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Water bridge coordination on metal-rich facets of Gd_2O_3 nanoplates confers high T_1 relaxivity

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Abstract

To realize the nature of water coordination on the solid surfaces may provoke essential understanding of T_1 relaxation enhancement, especially in nanoparticulate systems. We report herein that T_1 relaxivity of Gd_2O_3 nanoplates is highly dependent on water coordinating behaviors on different surfaces. Gd_2O_3 nanoplates with metal-rich {100} facets showed an approximately 4-fold higher r_1 value comparing to that with oxygen-terminated {111} facets. Density functional theory (DFT) calculations show that the enhanced T_1 relaxivity of Gd_2O_3 {100} nanoplates may be ascribed to the high density of accessible Gd^{3+} , fast exchange of water, and more importantly, multicenter (one-to-two) coordination for water molecules with magnetic centers on the metal-rich surface.

Graphical Abstract

One-to-two bridge coordination of water molecules on metal-rich Gd_2O_3 {100} facet was investigated by experimental MRI study and DFT calculations, which provides a new insight for T_1 relaxation enhancement in nanoparticulate systems.

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Introduction

The rise of two-dimensional (2D) nanomaterials has provoked invaluable opportunities for scientists to investigate structure-property relationships in solid state nanochemistry.^{1–4} Due to the intriguing electronic and physical properties by morphological confinement effect, these 2D nanomaterials have shown unprecedented performance in electronics,^{3, 5} catalysis,^{6–8} energy storage,^{9, 10} and nanomedicine.^{11–13} The classical Solomon-Bloembergen-Morgan (SBM) theory for magnetic resonance imaging (MRI) contrast agents indicates that T_1 relaxation of protons is related to their chemical exchange efficiency in paramagnetic molecular systems.^{14, 15} However, there is still a major gap to bridge T_1 relaxivity and water interacting behaviors in nanoparticulate systems. We have recently recognized that iron oxide nanoplates with metal-rich exposed facets showed enhanced T_1 relaxivity, probably due to the more favorable water coordination and chemical exchange on such surface as compared to spherical nanoparticles.^{16, 17} One major concern for iron oxide nanoplates is, however, they are superparamagnetic thus T_1 relaxation enhancement efficiency may be blurrily disturbed by the strong T_2 decaying effect.^{18, 19} A suitable model to reveal the relationship between surface structure and T_1 relaxivity of magnetic nanoparticles is highly desirable, which would arouse the great research interest in innovating the design considerations for high-performance MRI contrast agents.^{20–25}

Traditional theoretic models were established on molecular systems, which only focused on the case that one water molecule (for systems with $q = 1$) interacts with one paramagnetic metal ion (noted as one-to-one coordination hereafter).^{26–28} For magnetic nanomaterials, however, the packed crystal structure may allow one water molecule interacting with two or more paramagnetic metal ions in their vicinity (multicenter coordination).²⁹ Moreover, specific surface would permit the fast exchange of water molecules on magnetic centers, thus holding great potential to enhance the T_1 relaxivity. Fortunately, advanced synthetic methodologies allow us to achieve controlled synthesis of nanomaterials with different surface features.^{30, 31} We propose here that metal-rich surface of magnetic nanomaterials could allow water bridging coordinate with two magnetic centers (Fig. 1a). Therefore, it is conceivable that the spin-lattice relaxation effects between water molecules and magnetic centers would be significantly enhanced comparing with that of one-to-one situation, which may confer the efficient recovery of protons longitudinal magnetizations within one relaxation time slot (Fig. 1b). Owing to the low magnetic susceptibility and diminished T_2 interference at room temperature, paramagnetic gadolinium oxide (Gd_2O_3) nanoparticles have shown great promise in T_1 contrast imaging.^{32, 33} Ultrasmall Gd_2O_3 nanoparticles and nanoplates have been reported to show high T_1 relaxivity.^{34–36} However, the relationship between surface structure and T_1 relaxivity on Gd_2O_3 nanoparticles is rarely investigated.

Herein, we present the successful controlled synthesis of Gd_2O_3 nanoplates with two types of surface exposure, $\text{Gd}_2\text{O}_3\{100\}$ and $\text{Gd}_2\text{O}_3\{111\}$ facets, respectively. The $\text{Gd}_2\text{O}_3\{100\}$ facet is exposed with gadolinium ions at the outermost layer, while the $\text{Gd}_2\text{O}_3\{111\}$ facet is terminated by oxygen ions. We illustrated that metal-rich exposed $\text{Gd}_2\text{O}_3\{100\}$ facet plays a decisive role in the enhanced T_1 relaxivity, showing approximately 4-fold higher r_1 values than that of $\text{Gd}_2\text{O}_3\{111\}$ nanoplates at different magnetic fields (0.5, 1.5, and 3.0 T). Density functional theory (DFT) calculation confirmed that water molecule coordinating on

$\text{Gd}_2\text{O}_3\{100\}$ facet requires lower energy than that on $\text{Gd}_2\text{O}_3\{111\}$ facet, indicating higher coordination efficiency on the $\text{Gd}_2\text{O}_3\{100\}$ nanoplates. More importantly, DFT results also suggested that water hopping and re-coordination on $\text{Gd}_2\text{O}_3\{100\}$ facet require very low transition state energy (0.08 and 0.13 eV, respectively), indicating a distinct mechanism for studying the chemical exchange of water molecules on Gd_2O_3 nanoplates.

Results and discussion

We used gadolinium(III) acetate as the precursor to synthesize Gd_2O_3 nanoplates with $\{100\}$ facet as exposed surfaces. Transmission electron microscopy (TEM) image showed the side length and width are about 120 and 40 nm, respectively (Fig. 2a). High-resolution TEM (HRTEM) image of a flat nanoplate showed a pair of perpendicularly crossed lattices with a spacing distance of 2.7 Å, which can be matched to (400) plane of cubic Gd_2O_3 phase (Fig. 2b). The in-plane fast Fourier transformation (FFT) pattern suggested $[100]$ zone axis (Fig. 2b, inset). Additionally, the HRTEM image of a perpendicular nanoplate showed interplanar distances of 2.7, 5.4, and 10.8 Å corresponding to (400), (200), and (100) plane of cubic Gd_2O_3 phase, respectively, indicating that the obtained Gd_2O_3 nanoplates (named as $\text{Gd}_2\text{O}_3\{100\}$ square nanoplates) are only one unit cell in thickness (Fig. 2c). It is worth noting that $\text{Gd}_2\text{O}_3\{100\}$ facet is a metal-rich surface terminated by gadolinium ions (Fig. 2d and Fig. S1). We can also tune the length and width of Gd_2O_3 nanoplates by controlling the molar ratio of surfactant to precursor (Fig. S2). The synthesis of $\text{Gd}_2\text{O}_3\{111\}$ nanoplates using gadolinium oleate as the precursor showed dendritic morphology at in-plane direction (named as $\text{Gd}_2\text{O}_3\{111\}$ dendritic nanoplates) with an edge length of about 65 nm (Fig. 2e). HRTEM image of a flat plate exhibited a lattice spacing distance of 1.9 Å corresponding to (440) of cubic Gd_2O_3 phase. The in-plane FFT pattern indicated $[111]$ zone axis (Fig. 2f and inset). HRTEM image of perpendicular plates further showed (222) plane with a spacing distance of 3.2 Å (Fig. 2g). Taken together, it is concluded that the obtained nanoplates are exposed with $\text{Gd}_2\text{O}_3\{111\}$ facet on the surfaces. In contrast, $\text{Gd}_2\text{O}_3\{111\}$ facet is terminated by oxygen ions rather than gadolinium ions (Fig. 2h and Fig. S1). The role of sodium oleate during the formation of $\text{Gd}_2\text{O}_3\{111\}$ nanoplates is likely to serve as both facet controlling agents in the early stage of nucleation and particle coalescence molecules during the later stage of growth of $\text{Gd}_2\text{O}_3\{111\}$ nanoplates (Fig. S3).^{37, 38}

We then used X-ray diffraction (XRD) pattern to identify the crystalline phase of these two Gd_2O_3 nanoplates. Both $\text{Gd}_2\text{O}_3\{100\}$ and $\text{Gd}_2\text{O}_3\{111\}$ nanoplates showed typical cubic phase (JCPDS. 012-0797) rather than monoclinic structure, which are consistent with those derived from HRTEM images and FFT patterns. Interestingly, XRD pattern of $\text{Gd}_2\text{O}_3\{100\}$ nanoplates showed an enhanced diffraction peak at 33.2 degrees corresponding to (400) planes, probably due to the face-by-face Lamer assembly structure on the substrate for XRD measurements (Fig. 2i and inset).³⁹ Likewise, $\text{Gd}_2\text{O}_3\{111\}$ nanoplates showed an enhanced diffraction peak at 47.5 degrees corresponding to (440) planes in the XRD pattern (Fig. 2j and inset). These results further confirmed that both $\text{Gd}_2\text{O}_3\{100\}$ and $\text{Gd}_2\text{O}_3\{111\}$ nanoplates are dominated with an ultrathin plate structure. The X-ray photoelectron spectroscopy (XPS) analysis of the Gd_2O_3 nanoplates revealed two distinctive peaks at binding energy of 142.6 and 1187.3 eV corresponding to Gd 4d and Gd 3d5 transitions, respectively (Fig. S4).

The hysteresis curves indicated that both $\text{Gd}_2\text{O}_3\{100\}$ and $\text{Gd}_2\text{O}_3\{111\}$ nanoplates are paramagnetic at 300 K (Fig. 3a). The unsaturated magnetic moments reached to 3.4 and 4.4 emu/g for the $\text{Gd}_2\text{O}_3\{100\}$ and $\text{Gd}_2\text{O}_3\{111\}$ nanoplates under magnetic field of 5 T at 300 K, respectively, indicating typical paramagnetism. When measured at low temperature of 5 K, the nearly saturated magnetization (M_s) values of the $\text{Gd}_2\text{O}_3\{100\}$ and $\text{Gd}_2\text{O}_3\{111\}$ nanoplates are about 88.9 and 96.3 emu/g, respectively (Fig. 3b). It is interesting that the $\text{Gd}_2\text{O}_3\{100\}$ nanoplates showed a slight tendency to be saturated at high field range (3–5 kOe) at low temperature, indicating a phase transition on such ultrathin nanoplates. This phenomenon was also observed at the hysteresis curves of other ultrathin Gd_2O_3 nanoplates (Fig. S5). The typical paramagnetism of obtained Gd_2O_3 nanoplates has also been evidenced by the thermal dependent zero field cooling (ZFC) and field cooling (FC) curves (Fig. S6).

We used sodium citrate as a surface modifier to endow Gd_2O_3 nanoplates with thin-layer coating on surface and make them water-soluble (Fig. S7), which is in principle extremely important for their intrinsic T_1 relaxivity.^{16, 17} The T_1 contrast performance of Gd_2O_3 nanoplates was evaluated at three different magnetic fields (0.5, 1.5, and 3.0 T). The $\text{Gd}_2\text{O}_3\{111\}$ nanoplates showed relatively low r_1 values of 3.4, 2.6, and 2.7 $\text{mM}^{-1}\cdot\text{s}^{-1}$ at 0.5, 1.5, and 3.0 T, respectively (Fig. 3c). For the $\text{Gd}_2\text{O}_3\{100\}$ nanoplates, these r_1 values are 14.5, 11.9, and 12.4 $\text{mM}^{-1}\cdot\text{s}^{-1}$ at 0.5, 1.5, and 3.0 T, respectively, which are approximately 4-fold higher than those of $\text{Gd}_2\text{O}_3\{111\}$ nanoplates. Consequently, MR phantom study of $\text{Gd}_2\text{O}_3\{100\}$ nanoplates showed excellent T_1 contrast with clearly brighter signal as the metal concentration was increased (Fig. 3d). In contrast, the $\text{Gd}_2\text{O}_3\{111\}$ nanoplates showed weak T_1 contrast due to the low T_1 relaxivity under the same conditions.

DFT study has received increasingly broad applications for interpreting and predicting complex behaviors at atomic scale in chemical and material sciences, for example, water splitting on the surface of nanoparticles.^{40, 41} Proton T_1 relaxation is highly dependent on the coordination and chemical exchange of water molecules on the surfaces when nanoparticles were employed. The thermodynamic phenomena and kinetic behaviors between water molecules and magnetic centers are of great importance in T_1 contrast efficiency. Therefore, we investigated the water interacting behaviors with crystal surfaces by means of DFT calculation.

$\text{Gd}_2\text{O}_3\{111\}$ facet is terminated with oxygen ions, while Gd^{3+} ions are at the second outermost layer. The $\text{Gd}_2\text{O}_3\{111\}$ facet exists 16 surface Gd^{3+} ions in one unit cell, 4 of which are six-coordinated and inaccessible for water (Fig. 4a, top view, and Fig. S8). The remaining 12 Gd^{3+} ions are in five-coordinated configuration, which still have vacancy to coordinate with one water molecule. DFT calculations indicated that the coordinated water molecules can be in the dissociated molecular form. As shown in Fig. 4a, 5 of 12 five-coordinated Gd^{3+} ions (pink dash circle) could induce the dissociation of H_2O into two -OH groups with the assistance of nearby oxygen atoms, yielding average adsorption energy of -1.32 eV. On the other hand, water molecules would be weakly adsorbed on the top sites of the other 7 Gd^{3+} ions with average adsorption energy of -0.75 eV (Fig. 4a, black dash circle). The high stability for dissociated water indicated extremely low exchange efficiency such that the dissociated water only acts as a ‘spectator’ during relaxation process. Thus, the density of exchangeable water on $\{111\}$ facet can be estimated to be ~ 3.4 per nm^2 (Fig. S9).

For $\text{Gd}_2\text{O}_3\{100\}$ facet, there are 8 three-coordinated Gd^{3+} ions in one unit cell, resulting 8 top sites, 16 bridge sites and 8 hollow sites (Fig. S10). We found that all these sites are able to be coordinated with water molecules, and the surface is able to accommodate at most 8 water molecules (Fig. 4b, red dash circle). Test calculations demonstrated that more water addition would lead to formation of multilayer adsorption. For simplicity, we assumed 8 water molecules occupied on the same type sites. According to DFT calculations, the average adsorption energy for top site, bridge site and hollow site were predicted to be -0.80 , -0.74 , and -0.81 eV, respectively, indicating that all water molecules on $\{100\}$ facet could be highly exchangeable (Fig. S10). An ideal way to compare the relaxivity difference of $\text{Gd}_2\text{O}_3\{100\}$ and $\text{Gd}_2\text{O}_3\{111\}$ facets is the corresponding nanoplates with same size and morphology. However, the facets exposed on a nanocrystal have a strong correlation with the shape. Gd_2O_3 crystal of cubic phase tends to form $\text{Gd}_2\text{O}_3\{100\}$ and $\text{Gd}_2\text{O}_3\{111\}$ nanoplates with cubic and spherical shape due to the anisotropic crystal growth under controllable condition. Thus, so far it is difficult to obtain Gd_2O_3 nanoplates with same morphology but with different exposed facets. In this respect, we carefully calculated the densities of water coordination on $\text{Gd}_2\text{O}_3\{100\}$ and $\text{Gd}_2\text{O}_3\{111\}$ facets. The density of water coordination on $\text{Gd}_2\text{O}_3\{100\}$ facet was estimated to be ~ 6.8 per nm^2 , nearly twice as that on $\text{Gd}_2\text{O}_3\{111\}$ facet (Fig. S9). Thus, the higher density of exchangeable water on $\text{Gd}_2\text{O}_3\{100\}$ may offer part of the explanation for the observed higher r_1 values than that of $\text{Gd}_2\text{O}_3\{111\}$. In addition, we disclosed that, besides the one-to-one coordinate mode (top site), there is one-to-two mode on bridge and hollow sites (note that the water molecules on the hollow sites deviated from the central position), resulting in two short and two long Gd-O bonds. Such new coordinated modes would promote spin-lattice relaxation effects between protons and nearby Gd^{3+} ions, which in turn increases the T_1 relaxivity. More significantly, nearly degenerate energies of water coordination on $\text{Gd}_2\text{O}_3\{100\}$ suggested that the potential energy surface was very smooth, thus facilitating the fast migration of water from one magnetic center to another.

We further explore the possible migration process of water molecules on the $\text{Gd}_2\text{O}_3\{100\}$ facets (Fig. 5a). DFT calculations demonstrated that water migration from one top site to another through a bridging-mediated process was calculated with transition energy barriers as low as 0.08 and 0.13 eV for two transition states TS1 and TS2, respectively, indicating a great potential for water dissociation and re-coordination from one Gd^{3+} ion to another Gd^{3+} ion in vicinity (Fig. 5b).^{42, 43} As reported previously,^{44, 45} T_1 relaxivity is not only related to the coordination status but also much dependent on the kinetic exchange of water molecules on magnetic centers (Fig. 5c,d). Our findings indicated that $\text{Gd}_2\text{O}_3\{100\}$ facet not only provides rich and multicenter sites for water coordination, but also facilitates the migration of water molecules among magnetic centers, thus enhancing T_1 relaxivity.

Prior to conducting *in vivo* study, we first evaluated the potential toxicity of Gd_2O_3 nanoplates at cellular level and in living animals. The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl- tetrazolium bromide) assay showed that more than 95% of both Hela and SMMC-7721 cells were viable after being treated with $\text{Gd}_2\text{O}_3\{100\}$ and $\text{Gd}_2\text{O}_3\{111\}$ nanoplates for 24 h even with a maximum concentration (with respect to Gd ions) up to 10 μM , indicating good biocompatibility *in vitro* (Fig. S11). The histological study further revealed that no organ abnormalities or lesions were found in mice ($n = 3$) treated with either

Gd₂O₃{100} or Gd₂O₃{111} nanoplates (2.0 mg [Gd]/kg mouse body weight) for 24 h, as indicated by the histology of major organs of liver, kidney, muscle, heart, lung, and spleen (Fig. S12). The toxicity of Gd-based agents is mainly related to the release of free Gd³⁺ ions. Our *in vitro* and *in vivo* results show that both Gd₂O₃{100} and Gd₂O₃{111} nanoplates are nontoxic at the treatment period of 24 h, suggesting little to no release of free Gd³⁺ ions from Gd₂O₃ nanoplates during this period. The long-term biosafety study should be conducted in future. For *in vivo* imaging study, we injected either Gd₂O₃{100} or Gd₂O₃{111} nanoplates in mice through tail vein with a dose of 2.0 mg [Gd]/kg mouse body weight. The T_1 MRI contrast performance was evaluated at a 3.0 T clinical scanner both at coronal and transverse planes at the region of interest (ROI) of liver, due to the fact that circulating nanoparticles are prone to be accumulated in the liver by mononuclear phagocyte system (MPS).^{46–48} The contrast-enhanced MRI results showed an obviously brighter signal at liver region after 0.5 h post-injection (p.i.) of Gd₂O₃{100} nanoplates, which continuously increased over time to 2 h p.i. (Fig. 6a). After that, decreased liver signal was found at 4 h p.i., the reason for which might be multifold: either the excretion of nanoplates from liver or stacking of nanoplates in liver will cause the loss of T_1 signal.¹⁷ On the contrary, the Gd₂O₃{111} nanoplates exhibited little to no contrast in T_1 MRI at ROI under the similar conditions (Fig. 6b). We used SNR (signal-to-noise ratio, $SNR = |SNR_{post} - SNR_{pre}|/SNR_{pre}$) to quantify the T_1 signal changes in ROI.⁴⁶ The results implied that SNR at ROI treated with Gd₂O₃{100} nanoplates are 2–4 fold higher than those being treated with Gd₂O₃{111} nanoplates at different time points (Fig. 6c,d). These results are consistent with the MR phantom study, further indicating the superior T_1 relaxation enhancement of Gd₂O₃{100} nanoplates both *in vitro* and *in vivo*.

Conclusions

In conclusion, we report that gadolinium oxide nanoplates with metal-rich Gd₂O₃{100} exposed facets exhibited significantly enhanced T_1 contrast ability, comparing to that with oxygen terminated Gd₂O₃{111} facets. The enhanced T_1 relaxivity of Gd₂O₃{100} nanoplates can be attributed to the following factors: (i) the higher density of water coordination due to the large number of exposed Gd³⁺ ions on Gd₂O₃{100} nanoplates; (ii) the one-to-two coordinated configurations of water coordination on metal-rich exposed Gd₂O₃{100} facets permit significantly enhanced spin-lattice relaxation effects; (iii) the smooth potential energy surface for water coordination enables bridge-mediated fast migration among different magnetic sites, thus facilitating cascade recovery of longitudinal magnetizations. The present work by integrating experimental results with theoretical simulation may not only provoke essential understanding of T_1 relaxation enhancement effects in nanoparticulate systems, but also shed light on innovations of T_1 contrast agents for high-performance MRI applications.

Experimental

Materials and characterization

1-octadecene (ODE, tech. 90%) and oleic acid (tech. 90%) were purchased from Acros. Gadolinium (III) chloride hexahydrate (99.99%) and gadolinium acetate (99.9%) were

purchased from Alfa Aesar. Sodium oleate, sodium citrate, iron chlorides and other reagents are purchased from Sinopharm Chemical Reagent Co. Ltd. All chemicals were used as received without further purification. TEM and HRTEM images were recorded on JEM-2100 microscope at an accelerating voltage of 200 kV. X-ray diffraction (XRD) patterns were recorded by Rigaku Ultima IV X-ray diffractometer with Cu K α radiation. The X-ray photoelectron spectroscopy (XPS) measurements were carried out by a PHI Quantum-2000 photoelectron spectrometer. The hysteresis loops (at 300 K and 5 K) and temperature-dependent magnetization measurements were recorded on Quantum Design MPMS-XL-7 system. The element analysis of metal ions was measured by inductively coupled plasma atomic emission spectroscopy (ICP-AES). The dynamic light scattering measurements were performed on Malvern Zetasizer nano ZS instrument. The MRI measurements and T_2/T_1 relaxation time testing were performed on 0.5 T NMI20-Analyst NMR Analyzing & Imaging system (Niumag Corporation, Shanghai, China), 3.0 T imaging system (Philips Medical System, ACHIEVA 3.0 T).

Synthesis of Gd₂O₃{111} nanoplates

The gadolinium oleate complex was synthesized as precursor through a general procedure reported elsewhere (ref. 16). We synthesized {111} facets exposed Gd₂O₃ nanoplates by decomposition of gadolinium oleate complex while in the presence of oleic acid and sodium oleate. The 1-octadecene (ODE) was used as solvent with boiling temperature at 314 °C. The addition of sodium oleate leads to the formation of circular, triangular, and dendritic shaped nanoplates by controlling the molar ratio to gadolinium oleate precursor. For example, 1 mmol (1.0 g) of gadolinium oleate complex was dissolved in 15 mL of ODE in the presence of 160 μ L of oleic acid. 0.5 mmol (151 mg) of sodium oleate was added in the solution and the system was heated to reflux under N₂ atmosphere. The reaction was then ceased by removing of heating source after 2 h reflux and allowed to cooling to room temperature. The dendritic Gd₂O₃ nanoplates was obtained by centrifugation and washed by hexane and ethanol solution for three times. The formation of circular and triangular shaped Gd₂O₃ nanoplates was carried out by a similar procedure but with addition of 0.1 mmol (30 mg) and 0.2 mmol (60 mg) of sodium oleate, respectively. The final product was redispersed in hexane and stored at 4 °C for further use.

Synthesis of Gd₂O₃{100} nanoplates

The synthesis of Gd₂O₃{100} nanoplates are followed by the decomposition of gadolinium(III) acetate precursor in the presence of oleic acid in the solvent of ODE. For example, 0.334 g (1 mmol) of gadolinium acetate were dissolved in 10 mL of ODE solvent with the addition of 0.34 mL (1 mmol) of oleic acid. The system was degassed with nitrogen and heated to reflux with a constant heating rate of ~8 °C/min. The reaction was then ceased and allowed to cooling to room temperature after 2 h reflux. After the addition of excess of isopropanol, a white product was obtained through centrifugation. The product was redispersed in hexane and stored at 4 °C for further use. The side length and width of Gd₂O₃{100} nanoplates can be controlled by tuning the molar ratio of precursor to surfactant. The Gd₂O₃{100} nanoplates with side length and width of 120 $\times$ 40 nm and 90 $\times$ 15 nm were obtained with the precursor to surfactant molar ratio of 1:1 and 1:2, respectively.

Preparation of water-soluble Gd₂O₃ nanoplates

The preparation of sodium citrate coated Gd₂O₃ nanoplates were carried out straightforward as following: excess of sodium citrate (10 mg) were dissolved in flask containing 5 mL of ultra-pure water and 10 mL of tetrahydrofuran, the as-prepared hexane-dispersed Gd₂O₃ nanoplates (0.1 mmol) was added to the flask. The solution was then heated to reflux for 2 h before the nanoparticles were transferred to the lower layer. The solution in the lower layer was then collected and centrifuged at 8000 rpm/min to obtain the precipitation. The final product was redispersed in distilled water (or PBS) and stored at 4 °C for further use.

MR relaxivity and MR phantom study

The Gd₂O₃ nanoplates with various of gadolinium metal concentrations were prepared within 1% agar for MR phantom study. The relaxivity and phantom study of Gd₂O₃ nanoplates were conducted at three different magnetic fields (0.5, 1.5, 3.0 T). Longitudinal (r_1) and transverse (r_2) relaxivities of Gd₂O₃ nanoplates were obtained from the slopes of reciprocal of each relaxation times against concentrations. T_2 - and T_1 -weighted MR images were acquired by the following parameters: TR/TE = 2000/60 ms (T_2), TR/TE = 300/10 ms (T_1), 128×128 matrices, repetition times = 8.

Density functional theory (DFT) calculations

All the calculations were performed with the density functional theory (DFT) provided by Vienna ab initio simulation package (VASP). The exchange and correlation were treated with the generalized gradient approximation (GGA) via the Perdew Burke Ernzerhof (PBE) function. The 5s²5p⁶4f⁷5d¹6s² shell of Gd and 2s²2p⁴ shell of O have been considered explicitly in the spin-polarized density functional theory (SDFT) calculations. The GGA + U approach was utilized for all calculations, where the parameters U and J were not entered into the density functional separately but considered as a combined effective interaction parameter. We used U = 7.5 eV, J = 0.6 eV in all GGA + U calculations, resulting U_{eff} of 6.9 eV applied to the 4f orbital of Gd atoms. A charge density cutoff energy of 400eV was used for the smooth part of the electronic wave functions and the augmented electron density. Brillouin zone integration was optimized at Γ -point with a Monkhorst-Pack k-point grid of 1*1*1 for the bulk and slab model. All the atomic positions in bulk structure were relaxed, while we fixed the bottom two layers in the slab. The convergence criteria for the energy calculation and structure optimization are set to a self-consistent field tolerance of 1.0×10^{-5} eV and a maximum Hellmann-Feynman force tolerance of 0.02 eV/Å. We consider the C-type cubic structure of Gadolinium sesquioxide with a space group Ia-3. We have performed a full optimization (lattice constant and atomic position) of the bulk. The Gd-terminated {100} surface with 8 atomic layers and a vacuum region of 15 Å were employed. The O-terminated {111} surface has been modeled for 3-atmoic-layer slab with 120 atoms, and with the bottom one layer frozen. We performed an antiferromagnetic order for the Gd magnetic moments. Water adsorption energy is calculated using the following equation:

$E_{\text{ads}}(\text{H}_2\text{O}) = E(\text{H}_2\text{O}/\text{surf}) - E(\text{surf}) - E(\text{H}_2\text{O})$, where $E(\text{H}_2\text{O})$ is the energy of water molecule, and $E(\text{H}_2\text{O}/\text{surf})$ and $E(\text{surf})$ refer to energies of the chosen surface with or without water, respectively.

***In vivo* MRI study**

Animal experiments were executed according to the protocol approved by Institutional Animal Care and Use Committee of Xiamen University. We conducted *in vivo* MRI study in mouse model (~20 g, female ICR) at a clinical 3 T MRI scanner (Philips Medical System, ACHIEVA 3.0 T). The pre-injection T_1 images of anaesthetized mice both at coronal and transverse planes were acquired for comparison purpose. The mice were injected with water-soluble $\text{Gd}_2\text{O}_3\{100\}$ or $\text{Gd}_2\text{O}_3\{111\}$ nanoplates with a dose of 2.0 mg [Gd]/kg to the mouse body weight. The post-injection (p.i.) time points of 0.5, 1, 2, and 4 h were acquired both at coronal and transverse planes. All the T_1 images were acquired using a fast spin-echo sequence (FSE) under the following parameters: TR/TE = 300/14 ms, thickness = 1 mm, 144×144 matrices, FOV = 100×100 mm (coronal) or 50×50 mm (transverse), flip angle = 90° .

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Fig. 1.

Different phenomena proposed for water coordination on magnetic crystal with different surfaces. (a) Metal-rich surface may permit one-to-two coordination for water, in contrast to traditional one-to-one coordination. (b) Proposed recovery of longitudinal magnetizations for protons with different water coordinating behaviors on solid surfaces.

Fig. 2.

TEM and HRTEM images of (a–c) $\text{Gd}_2\text{O}_3\{100\}$ and (e,g) $\text{Gd}_2\text{O}_3\{111\}$ nanoplates. The interplanar distances of 2.7, 5.4, 10.8, 1.9, and 3.2 Å are assigned to (400), (200), (100), (440), and (220) planes of cubic Gd_2O_3 phase, respectively. Insets show the cartoon models (a,e) and FFT patterns (b,f) corresponding to two nanoplates, respectively. Crystal structure side views of (d) $\text{Gd}_2\text{O}_3\{100\}$ and (h) $\text{Gd}_2\text{O}_3\{111\}$ facets. (i,j) XRD patterns indicate an enhanced diffraction peak for (400) and (440) planes, corresponding to the Lamer assembled $\text{Gd}_2\text{O}_3\{100\}$ and $\text{Gd}_2\text{O}_3\{111\}$ nanoplates, respectively.

Fig. 3. (a, b) Magnetic hysteresis ($M-H$) loops of $\text{Gd}_2\text{O}_3\{100\}$ and $\text{Gd}_2\text{O}_3\{111\}$ nanoplates at 300 and 5 K. (c) Bar chart shows T_1 relaxivity for the two nanoplates at 0.5, 1.5, and 3.0 T. (d) MR phantom of the two nanoplates at 0.5, 1.5, and 3.0 T. Concentrations correspond to Gd^{3+} ions.

Fig. 4.

Water coordinating behaviors on (a) $\text{Gd}_2\text{O}_3\{111\}$ and (b) $\text{Gd}_2\text{O}_3\{100\}$ facets (upper: side view, lower: top view) according to DFT calculations. Blue balls represent Gd^{3+} ions with saturated six-coordinated configuration. Black and pink dash circles represent one-to-one top coordination and dissociated coordination for water molecules on $\text{Gd}_2\text{O}_3\{111\}$ facet, respectively. Red dash circle represents one-to-two bridge coordination for water molecules on $\text{Gd}_2\text{O}_3\{100\}$ facet.

Fig. 5.

Water migration on the metal-rich exposed $\text{Gd}_2\text{O}_3\{100\}$ facet. (a, b) Simulation and calculated energies for one water molecule migrating from Top1 to Top2 through the bridge-mediated configuration on $\text{Gd}_2\text{O}_3\{100\}$ facet, showing the transition energy barriers as low as 0.08 eV (TS1) and 0.13 eV (TS2). (c) The water coordination and dissociation from position 1 (P1) to P2 and P3, or migration and re-coordination from P2 to P4 during the time slot of T_1 relaxation. (d) P1 to P2 and P3 are considered with moderate recovery for longitudinal magnetizations, while the migration immediately after the dissociation from P2 and re-coordination on P4 may promise cascade recovery of protons longitudinal magnetizations during the time slot of T_1 relaxation.

Fig. 6.

(a,b) T_1 MRI study in mouse model injected with $\text{Gd}_2\text{O}_3\{100\}$ and $\text{Gd}_2\text{O}_3\{111\}$ nanoplates in a dose of 2.0 mg [Gd]/kg mouse body weight. The pre-injection and 0.5, 1, 2, and 4 h post-injection images at coronal (top) and transverse (bottom) planes were acquired focusing ROI of liver (yellow circle). The upper right circles at each of transverse images indicate water. (c,d) Comparison of the quantitative signal changes ΔSNR (signal-to-noise ratio) at ROI after injected with $\text{Gd}_2\text{O}_3\{100\}$ and $\text{Gd}_2\text{O}_3\{111\}$ nanoplates at coronal and transverse planes, respectively.