

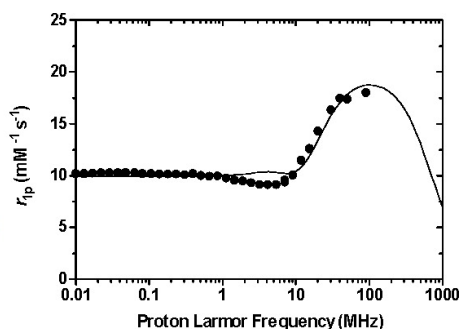
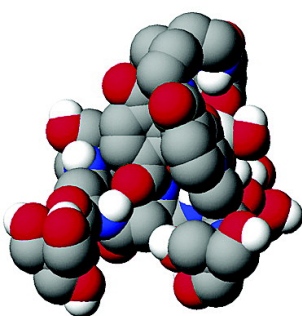
Communication

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## Dendrimeric Gadolinium Chelate with Fast Water Exchange and High Relaxivity at High Magnetic Field Strength

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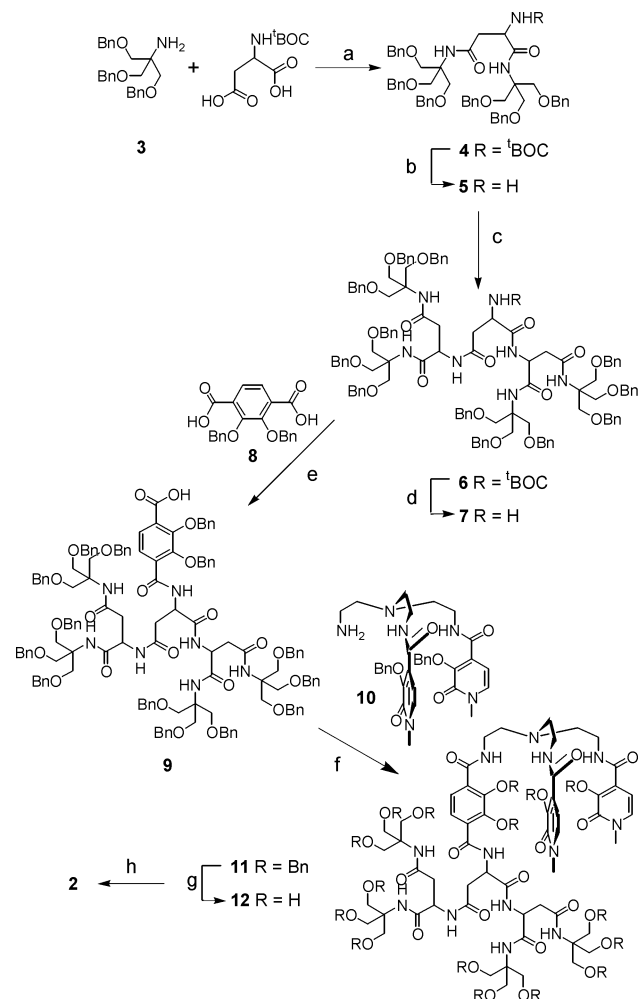
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Gd<sup>III</sup> is highly paramagnetic, with seven unpaired electrons and a long electronic relaxation time, making it ideal as a relaxation agent for magnetic resonance imaging (MRI). However, current commercial, poly(amino carboxylate)-based chelates demonstrate mediocre image-enhancing capability (relaxivity  $r_{1p}$ ), only a few percent of that the Solomon–Bloembergen–Morgan theory predicts.<sup>1–3</sup> These agents have only one water coordinated to the Gd, slow water exchange rate, and fast molecular tumbling, three parameters that are crucial in attaining high relaxivity. The development of site-specific, second-generation agents requires much higher relaxivity. It therefore becomes important to optimize all of these parameters to obtain adequate contrast at higher magnetic field, those of the next generation of MRI scanners.

Recently, hydroxypyridonate (HOPO)-based chelates such as the heterotripodal Gd-TREN-bisHOPO-TAM-Me (Gd-1) showed promise due to the high relaxivity<sup>4</sup> they achieved while maintaining high stability and selectivity, regardless of any functionalization on the TAM moiety.<sup>5,6</sup> This high relaxivity is attributed to the two water molecules coordinated to the Gd<sup>III</sup> ion and to their near-optimal residence time ( $\tau_m$ ). These compounds thus represent an advance in the development of high relaxivity contrast agents, especially given the importance of  $\tau_m$  for macromolecular complexes. Indeed, it has been demonstrated that the relaxivity of a Gd<sup>III</sup> complex will increase upon decelerating its molecular tumbling insofar as its water residence time is optimal.<sup>7–10</sup> Theoretically, the optimal water residence time of HOPO-based complexes enables them to achieve high relaxivity upon deceleration of their molecular tumbling.<sup>8</sup> This can be achieved by grafting the Gd chelate to a rigid, spherical macromolecule such as a protein or a dendrimer. However, the solubility of a dendrimer is primarily determined by that of its terminal groups.<sup>11</sup> Low-generation dendrimers in which all terminal groups were functionalized with hydrophobic Gd-TREN-bisHOPO-TAM complexes were thus insoluble in water. The poor water solubility of the parent complex therefore requires that it be grafted upon a "water-solubilizing dendron" terminated by hydrophilic hydroxyl groups. Furthermore, to fully take advantage of the structure of the dendrimer, it has to be as rigid as possible to avoid the Gd<sup>III</sup> chelate from freely rotating or folding back.<sup>7</sup>

In the molecule described here, Gd-TREN-bisHOPO-TAM-Asp-Asp<sub>2</sub>-12OH (Gd-2), the Gd<sup>III</sup> chelate is grafted on a dendron consisting of four tris(hydroxymethyl)aminomethane (TRIS) groups linked by three aspartic acids. The resulting 12 hydroxyl groups ensure the overall water solubility of the complex (solubility  $\geq 15$  mM as compared to  $<0.5$  mM for (1)), whereas the short linker between two branching points of each aspartic moiety ensures the compactness of the dendrimer. A geometry optimization of (Gd-2)

Scheme 1<sup>a</sup>



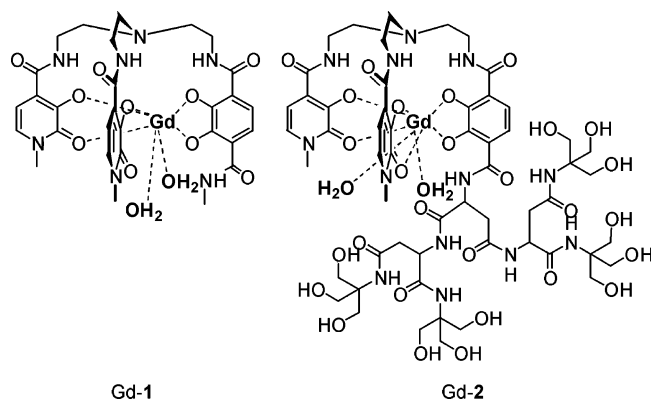
<sup>a</sup> Reagents and conditions: (a) HATU, DIPEA, DMA, 20 °C, 15 h. (b) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 5 h. (c) HATU, DIPEA, DMA, 20 °C, 18 h. (d) TFA, CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 2 h. (e) (1) C<sub>2</sub>O<sub>2</sub>Cl<sub>2</sub>, toluene, DMF, 20 °C, 2 h; (2) DIPEA, THF, 20 °C, 18 h. (f) HATU, DIPEA, CH<sub>2</sub>Cl<sub>2</sub>, 20 °C, 18 h. (g) 80 atm of H<sub>2</sub>, Pd/C, acetic acid, 20 °C, 48 h. (h) Gd(acac)<sub>3</sub>, pyridine, CH<sub>3</sub>OH, reflux, 4 h.

(Supporting Information) indicates that maximum compactness is achieved for this spherical molecule.

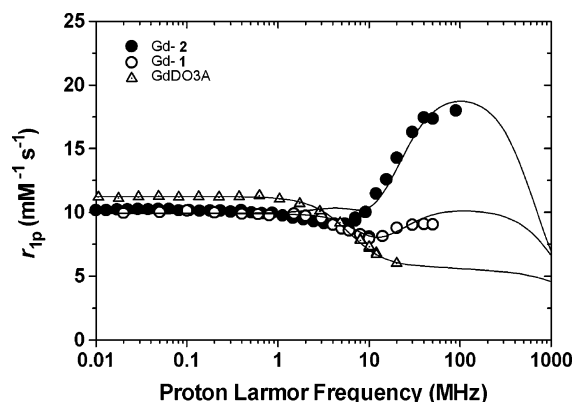
The synthesis of Gd-TREN-bisHOPO-TAM-Asp-Asp<sub>2</sub>-12OH (Gd-2) is outlined in Scheme 1. First, two benzyl (Bn)-protected TRIS (3) moieties<sup>12</sup> were coupled on an aspartic acid. Deprotection of the central amine enabled further coupling of two of the resulting H<sub>2</sub>N-Asp-6OBn (5) moieties to another aspartic acid. Deprotection of the central amine yielded the benzyl-protected water-solubilizing

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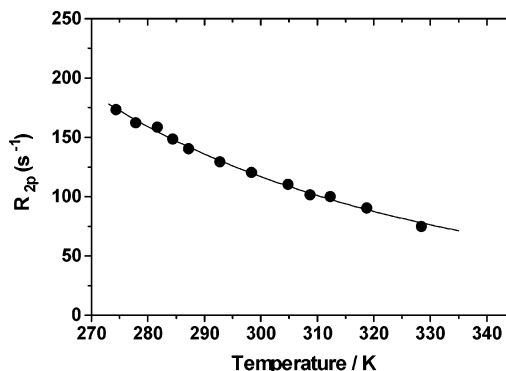
**Figure 1.** Gd-TREN-bisHOPO-TAM-Me(H<sub>2</sub>O)<sub>2</sub> (Gd-1) and Gd-TREN-bisHOPO-TAM-Asp-Asp<sub>2</sub>-12OH(H<sub>2</sub>O)<sub>2</sub> (Gd-2).



**Figure 2.**  $1/T_1$  NMRD profile at 298 K of Gd-2 versus Gd-1<sup>4</sup> and the commercial Gd-DO3A.<sup>13</sup> The fitting parameters for Gd-2 are the following:  $\Delta^2$  ( $s^{-2} \times 10^{19}$ ) = 10.5,  $\tau_v$  (ps) = 23.4,  $\tau_R$  (ps) = 238,  $q = 2$ ,  $r$  (Å) = 3.00.

dendron (7). The acid-terminated heteropodal ligand was grafted to the central amine of the dendron in two steps. First, the 2,3-dibenzyloxy-terephthalamide (TAM-Bn<sub>2</sub>) was coupled, followed by the hydroxypyridinone moiety, TREN-bis(HOPO-Bn). The ligand and the dendron were simultaneously deprotected by hydrogenolysis (Pd/C, H<sub>2</sub>), enabling further complexation with Gd<sup>III</sup>.

The  $1/T_1$  NMRD profile (Figure 2) indicates that Gd-2 has a relaxivity three times that of the comparative  $q = 2$  commercial agent Gd-DO3A.<sup>13</sup> Furthermore, a distinct peak of relaxivity was centered around 90 MHz, the frequency for which the dendrimeric chelate has an optimal water residence time. Indeed, <sup>17</sup>O NMR studies (Figure 3) indicate that for Gd-2,  $\tau_m \approx 10$  ns and is comparable to that of the parent complex Gd-1. Furthermore,  $q = 2$  for Gd-2, indicating that none of the nearby alcohols coordinate the Gd<sup>III</sup>. Detailed refinements of the NMRD and <sup>17</sup>O NMR studies of the dendrimeric analogue Gd-2 as compared to the parent Gd-1<sup>4</sup> indicate that most of the increase in molecular weight is translated into an increase in rotational correlation time. The macromolecule Gd-2 ( $M_w = 1576$  g/mol) is 1.9 times larger than Gd-1 ( $M_w = 831$  g/mol), and its rotational correlation time ( $\tau_R = 238$  ps) is 1.9 times that of Gd-1 ( $\tau_R = 125$  ps). At 20 MHz, Gd-TREN-bisHOPO-TAM-Asp-Asp<sub>2</sub>-12OH (2) has a relaxivity  $r_{1p} = 14.3$  mM<sup>-1</sup> s<sup>-1</sup> (pH 7.2, 25 °C), barely 1.6 times greater than that of the monomer Gd-1 ( $r_{1p} = 8.8$  mM<sup>-1</sup> s<sup>-1</sup>, pH 8.5, 25 °C). However, at 90 MHz, the dendrimer 2 has a relaxivity  $r_{1p} = 18.0$  mM<sup>-1</sup> s<sup>-1</sup> (pH 7.2, 25 °C), 1.8 times that of 1 ( $r_{1p} \approx 9.8$  mM<sup>-1</sup> s<sup>-1</sup>; pH 7.2, 25 °C). This increase in relaxivity is thus consistent with the increase in rotational



**Figure 3.** Temperature dependence of the paramagnetic contribution to the water <sup>17</sup>O NMR transverse relaxation rate ( $R_{2p}$ ) for 2 (0.015 M, pH 7.2) at 2.1 T. The fitting parameters are the following:  $\Delta^2$  ( $s^{-2} \times 10^{19}$ ) = 12,  $\tau_v^{298}$  (ps) = 22,  $\Delta H_v$  (kJ mol<sup>-1</sup>) = 3.0,  $\tau_M^{298}$  (ns) = 10,  $\Delta H_M$  (kJ mol<sup>-1</sup>) = 14,  $\Delta H_R$  (kJ mol<sup>-1</sup>) = 20.

correlation time, which results both from the increase in molecular weight and maximum compactness of the structure.

In summary, this report describes a new dendrimeric derivative of a hydroxypyridonate-based Gd<sup>III</sup> chelate. The alcohols of the solubilizing dendron increase the water solubility of the complex, whereas its compactness ensures an efficient increase in rotational correlation time. The combination of a very short water residence time and a short electronic relaxation time results in a complex with high relaxivity, peaking at ca. 100 MHz. To the best of our knowledge, this is the first example of a dendrimeric Gd<sup>III</sup> complex with fast water exchange displaying high relaxivity at high magnetic field. This is perhaps the first contrast agent that has optimal efficacy at the frequency of the scanners of the new generation.<sup>14</sup>

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**Supporting Information Available:** Space filling model of 2, second sphere contribution to the relaxivity, and detailed experimental procedures and characterization data (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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