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A self-assembly heterotrinuclear gadolinium(III)–iron(II) complex as a MRI contrast agent

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ABSTRACT

A new self-assembly gadolinium(III)–iron(II) complex (Gd_2Fe) was synthesized and characterized. Relaxivity studies showed that complex Gd_2Fe exhibited higher relaxation efficiency compared with the clinically used Gd-DTPA. In vitro MR images on a 0.5 T magnetic field exhibited a remarkable enhancement of signal contrast for Gd_2Fe than Gd-DTPA. The results indicated that Gd_2Fe could serve as a potential MRI contrast agent.

Magnetic resonance imaging (MRI) is one of the most useful diagnostic techniques in clinical medicine because it allows researchers and doctors to image the body in a noninvasive manner [1,2]. Image quality can be improved by the means of contrast agents which enhance various portions of the MR image by changing, usually decreasing, the relaxation time of the tissue water, thus allowing the area of interest to be much more conspicuous than the surrounding tissues. Currently, more than 35% of MRI examinations are performed by means of contrast agents [3].

Over the past decades, there have been many studies in the development of new gadolinium based MR contrast agents. Particularly, much effort has been focused on the development of targeted, high relaxivity, and bioactivated contrast agents [4–19]. Recently, several self-assembly heterobimetallic gadolinium(III)–iron(II/III) complexes as MRI contrast agents with high relaxivity have been reported [20–25]. These supramolecular assemblies were prepared by linking multiple Gd^{3+}-chelated components with one Fe^{n+} (n = 2 or 3) ion to afford multicomponent complexes with correspondingly longer rotational correlation times and higher relaxivity values [26].

We have developed some tissue-targeted and Cu^{2+} responsive MRI contrast agents with high T_1 relaxivity in recent years [27–29]. In this report, we wish to describe designed synthesis and relaxivity study of a new heterotrinuclear iron(II)–gadolinium(III)–iron(II) complex (Gd_2Fe). This Gd_2Fe array was prepared by incorporation of two Gd-containing units with an Fe^{2+} ion by self-assembly coordination. Subsequently, the T_1 relaxivity was determined in hydroxyethyl piperazine ethanesulfonic acid (HEPES, pH = 7.2) buffer and human serum albumin (HAS) solution. The potential application of Gd_2Fe as a new contrast agent was evaluated by in vitro T_1-weighted phantom images.

Synthetic routes to ligand H_3L and complex Gd_2Fe are shown in Schemes 1 and 2, respectively. The syntheses of 1,4,7,10-tetraazacyclododecane-1,4,7-tetraacetate (*Tris-tert*-Bu-DO3A) (**1**) [29,30] and 4′-(4-bromomethyl-phenyl)-[2,2′;6′2″] terpyridine (tpy-ph-CH_2Br) (**2**) [31] have been previously reported. The synthesis was carried out by the reaction of *Tris-tert*-Bu-DO3A (**1**) with tpy-ph-CH_2Br (**2**) in CH_3CN and CH_2Cl_2 (v/v = 1:1) in the presence of K_2CO_3 with stirring at 40°C overnight to form 1-(4′-(4-methyl-phenyl)-[2,2′;6′2″] terpyridine)-4,7,10-tris(tert-butoxycarbonyl-methyl)-1,4,7,10-tetraazacyclododecane (tpy-ph-CH_2-*Tris-tert*-Bu-DO3A) (**3**) in 62% yield. The tpy-ph-CH_2-*Tris-tert*-Bu-DO3A (**3**) was then deprotected in trifluoroacetic acid (TFA) and CH_2Cl_2 (v/v = 1:1) to give tpy-ph-CH_2-*Tris-tert*-DO3A (H_3L) in 85% yield. Complex Gd_2Fe was synthesized in aqueous solution by two-step procedures. The bis-complex $Fe(H_3L)_2$ was firstly prepared by the reaction of $Fe(NH_4)_2(SO_4)_2\cdot 6H_2O$ with 2 equiv H_3L. Complexation of $Fe(H_3L)_2$ with Gd^{3+} was then performed by a portion addition of $GdCl_3\cdot 6H_2O$ to an aqueous solution of the $Fe(H_3L)_2$ by maintaining pH at 7.1 using an aqueous ammonia solution. Upon stirring at ambient temperature for 2 d, Gd_2Fe complex was precipitated by addition of acetone and isolated as a deep violet power over dryness in vacuo.

The T_1-relaxivities of Gd_2Fe complex in 50 mM HEPES buffer (pH = 7.2) and 0.725 mM HSA solutions are depicted in Fig. 1. The T_1-relaxivity of the Gd_2Fe complex in 50 mM HEPES buffer (pH = 7.2) solution is 7.56 $mM^{-1}\cdot s^{-1}$ with a correlation coefficient being better than 0.99. For the purpose of comparison, the attempt to

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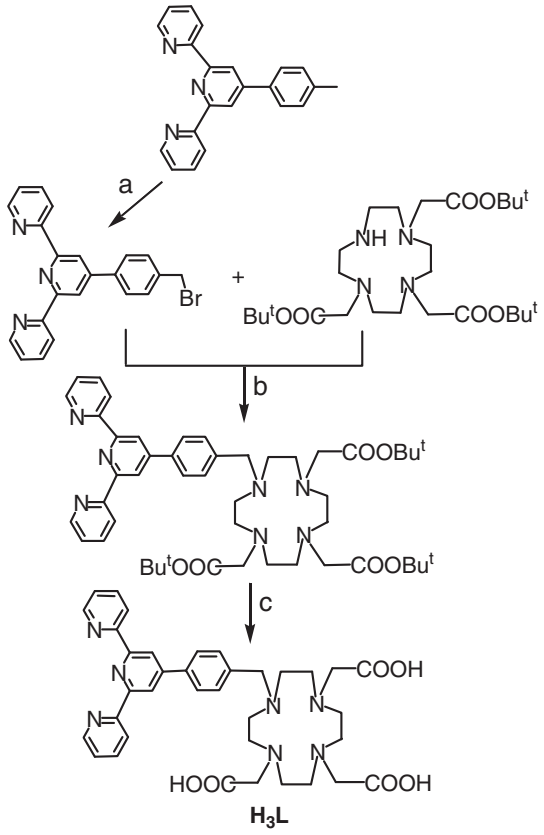
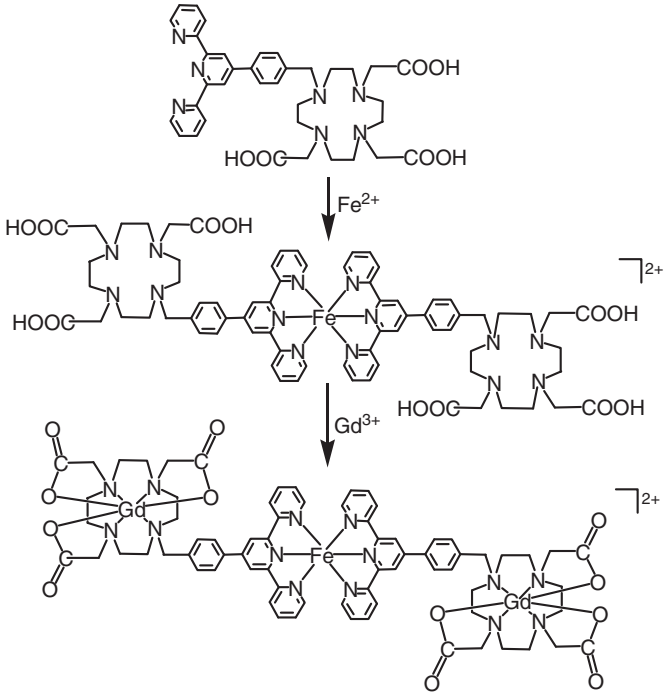


Scheme 1. Synthetic routes to ligand H_3L. (a) N-bromosuccinimide (NBS). azodiisobutyronitrile(AIBN). CCl_4, 80 °C; (b) K_2CO_3, CH_2Cl_2 and CH_3CN, 40 °C; (c) F_3CCOOH, CH_2Cl_2, rt.

measure the relaxivity of complex GdL was unsuccessful due to its poor solubility, which is similar to tpy-DTTA^{4-} [23]. The relaxivity of Gd_2Fe complex (7.56 $mM^{-1}\cdot s^{-1}$) in 50 mM HEPES buffer (pH = 7.2) is higher than that of commercial contrast agent Gd-DTPA (5.29 $mM^{-1}\cdot s^{-1}$) [27].



Scheme 2. Synthetic routes to Gd_2Fe complex.

The increased relaxivities of the Gd_2Fe complex relative to that of Gd-DTPA arise likely from the rigidity of the low-spin $Fe(tpy)_2$ unit which also functions as an efficient spacer between the two Gd^{3+} ions to avoid dipolar interactions that could accelerate electronic relaxation. Consequently, the high relaxivity of complex Gd_2Fe complex is attributed to both the rigidity of the whole complex ensured by the rationally designed molecular framework and the relatively long Gd—Gd distance which excludes dipole–dipole interactions between the paramagnetic centers [23].

Serum albumin is the richest protein of mammal blood plasma and plays a crucial role in the uptake, transportation, biodistribution, and excretion of the contrast agent in human body [32]. The relaxation times (T_1) for various concentrations of the Gd_2Fe complex (0–1.8 mM) in 0.725 mM HSA solution were measured. The relaxivity was also obtained from the linear regression according to Eq. S1 (Supporting information). Fig. 1 illustrates a reasonable enhancement of solvent proton relaxation rates for the Gd_2Fe complex in HSA solution. It is 8.66 $mM^{-1}\cdot s^{-1}$ with a correlation coefficient better than 0.99, which is 1.15 times of that for the Gd_2Fe complex in 50 mM HEPES buffer (pH = 7.2). It is most likely that other paramagnetic species exist in HSA solution besides free Gd_2Fe complex. Since the equilibrium constant for the binding of Gd^{3+} to the serum albumin is very small relative to the stability constant of Gd_2Fe complex [33], the possible release of Gd^{3+} from Gd_2Fe complex could be ignored. The enhancement is attributable to Gd_2Fe complex which is likely non-covalently bound to HSA.

MR images of Gd_2Fe and Gd-DTPA complexes were obtained in glass capillaries (1 mm) at 0.5 T (Fig. 2). The concentrations of the Gd_2Fe complex are ranged from 100 μM to 1 μM and that of Gd-DTPA was 100 μM. The images were obtained using an NMI20-Analyst NMR Analyzing and Imaging system with a TE and TR of 60 and 4000 ms, number of acquisitions = 1. As shown in Fig. 2, the intensity was distinctly brighter in comparison with the one taken in the absence of any contrast agent. There was sufficient enhancement of the contrast in the images at concentration above 10 μM. Obviously, the image of 100 μM Gd_2Fe complex is much brighter than that of 100 μM Gd-DTPA complex.

In summary, a new gadolinium(III)–iron (II) complex with high T_1-relaxivity was synthesized and characterized, which is a potential MRI contrast agent due to its facile synthetic procedures. The Gd_2Fe complex has a well-defined topology with favorable features to attain high relaxivities. It has a rigid Fe^{2+}(tpy-ph-CH_2) core and an efficient separation of the two Gd^{3+} centers.

Acknowledgments

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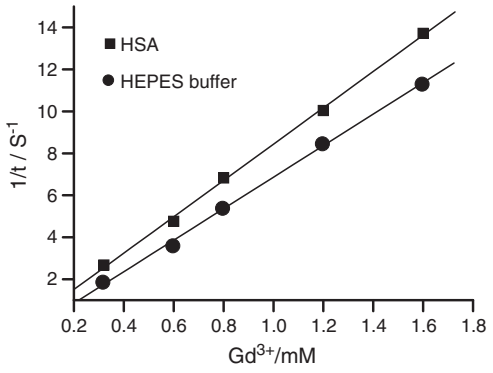

Fig. 1. The relaxation rates of water proton vs the concentrations of Gd_2Fe complex in 50 mM HEPES buffer (pH = 7.2) and 0.725 mM HSA solutions. The T_1-relaxivities, calculated from the slopes of the fitting curves, are 7.56 $mM\cdot s^{-1}$ in 50 mM HEPES buffer and 8.66 $mM\cdot s^{-1}$ in 0.725 mM HSA solutions.

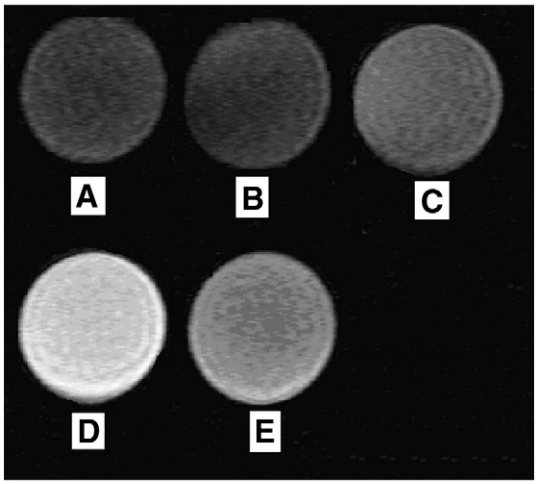

Fig. 2. T_1-weighted phantom MR images for Gd_2Fe complex. H_2O (A); 1 μM Gd_2Fe complex (B); 10 μM Gd_2Fe complex (C); 100 μM Gd_2Fe complex (D); and 100 μM Gd-DTPA complex (E).

Appendix A. Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.inoche.2011.09.006.

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