kyung Kim, Eun Jung Lee, Tae-Jeong Kim,\* Duk-Sik Kang,<sup>†</sup> Yongmin Chang,<sup>‡,\*</sup> Sang Ook Kang,<sup>‡</sup> and Won-Sik Han<sup>‡</sup>

Department of Applied Chemistry, Kyungpook National University, Daegu 702-701, Korea. \*E-mail: tjkim@knu.ac.kr

<sup>†</sup>Department of Diagnostic Radiology, Kyungpook National University, Daegu 702-701, Korea

<sup>‡</sup>Department of Chemistry, Korea University, 208 Seochang, Chochiwon, Chungnam 339-700, Korea

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A new type of DTPA-bis-amides (**L1-L4**) and their Gd(III)-complexes of the type [Gd(L)(H<sub>2</sub>O)]·nH<sub>2</sub>O (**5**: **L1**; **6**: **L2**; **7**: **L3**; **8**: **L4**) have been prepared and characterized by analytical and spectroscopic techniques. The X-ray crystal structure of **8** has been determined for structural confirmation. The coordination geometry adopts a tricapped trigonal prism geometry with **L4** acting as a chelate octadentate and a water molecule in the coordination sphere. Crystals are monoclinic, *P*2<sub>1</sub>, *a* = 14.468(3), *b* = 19.235(4), *c* = 13.527(2) Å, β = 107.245(3)°, *V* = 3595.2(11) Å<sup>3</sup>, *Z* = 4, *D*<sub>calc</sub> = 1.570. Significant increases in relaxivities are observed with **6** and **7** as compared with that of Omniscan<sup>®</sup>, a commercial MR agent: R<sub>1</sub> = 12.46 mM<sup>-1</sup> s<sup>-1</sup>, R<sub>2</sub> = 8.76 mM<sup>-1</sup> s<sup>-1</sup> for **6**; R<sub>1</sub> = 12.77 mM<sup>-1</sup> s<sup>-1</sup>, R<sub>2</sub> = 7.60 mM<sup>-1</sup> s<sup>-1</sup> for **7**; R<sub>1</sub> = 4.9 mM<sup>-1</sup> s<sup>-1</sup>, R<sub>2</sub> = 4.8 mM<sup>-1</sup> s<sup>-1</sup> for Omniscan<sup>®</sup>. In the case of **5**, however, both R<sub>1</sub> and R<sub>2</sub> are found to be lower to show 2.09 mM<sup>-1</sup> s<sup>-1</sup> and 1.82 mM<sup>-1</sup> s<sup>-1</sup>, respectively.

**Key Words** : DTPA-bis(amide), Gd-complex, MRI contrast agent, Relaxivity

### Introduction

Magnetic Resonance Imaging (MRI) is a widely used diagnostic imaging technique. Although excellent soft-tissue images can be obtained by MRI, use of the contrast agents greatly enhances the contrast of the images and thereby increasing its diagnostic value.<sup>1</sup> Consequently the development of the efficient MRI contrast agents has recently drawn ample attention.<sup>2</sup> Among the early MRI contrast agents approved for use in humans are the ionic gadolinium(III) complex of diethylenetriamine-N,N,N',N'',N'''-pentaacetate, (N-Me-glucamine)<sub>2</sub>[Gd(DTPA)(H<sub>2</sub>O)] (Magnevist<sup>®</sup>, Schering) with a relaxivity of 4.7 mM<sup>-1</sup> s<sup>-1</sup> (20 MHz, 298 K)<sup>3</sup> and Neutral Gd(III) complexes, such as [Gd(DTPA-bismethylamide)(H<sub>2</sub>O)] (Omniscan<sup>®</sup>, Nycomed) with a relaxivity of 4.4 mM<sup>-1</sup> s<sup>-1</sup> (20 MHz, 298 K).<sup>4</sup> Thermodynamically stable, water-soluble, and highly paramagnetic Gd(III) ions bearing a multidentate ligand and at least one water molecule are expected to exhibit high water relaxivities and therefore suitable candidates for MRI contrast agents. In addition the MRI contrast agents should have chemical inertness, low *in vivo* toxicity, and should be completely excreted after the diagnostic examination.<sup>5</sup> Development of the neutral Gd(III) chelates with low osmolar and enhanced tolerance, measured as a higher acute LD<sub>50</sub> value, comply with the criteria of the second generation MRI contrast agents.<sup>6</sup>

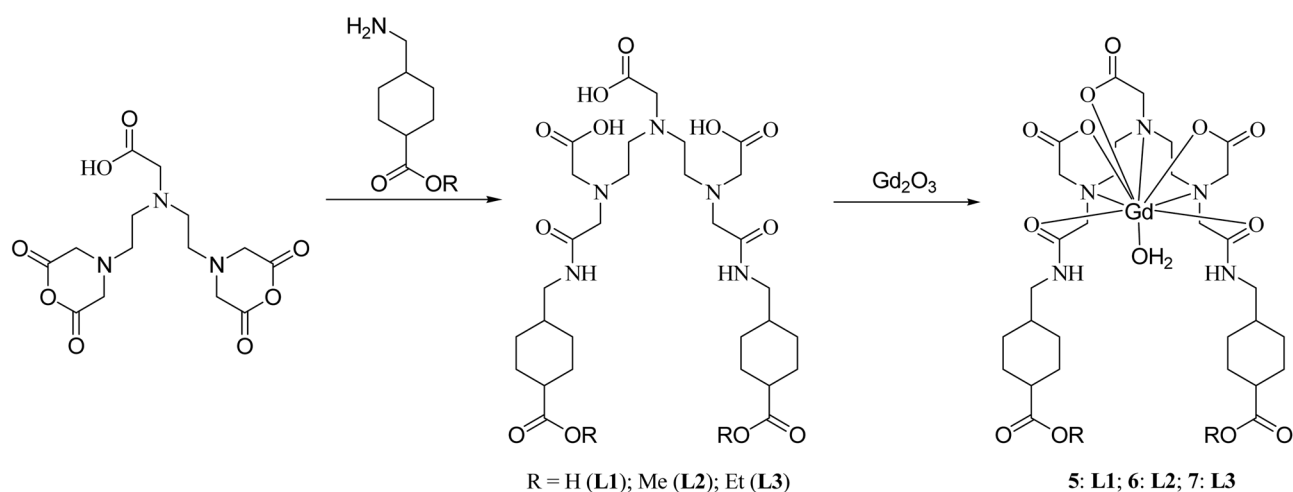
Herein we report the synthesis and characterization of Gd(III) complexes incorporating a new type of DTPA-bis-amides (**L1-L3**) functionalized by cyclohexyl carboxylates as the polar functional group to achieve enhanced solubility

in water. Replacement of the cyclohexyl carboxylates moiety with less water-soluble phenyl carboxylate to produce **L4** has also been carried out to confirm the formation of nine-coordinate complexes. Also presented in this report are the comparative studies on the water proton relaxivities (R<sub>1</sub> and R<sub>2</sub>) of **5-7** as compared with those of a commercial MR agent, Omniscan<sup>®</sup>.

### Results and Discussion

**Synthesis and Characterization.** Scheme 1 shows the preparative method leading to the formation of a new type of DTPA-bis-amide ligands (**L1-L3**). They can be easily prepared by simple condensation of DTPA-bis-anhydride with two equivalents of corresponding amines in DMF. The ligand **L4** was prepared separately for confirmation of the complex formation and the geometry adopted by the central Gd metal. Replacement of the cyclohexyl moiety in **L1-L3** with the phenyl one as found in **L4** is based on the belief that the corresponding Gd-complex would exhibit less solubility than those encompassing **L1-L3**. Indeed, all but **L4** are indefinitely soluble in most of polar solvents such as water, alcohol, DMF, and DMSO, yet insoluble in other organic solvents. The ligand **L4** is moderately soluble in water as well as common polar organic solvents.

All these ligands were characterized by analytical and spectroscopic techniques (<sup>1</sup>H NMR, IR, and FAB-mass). In particular, the presence of carbonyl groups in each ligand can be confirmed by a pair of intense carbonyl stretching bands assignable to the amide carbonyl (NHC=O) and



Scheme 1

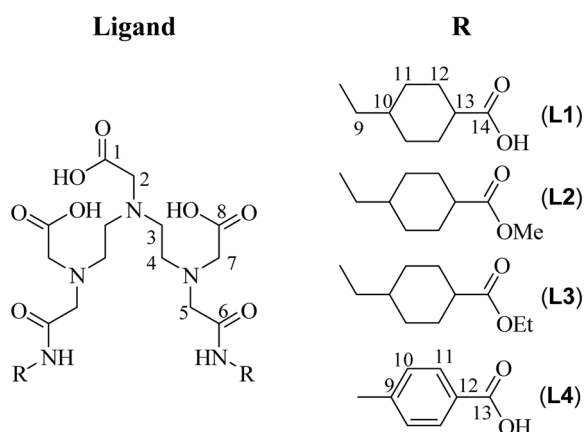


Chart 1. Numbering Scheme for NMR Assignment.

carboxylic carbonyl (C=O) groups in the range 1602-1672  $\text{cm}^{-1}$ . In Chart 1 is provided the numbering scheme for  $^1\text{H}$  NMR assignment for all ligands.

These ligands form Gd(III) complexes of the type  $[\text{Gd}(\text{L})(\text{H}_2\text{O})] \cdot n\text{H}_2\text{O}$  (**5: L1**; **6: L2**; **7: L3**; **8: L4**) by simple complexation with  $\text{Gd}_2\text{O}_3$  as illustrated in Scheme 1. They are highly hygroscopic, and isolated as a hydrated solid. The appearance of the  $\nu(\text{OH})$  band from the water of crystallization in the range 3235-3425  $\text{cm}^{-1}$ , supports this observation. Further structural confirmation comes from the X-ray crystal structure of **8** where three water molecules of crystallization are found (*vide infra*). Except for **8**, all complexes are highly soluble in water.

The characterization of the complexes is also straightforward according to the analytical and spectroscopic techniques. The carbonyl stretching bands show a slight red shift of approximately 90  $\text{cm}^{-1}$ , in all complexes indicating the participation of the carbonyl groups in coordination.

**The Crystal Structure of 8.** A more definitive structural confirmation can be obtained from the X-ray crystal structure of **8**. A summary of crystal data and intensity collection is presented in Table 1, and the relevant bond lengths and the

Table 1. Summary of Crystallographic data for **8**

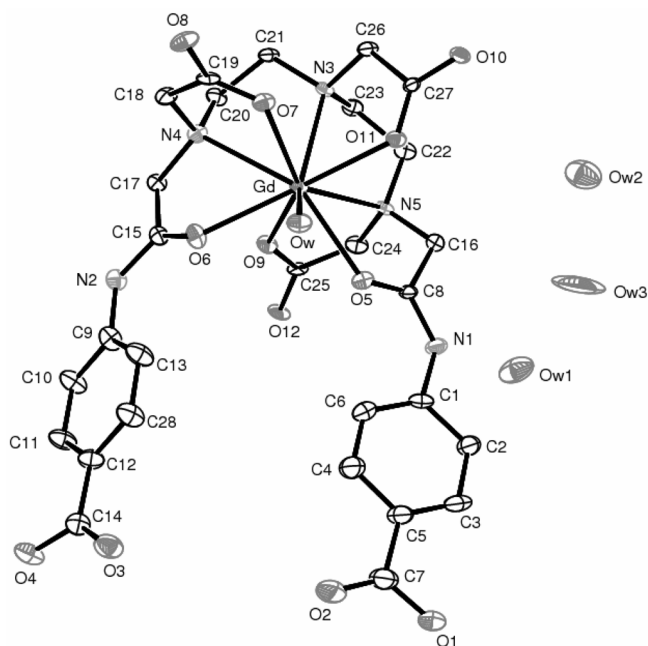
<b>8</b>	
empirical formula	$\text{C}_{28}\text{H}_{30}\text{N}_5\text{O}_{16}\text{Gd}$
Fw	849.82
$T$ ( $^\circ\text{K}$ )	233(2)
radiation, $\lambda$ ( $\text{\AA}$ )	Mo $\text{K}\alpha$ 0.71073
Crystal system	Monoclinic
space group	$\text{P}2(1)/c$
$a$ ( $\text{\AA}$ )	14.468(3)
$b$ ( $\text{\AA}$ )	19.235(4)
$c$ ( $\text{\AA}$ )	13.527(2)
$\alpha$ (deg)	90
$\beta$ (deg)	107.245(3)
$\gamma$ (deg)	90
$V$ ( $\text{\AA}^3$ )	3595.2(11)
$Z$	4
$D_{\text{calc}}$ ( $\text{g cm}^{-3}$ )	1.570
$\mu$ ( $\text{mm}^{-1}$ )	1.920
$F(000)$	1700
cryst size ( $\text{mm}^3$ )	$0.25 \times 0.20 \times 0.19$
$2\theta$ range (deg)	1.47-28.39
data collected: $h; k; l$	-19,19; -24,25; -17,18
reflections collected	34375
independent reflections	8929 [ $R(\text{int}) = 0.0808$ ]
completeness to $\theta = 28.29^\circ$	99.0%
GOF	1.095
$R$ indices ( $I > 2\sigma(I)$ ) <sup>a</sup>	$R_1 = 0.0754$ ; $wR_2 = 0.1839$
Largest diff. peak and hole ( $e/\text{\AA}^3$ )	6.185, -2.947

angles in Table 2. The ORTEP view is shown in Figure 1.

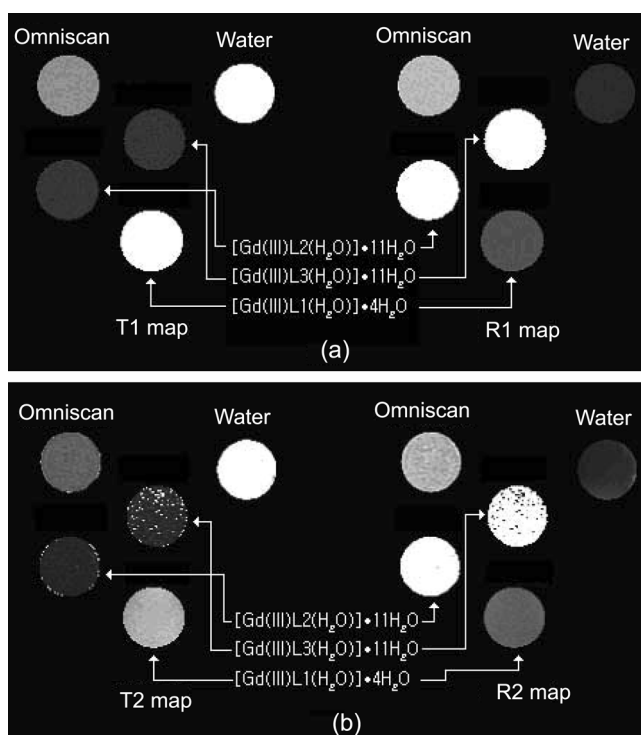
The central Gd(III) ion is present in an  $\text{N}_3\text{O}_6$  coordination sphere comprising of three amine nitrogen atoms [N(3), N(4), N(5)], three carboxylate oxygen atoms [O(7), O(9), O(11)], two amide oxygen atoms [O(5), O(6)], and one oxygen atom O(w) from coordinated water molecule. Three water molecules are present per molecule as the water of crystallization. The donor atoms in the metal coordination polyhedron are arranged in closely resembling the CSAP

**Table 2.** Selected bond lengths (Å) and angles (deg) for **8**

Gd-O(9)	2.311(6)	Gd-O(7)	2.346(7)
Gd-O(11)	2.384(7)	Gd-O(5)	2.424(7)
Gd-Ow	2.437(7)	Gd-O(6)	2.496(7)
Gd-N(3)	2.618(8)	Gd-N(4)	2.665(8)
Gd-N(5)	2.782(8)		
O(9)-Gd-O(11)	136.5(2)	O(7)-Gd-O(11)	77.5(2)
O(9)-Gd-O(5)	78.1(3)	O(7)-Gd-O(5)	138.2(2)
O(11)-Gd-O(5)	80.9(2)	O(9)-Gd-Ow	124.9(3)
O(7)-Gd-Ow	71.4(2)	O(11)-Gd-Ow	81.5(2)
O(5)-Gd-Ow	70.2(2)	O(9)-Gd-O(6)	70.8(2)
O(7)-Gd-O(6)	84.8(3)	O(11)-Gd-O(6)	150.1(2)
O(5)-Gd-O(6)	97.3(3)	Ow-Gd-O(6)	70.1(2)
O(9)-Gd-N(3)	96.2(3)	O(7)-Gd-N(3)	75.6(3)
O(11)-Gd-N(3)	67.8(2)	O(5)-Gd-N(3)	127.4(3)
Ow-Gd-N(3)	138.8(2)	O(6)-Gd-N(3)	130.6(3)
O(9)-Gd-N(4)	73.9(3)	O(7)-Gd-N(4)	66.2(2)
O(11)-Gd-N(4)	128.7(2)	O(5)-Gd-N(4)	149.3(3)
Ow-Gd-N(4)	116.8(3)	O(6)-Gd-N(4)	61.6(3)
N(3)-Gd-N(4)	69.0(3)	O(9)-Gd-N(5)	64.2(2)
O(7)-Gd-N(5)	138.8(2)	O(11)-Gd-N(5)	72.4(2)
O(5)-Gd-N(5)	63.1(2)	Ow-Gd-N(5)	129.1(2)
O(6)-Gd-N(5)	133.4(2)	N(3)-Gd-N(5)	67.4(2)
N(4)-Gd-N(5)	113.7(2)		

**Figure 1.** The ORPET view of **8** including the atom numbering scheme.

geometry, where the two trigonal faces are described by O(6), O(9), O(5) and O(7), N(3), O(11), respectively, while N(4), N(5), and O(w) atoms cap the rectangular faces. The average Gd–O<sub>carboxylate</sub> distance is 2.347(6) Å and shorter as compared with those found in the similar Gd(III) complexes

**Figure 2.** The relaxation time (T1 and T2) maps and the corresponding relaxivity (R1 and R2) maps on **5-7**, Omniscan, and pure water. The relaxation time map represents the signal intensity as a relaxation time: The bright signal intensity on the map means longer relaxation time. For relaxivity map, the bright signal intensity on the map represents higher relaxivity.

of DAPA-bis(ethylamide),<sup>7</sup> DAPA-bis(benzylamide)<sup>8</sup> and DTPA-bis (2-methoxyphenethylamide).<sup>9</sup> The average of the Gd-amide oxygen bond lengths, Gd-O(6) 2.496(7) and Gd-O(5) 2.424(7) Å, is higher compared with those found in the related Gd(III) complexes of DAPA-bis(ethylamide), DAPA-bis(benzylamide) and DTPA-bis (2-methoxyphenethylamide). The Gd-amide oxygen bond length distance, Gd-O(6) 2.496(7), is the longest among those reported in the literature. The Gd-N(5) distance 2.782(8) Å is the longest among the related complexes in the literature.

Finally, in connection with structural description, it is worth noting that one water molecule is retained in the coordination sphere since the potential donor, *para*-carboxylate groups of the benzoic acid are not involved in the coordination. Presence of this coordinated water is essential for the complex to show relaxivity in aqueous solution.

**Relaxivity Studies.** Table 3 summarizes the relaxation times and relaxivities measured in each of the samples. The values tabulated are mean values of measurements in the region of interest (ROI) in each sample. The uncertainties of all measurements are given in terms of the standard deviation. The least squares analysis program generates the standard error for the estimates of T<sub>1</sub> and T<sub>2</sub> values based on the variance of the signal intensity in each ROI in each individual sample. Figure 2 shows the T1 and R1 maps (a) and the T2 and R2 maps (b).

**Table 3.** T1, R1, T2 and R2 values for **5-7**, Omniscan, and pure water. Each value is presented as a mean value ( $\pm$  SD)

Sample	T1 (msec)	R1 (mM <sup>-1</sup> sec <sup>-1</sup> )	T2 (msec)	R2 (mM <sup>-1</sup> sec <sup>-1</sup> )
Omniscan	209.8 $\pm$ 5.82	4.9 $\pm$ 0.14	290.8 $\pm$ 21.02	3.4 $\pm$ 0.25
<b>6</b>	79.05 $\pm$ 3.99	12.7 $\pm$ 0.66	113.9 $\pm$ 14.39	8.7 $\pm$ 0.88
<b>7</b>	78.28 $\pm$ 4.68	12.9 $\pm$ 0.84	131.5 $\pm$ 0.002	7.2 $\pm$ 1.9
<b>5</b>	477.5 $\pm$ 9.94	2.1 $\pm$ 0.05	550.9 $\pm$ 22.05	1.8 $\pm$ 0.07
Water	842.5 $\pm$ 46.38	1.1 $\pm$ 0.06	1220 $\pm$ 167.20	0.82 $\pm$ 0.12

### Experimental Section

**General Remarks.** All reactions were carried out under an atmosphere of nitrogen using the standard Schlenk techniques. Solvents were dried using standard procedures. All commercial reagents were purchased from Aldrich and used as received. Deionized water was used for all experiments.

**Measurements.** The <sup>1</sup>H and <sup>13</sup>C NMR experiments were performed on a Bruker Advance 400 or 500 Spectrometer by Korea Basic Science Institute (KBSI). Chemical shifts were given as  $\delta$  values with reference to tetramethylsilane (TMS) as an internal standard. Coupling constants are in Hz. GC-Mass spectra were obtained by using a Micromass QUATRO II GC8000 series model with electron energy of 20 or 70 eV. IR spectra were run on a Mattson FT-IR Galaxy 6030E spectrophotometer by KBSI. Elemental analyses were performed by Center for Instrumental Analysis, KNU.

**X-ray Crystallographic Analyses.** Selected crystallographic data for **8** are collected in Tables 1 and 2. An ORTEP drawing showing the numbering scheme used in refinement is presented in Figure 1. Intensity data were collected at room temperature with a Bruker SMART 1000 CCD diffractometer using monochromated Mo K $\alpha$  radiation ( $\lambda = 0.71073$  Å). Lorentz and polarization reflections were applied and absorption corrections made with 3  $\Psi$  scans. The structure was solved by direct methods and refined by full-matrix least-squares methods based on  $F^2$  using SHELXS-97 and SHELXL-97.<sup>10</sup> Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were included in calculated positions. Additional crystallographic data are available in the Supporting Information.

**Relaxivity Measurements.** T<sub>1</sub> measurements were carried out using an inversion recovery method with a variable inversion time (TI) at 1.5T (64 MHz). The magnetic resonance (MR) images were acquired at 35 different TI values ranging from 50 to 1750 msec. T<sub>1</sub> relaxation times were obtained from the non-linear least square fit of the signal intensity measured at each TI value. For T<sub>2</sub> measurements the CPMG (Carr-Purcell-Meiboom-Gill) pulse sequence was adapted for multiple spin-echo measurements. Thirty four images were acquired with 34 different echo time (TE) values ranging from 10 to 1900 msec. T<sub>2</sub> relaxation times were obtained from the non-linear least squares fit of the mean pixel values for the multiple spin-echo measurements at each echo time. Relaxivity (R1 and R2) was then calculated as an inverse of relaxation time per mM.

### Diethylenetriamine-*N,N',N''*-triacetic-*N,N'*-dianhydride.

The title compound was prepared according to the method of Eckelman.<sup>11</sup> The product was obtained as a white solid (33.2 g, 93%). m.p. 185 °C. <sup>1</sup>H NMR (*d*<sub>6</sub>-DMSO)  $\delta$  3.70 (s, 8H, terminal NCH<sub>2</sub>CO<sub>2</sub>), 3.30 (s, 2H, central NCH<sub>2</sub>CO<sub>2</sub>), 2.75 (t,  $J = 7.6$ , 4H, NCH<sub>2</sub>) and 2.59 (t,  $J = 7.6$ , 4H, NCH<sub>2</sub>).

***trans*-4-(Aminomethyl)cyclohexanemethylcarboxylate Hydrochloride.** To a stirred suspension of *trans*-4-(aminomethyl)cyclohexanecarboxylic acid (1.57 g, 10 mmol) in methanol (40 mL) was added thionyl chloride (0.9 mL, 12 mmol) for 10 min at 0 °C. The reaction mixture was then left under reflux for 1 h, after which the mixture was cooled to RT. The solvent was removed under a reduced pressure, and the residue triturated twice with hexane (25 mL). The resulting solid was dried under vacuo for 6 h. Yield 1.93 g (93%). <sup>1</sup>H NMR (*d*<sub>6</sub>-DMSO)  $\delta$  3.57 (s, 3H, OCH<sub>3</sub>), 2.60 (m, 1H, H13), 2.23 (m, 1H, H10), 1.85 (m, 2H, H9), 1.26 (m, 4H, H12 H11) 0.96 (m, 4H, H12 H11). Anal. Calcd for C<sub>9</sub>H<sub>18</sub>ClNO<sub>2</sub>: C, 52.05; H, 8.74; N, 6.74. Found: C, 51.84; H, 8.34; N, 6.93.

***trans*-4-(Aminomethyl)cyclohexanemethylcarboxylate Hydrochloride.** The title compound was obtained by following the same procedure as for *trans*-4-(aminomethyl)cyclohexanemethylcarboxylate hydrochloride by replacing methanol with ethanol. Yield 2.13 g (96%). <sup>1</sup>H NMR (*d*<sub>6</sub>-DMSO)  $\delta$  4.03 (q,  $J = 7.08$ , 2H, OCH<sub>2</sub>CH<sub>3</sub>), 2.61 (m, 1H, H13), 2.21 (m, 1H, H10), 1.85 (m, 2H, H9), 1.27 (m, 4H, H12 H11), 1.16 (t,  $J = 7.06$ , 3H, OCH<sub>2</sub>CH<sub>3</sub>), 0.96 (m, 4H, H12 H11). Anal. Calcd for C<sub>10</sub>H<sub>20</sub>ClNO<sub>2</sub>: C, 54.17; H, 9.09; N, 6.32. Found: C, 53.78; H, 8.91; N, 6.34.

**L1·3H<sub>2</sub>O.** To a suspension of DTPA-bis-anhydride (0.71 g, 2 mmol) in DMF (15 mL) was added *trans*-4-(aminomethyl)cyclohexanecarboxylic acid (0.63 g, 4 mmol). The mixture was stirred at 65 °C for 4 h, after which the solvent was stripped off under reduced pressure, and the residue was taken up methanol (10 mL). The solution was passed through a short column of silica gel (60 mesh) with methanol as an eluent. An off-white solid was obtained after removal of the solvent under vacuo at 50 °C for 8 h. Yield 1.22 g (84%). <sup>1</sup>H NMR (*d*<sub>6</sub>-DMSO)  $\delta$  8.08 (s, 1H, CONH), 3.52 (s, 1H, H2), 3.33 and 3.27 (s, 4H, H3/H4), 3.08 (s, 2H, H9), 2.93 (s, 2H, H5), 2.88 (s, 2H, H7), 2.09 (m, 1H, H13), 1.86, 1.69, 1.25 and 0.90 (m, 8H, H11/H12), 1.36 (m, 1H, H5'). Anal. Calcd for C<sub>30</sub>H<sub>55</sub>N<sub>5</sub>O<sub>15</sub>: C, 49.65; H, 7.64; N, 9.65. Found: C, 49.66; H, 7.41; N, 9.72. FABMS (*m/z*): calcd for C<sub>30</sub>H<sub>49</sub>N<sub>5</sub>O<sub>12</sub> 671.73 (M<sup>+</sup>), found 672.33.

**L2·7H<sub>2</sub>O.** This compound was obtained essentially by

following the same procedure as that for **L1** by replacing *trans*-4-(aminomethyl)cyclohexanecarboxylic acid with *trans*-4-(aminomethyl)cyclohexanemethylcarboxylate hydrochloride. Yield 1.49 g (90%).  $^1\text{H NMR}$  ( $d_6$ -DMSO)  $\delta$  8.51 (s, 1H, CONH), 3.94 (s, 1H, H2), 3.79 (s, 2H, H9), 3.56 (s, 3H, OCH<sub>3</sub>), 3.27 and 3.20 (s, 4H, H4/H3), 2.88 (s, 2H, H5), 2.71 (s, 2H, H7), 2.23 (m, 1H, H13), 1.87, 1.71, 1.26 and 0.91 (m, 8H, H11/H12), 1.36 (m, 1H, H10). Anal. Calcd for C<sub>32</sub>H<sub>67</sub>N<sub>5</sub>O<sub>19</sub>: C, 46.54; H, 8.18; N, 8.48. Found: C, 46.63; H, 7.91; N, 8.62. FABMS ( $m/z$ ): calcd for C<sub>32</sub>H<sub>53</sub>N<sub>5</sub>O<sub>12</sub> 699.79 (M<sup>+</sup>), found 700.31.

**L3·6H<sub>2</sub>O**. This compound was obtained by following the same procedure as that for **L1** by replacing *trans*-4-(aminomethyl)cyclohexanecarboxylic acid with *trans*-4-(aminomethyl)cyclohexanemethylcarboxylate hydrochloride. Yield 1.40 g (84%).  $^1\text{H NMR}$  ( $d_6$ -DMSO)  $\delta$  8.63 (s, 1H, CONH), 4.00 (q,  $J = 7.02$ , 2H, OCH<sub>2</sub>CH<sub>3</sub>), 3.88 (s, 2H, H7), 3.79 (s, 1H, H2), 3.25 (s, 4H, H3, H4), 2.94 (s, 2H, H5), 2.17 (m, 1H, H13), 1.85, 1.71, 1.21 and 0.90 (m, 8H, H11/H12), 1.36 (m, 1H, H10), 1.13 (t,  $J = 7.04$ , 3H, OCH<sub>2</sub>CH<sub>3</sub>). Anal. Calcd for C<sub>34</sub>H<sub>69</sub>N<sub>5</sub>O<sub>18</sub>: C, 48.85; H, 8.32; N, 8.38. Found: C, 48.59; H, 8.53; N, 8.36. FABMS ( $m/z$ ): calcd for C<sub>34</sub>H<sub>57</sub>N<sub>5</sub>O<sub>12</sub> 727.84 (M<sup>+</sup>), found 728.34.

**L4·2H<sub>2</sub>O**. This compound was synthesized by following the same procedure as that for **L1** replacing *trans*-4-(aminomethyl)cyclohexanecarboxylic acid with 4-aminobenzoic acid. The product was isolated by the addition of methanol to the residue obtained after removal of the solvent from the reaction mixture. Yield 1.17 g (88%).  $^1\text{H NMR}$  ( $d_6$ -DMSO)  $\delta$  10.42 (s, 1H, CONH), 7.92 (d,  $J = 8.5$ , 2H, aromatic), 7.82 (d,  $J = 8.5$ , 2H, aromatic), 3.56 (s, 1H, H2), 3.54 (s, 2H, H5), 3.25 (s, 2H, H7), 3.07 and 3.00 (m, 4H, H3/H4). Anal. Calcd for C<sub>28</sub>H<sub>37</sub>N<sub>5</sub>O<sub>14</sub>: C, 50.37; H, 5.59; N, 10.49. Found: C, 50.40; H, 5.62; N, 10.80. FABMS ( $m/z$ ): calcd for C<sub>28</sub>H<sub>30</sub>GdN<sub>5</sub>O<sub>12</sub> 631.59 (M<sup>+</sup>), found 632.23.

**[Gd(L1)(H<sub>2</sub>O)]·4H<sub>2</sub>O (5)**. To a solution of **L1** (0.73 g, 1 mmol) in deionized water (10 mL) was added Gd<sub>2</sub>O<sub>3</sub> (0.18 g, 0.5 mmol). The suspension was stirred for 6 h at 100 °C during which time a pale yellow solution resulted. The reaction mixture was cooled to RT and passed through a Celite to remove any solid impurities. The solvent was removed and the residue was taken up in methanol (5 mL). Acetonitrile (100 mL) was added to precipitate the product as a white solid. Yield 0.71 g (78%). Anal. Calcd for C<sub>30</sub>H<sub>56</sub>GdN<sub>5</sub>O<sub>17</sub>: C, 39.33; H, 6.16; N, 7.65. Found: C, 39.44; H, 6.17; N, 7.71. FABMS ( $m/z$ ): calcd for C<sub>30</sub>H<sub>46</sub>GdN<sub>5</sub>O<sub>12</sub> 825.96 (M – H<sub>2</sub>O)<sup>+</sup>, found 825.25.

**[Gd(L2)(H<sub>2</sub>O)]·11H<sub>2</sub>O (6)**. This was synthesized by following the same procedure as that for **5** by replacing **L1** with **L2**. Yield 0.73 g (71%). Anal. Calcd for C<sub>32</sub>H<sub>74</sub>GdN<sub>5</sub>O<sub>24</sub>: C, 35.91; H, 6.97; Gd, 14.69; N, 6.54. Found: C, 36.18; H,

6.73; N, 6.78. FABMS ( $m/z$ ): calcd for C<sub>32</sub>H<sub>50</sub>GdN<sub>5</sub>O<sub>12</sub> 854.02 (M – H<sub>2</sub>O)<sup>+</sup>, found 855.25.

**[Gd(L3)(H<sub>2</sub>O)]·11H<sub>2</sub>O (7)**. This was synthesized by following the same procedure as that for **5** by replacing **L1** with **L3**. Yield 0.72 g (67%). Anal. Calcd for C<sub>34</sub>H<sub>78</sub>GdN<sub>5</sub>O<sub>24</sub>: C, 37.18; H, 7.16; N, 6.38. Found: C, 37.35; H, 6.83; N, 6.51. FABMS ( $m/z$ ): calcd for C<sub>34</sub>H<sub>54</sub>GdN<sub>5</sub>O<sub>12</sub> 882.09 (M – H<sub>2</sub>O)<sup>+</sup>, found 881.24.

**[Gd(L4)(H<sub>2</sub>O)]·3H<sub>2</sub>O (8)**. This was synthesized by following the same procedure as that for **5** by replacing **L1** with **L4**. The product precipitated as a white solid from the reaction mixture during the reaction, isolated by filtration, washed with water several times, and dried in vacuo at 50 °C for 4 h. Yield 0.58 g (68%). Anal. Calcd for C<sub>28</sub>H<sub>40</sub>GdN<sub>5</sub>O<sub>17</sub>: C, 38.40; H, 4.60; N, 8.00. Found: C, 38.77; H, 4.43; N, 8.11. FABMS ( $m/z$ ): calcd for C<sub>28</sub>H<sub>30</sub>GdN<sub>5</sub>O<sub>12</sub> 785.81 (M – H<sub>2</sub>O)<sup>+</sup>, found 785.13.

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**Supporting Information Available:** Crystallographic data for **8** have been deposited with the Cambridge Crystallographic Data Centre (Deposit No. CCDC-612057). The data can be obtained free of charge via <http://www.ccdc.cam.ac.uk/per/catreq/catreq.cgi> (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: [deposit@ccdc.cam.ac.uk](mailto:deposit@ccdc.cam.ac.uk)).

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