Synthesis of Gd$_2$O$_3$ nanoparticles for MRI contrast agents

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Abstract. Gd$_2$O$_3$ nanoparticles were synthesized by using our original method for application as MRI contrast agents. The sample diameters were controlled in the range 18–66 nm by adjusting the annealing temperature between 773 and 1273 K in air or in an Ar atmosphere. Magnetization measurements were performed at 300 K, and the effective magnetic moment of each sample was calculated. They showed paramagnetism at 300 K and they had large effective magnetic moment $\mu_{\text{eff}}$ of 7.15–8.05 $\mu_B$. MRI measurements were performed in 0.8 wt% agarose solution, and the Gd$_2$O$_3$ nanoparticles were found to work as effective T$_1$-shortening MRI contrast agents.

1. Introduction
Gadolinium in the form of a chelate complex is used as a T$_1$-shortening MRI (Magnetic Resonance Imaging) contrast agent [1]. MRI is a common medical imaging technique that allows visualization through measurement of the magnetic relaxation of protons in the human body. MRI contrast agents accelerate this magnetic relaxation through the magnetic interactions between the protons and agents, and define the contrast of the MR images obtained. Gd$^{3+}$ ions have a large calculated magnetic moment of 7.94 $\mu_B$, which gives a large magnetic interaction and strongly accelerates the magnetic relaxation of the proton. Efficient MRI contrast agents can alleviate the burden on patients through the shortening of the diagnosis time and the reduction in administering agents.

Metal oxide nanoparticles and their hybrid materials with organic compounds are anticipated to find use in the field of multifunctionalized nanomedicine [2], with possible applications in drug-delivery systems (DDSs) [3], magnetic hyperthermia [4], and as medical markers. Through the employment of these techniques, gadolinium oxide nanoparticles could be applied as new types of multifunctional MRI contrast agents [5].

Previously, one of the authors produced magnetic nanoparticles through a unique method and reported their magnetic properties [6][7]. In this study, Gd$_2$O$_3$ materials were produced in order to apply to MRI contrast agents. Their diameters were controlled by annealing temperature, and
magnetization measurements were performed for each sample. Same sample were selected for MRI measurements.

2. Experimental
Gd$_2$O$_3$ nanoparticles were prepared by mixing of aqueous solution of GdCl$_3$·6H$_2$O and NaOH [2][3]. Reagents were used to set the Na:Cl mole ratio to 1:1, and were dissolved individually in distilled water. These aqueous solutions were mixed to obtain precipitates. The precipitates were washed to remove the Na$^+$ and Cl$^-$ ions, and dried at about 350 K in a thermostat-controlled oven. Each precursor was annealed in an electric furnace. The annealing treatment was carried out in air or in an Ar atmosphere at temperatures of 773–1273 K for 10 hours.

X-ray powder diffraction measurements (CuK$_\alpha$, $\lambda = 0.154$ nm) were performed for each sample. The average sample diameters were analyzed by fitting the theoretical 222 diffraction peak to the measured diffraction peak of each sample. Theoretical diffraction patterns were calculated using the Stokes & Wilson method [8] with the software CSDA (Ver. 1.3, Rigaku Corporation, Japan). The morphology and diameter distribution of the nanoparticles were investigated using a transmission electron microscope (TEM; H-7100; Hitachi, Japan). Magnetization measurements were determined at 300 K under a magnetic field of ±50 kOe using a SQUID magnetometer.

MRI signal measurements were performed using a 0.3-T MRI system (Hitachi Medical Corporation, Japan). The particles annealed at 1173 K in air were dispersed in 0.8 wt% agarose solution, and the concentration of Gd$^{3+}$ ions was set to 1.0 mM. The MRI signal of this sample was measured by the $T_1$ spin echo sequence ($TE = 12$ ms) and $T_2$ spin echo sequence ($TR = 2000$ ms). For comparison, the same measurements were performed for 0.8 wt% agarose solutions without Gd$_2$O$_3$ nanoparticles, and $T_1$ measurements were performed for solution and a 0.5 mM aqueous solution of gadolinium-diethylenetriaminepentaacetic acid (Gd-DTPA), which is commonly used as a $T_1$ contrast agent. MR images of Gd$_2$O$_3$ solution were took with setting echo time of $TE = 12$ ms and repetition time of $TR = 50, 150, 300, 500, 700, 4000, 6000, 8000, 10000$ ms.

3. Results and Discussion

3.1. X-ray diffraction
The X-ray diffraction patterns of each sample are shown in figure 1. It was found that all the samples were single-phase Gd$_2$O$_3$. The average diameters of the Gd$_2$O$_3$ nanoparticles annealed in air were estimated to be 26, 30, 46, 59, and 66 nm for the samples annealed at 773, 873, 973, 1073, 1173, and 1273 K, respectively. For the samples annealed in an Ar atmosphere, the average diameters were estimated to be 18 and 22 nm for annealing at 823 and 873 K, respectively. These particles were rather smaller than those of the samples annealed in air. The representative TEM data is shown in Fig. 2. Figure 3 shows the relationship between the particle diameter and the annealing temperature. From these results, it was found that the average diameter of Gd$_2$O$_3$ nanoparticles could be controlled by adjusting the temperature and atmosphere of the annealing process. The diameter of the Gd$_2$O$_3$ nanoparticles (823 K in Ar) was deduced to be 23 ±1.0 nm (statistics: 288 measurements; ±1.0 nm means the standard error of the mean (S.E.M.)) which was good agreement with the result of XRD.
Figure 1. X-ray powder diffraction patterns of the samples annealed at 823 and 873 K in an Ar atmosphere and at 773, 873, 973, 1073, 1173, and 1273 K in air.

Figure 2. TEM image of Gd$_2$O$_3$ nanoparticles. Scale bar is 100 nm.

Figure 3. Average diameters estimated from the 222 X-ray diffraction peak of the samples treated under different annealing conditions.
3.2. Magnetization measurements

The results of the magnetization measurements are shown in figure 4. It was found that the Gd$_2$O$_3$ nanoparticles of all sizes were paramagnetic at 300 K. The effective magnetic moments $\mu_{\text{eff}}$ of the Gd$^{3+}$ ions calculated from the magnetization values at 300 K are summarized in table 1. These $\mu_{\text{eff}}$ values were in good agreement, within experimental error, with the theoretical value of 7.94 $\mu_B$. Temperature dependence of magnetization followed Curie-Weiss law. Paramagnetic Curie temperature of $\theta_p$ was determined to be $-10$–$5$ K. These results indicated that large magnetic moments of Gd$^{3+}$ ions fluctuated because of thermal energy at 300 K.

![Figure 4](image)

**Figure 4.** Magnetization of each sample at 300 K, for particle diameters of 18, 22, 26, 30, 36, 46, 59, and 66 nm.

**Table 1.** Effective magnetic moment ($\mu_{\text{eff}}$) of each sample calculated from magnetic measurement at 300 K.

| Diameter (nm) | 18  | 22  | 26  | 30  | 36  | 46  | 59  | 66  |
|--------------|-----|-----|-----|-----|-----|-----|-----|-----|
| $\mu_{\text{eff}}$ ($\mu_B$) | 8.05 | 7.36 | 7.54 | 7.31 | 7.15 | 7.28 | 7.49 | 7.95 |

3.3. MRI measurements

The T$_1$ relaxation curves of Gd$_2$O$_3$ with diameter of 59 nm and non-Gd$_2$O$_3$ solutions are shown in figure 5(a). The T$_1$ relaxation time was estimated to be 0.196 s in Gd$_2$O$_3$ solution and 2.16 s in non-Gd$_2$O$_3$ solution. The T$_1$ relaxation rate ($R_1$) was calculated to be 5.1 s$^{-1}$ mM$^{-1}$ in Gd$_2$O$_3$ solution and 0.46 s$^{-1}$ mM$^{-1}$ in non-Gd$_2$O$_3$ solution. The $R_1$ value of the Gd$_2$O$_3$ solution was comparable to the value of 6.1 s$^{-1}$ mM$^{-1}$ for Gd-DTPA in aqueous solution. The phantom images of Gd$_2$O$_3$ solution were shown in Fig. 6. The obtained images showed very high contrast in even short repetition time of TR, and they became brighter as repetition time of TR increased. It was found that the Gd$_2$O$_3$ nanoparticles have a strong T$_1$-shortening capability as MRI contrast agents.
Figure 5. T₁ relaxation curve (a) and T₂ relaxation curve (b) of 0.8 wt% agarose solution with Gd₂O₃ (59 nm) and agarose solution without particles.

Figure 6. Phantom images of Gd₂O₃ solution with setting echo time of TE = 12 ms and repetition time of TR = 50, 150, 300, 500, 700, 4000, 6000, 8000, 10000 ms.

The T₂ relaxation curves of Gd₂O₃ and non-Gd₂O₃ solutions are shown in figure 5(b). The T₂ relaxation time was estimated to be 6.67 × 10⁻² s in Gd₂O₃ solution and 13.3 × 10⁻² s in non-Gd₂O₃ solution. The T₂ relaxation rate (R₂) was calculated to be 15 s⁻¹ mM⁻¹ in Gd₂O₃ solution and 7.5 s⁻¹ mM⁻¹ in non-Gd₂O₃ solution. This value of R₂ is enough to emphasize the contrast in T₂-weighted MR images.

Remarkably, these results show that Gd₂O₃ nanoparticles have effects both as T₁- and T₂-shortening MRI contrast agents, especially with their large T₁ relaxation rate. In the case of the Gd³⁺ chelate complex, T₁ relaxation is accelerated by the dynamic local magnetic field, which is derived from the magnetic coupling of the proton and the Gd³⁺ ions [1][9]. It is considered that the Gd³⁺ ions of these nanoparticles exhibit the same relaxation process as that observed in Gd³⁺ chelate complexes. This relaxation process is due to the paramagnetic behavior and large magnetic moment of this Gd₂O₃ nanoparticle system [10].

4. Conclusion

Gd₂O₃ nanoparticles were synthesized by the wet chemical method, and their diameters were controlled between 18 and 66 nm by adjusting the conditions of the annealing process. All the samples showed paramagnetic behavior at 300 K, and their effective magnetic moments were calculated to be in the range 7.15–8.05 μB. From the MRI measurements, Gd₂O₃ particles with a diameter of 59 nm were found to have relaxation rate of R₁ = 5.1 s⁻¹ mM⁻¹ and R₂ = 15 s⁻¹ mM⁻¹. From these results, it is concluded that Gd₂O₃ nanoparticles could be used as both T₁- and T₂-shortening MRI contrast agents, and that they have an especially strong ability in the shortening of T₁.
Acknowledgements
This study was partially supported by the Precursory Research for Embryonic Science and Technology of the Japan Science and Technology Agency and the Takahashi Industry Foundation for Economic Research 2010.

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