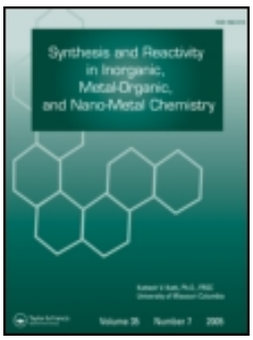

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Synthesis and Evaluation of Neutral Gd(III), Mn(II) Complexes From DTPA-Bisamide Derivative as Potential MRI Contrast Agents

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A strong chelating ligand was synthesized through the modification of DTPA by bioactive 5-fluorouracil derivatives and characterized by means of mass spectra, Fourier transform infrared spectra, elemental analysis, and nuclear magnetic resonance spectroscopy. Its complexes of Gd(III) and Mn(II) were designed as potential MRI contrast agents. Thermodynamic stability constant of the complexes indicated that they were stable enough to prevent the metal ions from releasing. Relaxivity studies showed that the two complexes provided higher T_1-weighted relaxivity than that of commercial contrast agent Gd-DTPA and the Mn(II) complex owned much higher T_2-weighted relaxation property. Both the Gd(III) and Mn(II) complexes had the advantage of becoming promising T_1-weighted MRI contrast agents.

Keywords: 5-fluorouracil derivatives, DTPA-bisamide, neutral complexes, MRI contrast agents, relaxivities

Introduction

Magnetic resonance imaging (MRI) has become a widely used medical diagnostic technique of the human anatomy, physiology, and pathophysiology by providing its non-invasive nature and superb spatial resolution at the submillimeter range.[1] During the development of this imaging modality, application of suitable contrast agents that achieve their effect by enhancing the relaxation rate of water protons significantly improves the image quality in MRI.[2] In general, contrast agents consist of a paramagnetic metal centre, typically gadolinium(III), which must be complexed to a strong chelating ligand, since the free metal ions are toxic at the concentrations needed for diagnosis.[3] Gadolinium complexes that incorporate the strong chelating ligands diethylenetriaminepentaacetic acid (DTPA) or 1,4,7,10-tetracarboxymethyl-1,4,7,10-tetraazacyclododecane (DOTA) form the radiologically active components of the MRI contrast agents Magnevist and Dotarem, respectively. Furthermore, most reported contrast agents are derivatives from modifications of DTPA and DOTA to endow them with high relaxivities and potential target specificities towards certain tissues and cells.[4–8]

Magnevist ($[Gd(DTPA)(H_2O)]^{2-}$) was the first contrast agent approved for use in humans and is currently in routine use as a clinical magnetic resonance imaging agent with good solubility, low cytotoxicity, and high efficiency. This paramagnetic complex contains one inner-sphere water molecule that exchanges rapidly with the bulk water in the human body, therefore providing an efficient mechanism for the enhancement of the relaxation rates of the water protons.[9–13] However, the two negative charges of $[Gd(DTPA)(H_2O)]^{2-}$ results in a relatively high osmolality of the clinical formulation,[14] and minimum osmolality is predicted for a neutral complex because of existing as a single particle in aqueous solution.[15,16] Therefore, in order to neutralize the two negative charges, numerous bis-amide derivatives of DTPA have been developed to achieve neutral complexes with low osmolality.[4–8] In this study, DTPA was modified by bis-amide 5-fluorouracil derivatives to reduce the osmolality of the complexes, and also improve the relaxivity. Moreover, 5-fluorouracil is an antimetabolite and has been used as an active chemotherapeutic agent against treatment of solid tumors, which is a positive factor for the fabrication of contrast agents. Therefore, we have designed and synthesized N^1,N^7-di(5′-fluorouracil-1′-acetyl)aminoethyleneaminocarboxymethyl-diethylenetriamine-N^1,N^4,N^7-triacetic acids (**L**) and its Gd-complex as contrast agents for MRI.

Today, the majority of T_1 contrast agents are complexes of Gd^{3+} (seven unpaired electrons), and a large amount of data has been published on their *in vitro* or *in vivo* properties.[17–20] However, in recent years, the administration of Gd-based MRI contrast agents can generate serious side effects such as nephrogenic systemic fibrosis (NSF) in some patients, leading to numerous interests involved in alternatives to Gd^{3+},

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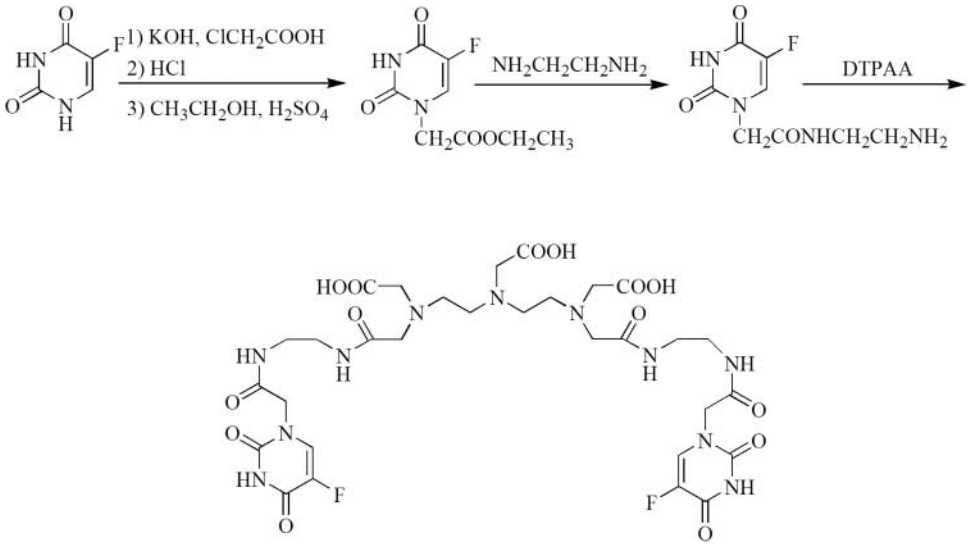

Fig. 1. The synthetic routes of **L**.

namely to paramagnetic transition metals.[21] Among them, Mn^{2+} ion has five unpaired electrons, slow electron relaxation, fast water exchange rate, and lower intrinsic toxicity than Gd^{3+}, which makes it an attractive alternative of Gd^{3+} for enhanced MRI applications.[22–24] Here, we have synthesized and studied the relaxivity properties of Mn(II)**L**, and the result shows that Mn(II)**L** may be a prospective MRI contrast agent.

In clinical MRI, complexes of paramagnetic metals (Gd^{3+} and Mn^{2+}) are widely used as T_1 contrast agents and are rarely studied for their T_2-shortening property. Recent studies reported the usefulness of manganese-enhanced T_2-weighted MR imaging.[25,26] MRI at stronger magnetic fields facilitates achievement of higher signal-to-noise ratio that assures better spatial resolution and reduced acquisition times. Longitudinal (T_1) relaxivity typically decreases with increasing field strength above a certain level, which presents its application at high field strength. This problem can be solved by using ultrasensitive transverse (T_2) contrast agents. Therefore, we studied the T_2-shortening properties of Gd(III)**L** and Mn(II)**L**, and Mn(II)**L** showed good T_2-weighted MR imaging.

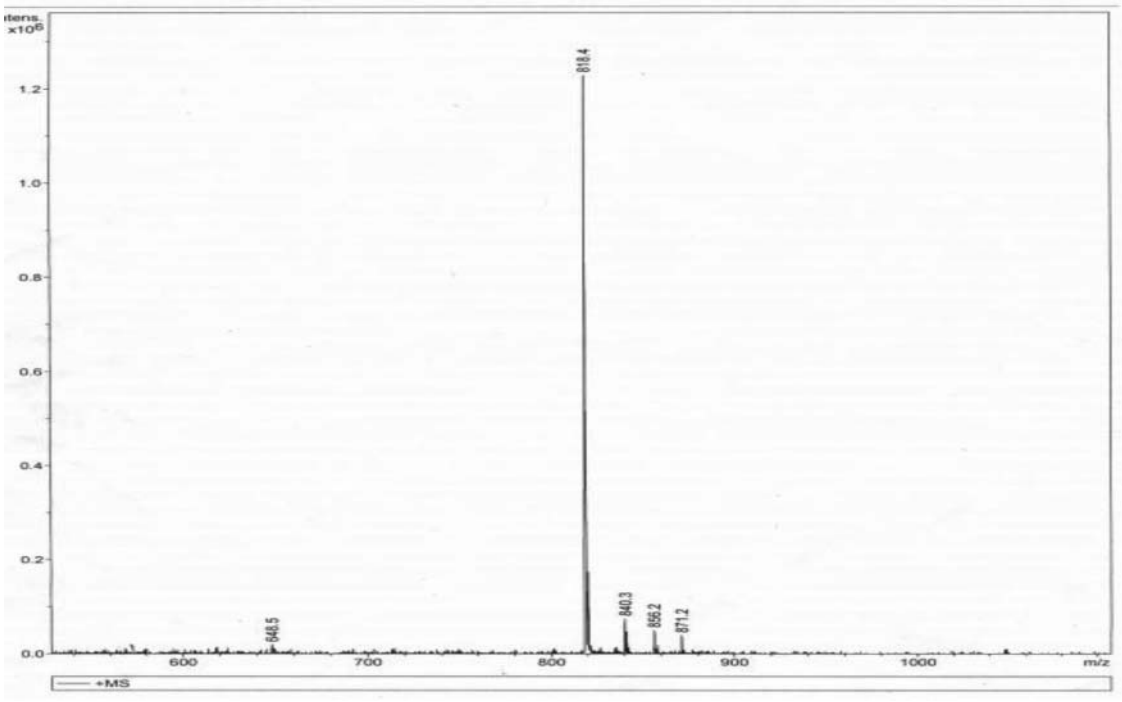

Fig. 2. The mass spectrum of **L**.

Table 1. Elemental analyses and molar conductivity

Compound	Yield (%)	color	C (%)	N (%)	H (%)	M (%)	Λ ($s \cdot cm^2 \cdot mol^{-1}$)
L	85.6	white	43.96 (44.06)	18.78 (18.85)	5.06 (5.01)		
Gd(III)L	98.1	light yellow	34.01 (33.93)	14.47 (14.51)	4.50 (4.52)	14.72 (14.80)	9.1
Mn(II)L	97.5	light yellow	38.91 (38.96)	16.60 (16.67)	4.91 (4.87)	5.88 (5.95)	17.9

Λ: molar conductivity of the complexes.

Experimental

Materials and Instrumentation

All solvents and reagents were obtained from commercial suppliers and used without further purification unless specially notified. ^{1}H NMR spectra were measured on a Varian VR 200 or 400 MHz spectrometer with TMS as an internal standard. ESI-MS were determined on a VG ZAB-HS (FAB) instrument. Elemental analyses were carried out on an Elemental Vario EL analyzer. IR spectra were obtained in KBr discs on a Thermo Mattson FTIR spectrometer in the 4,000–400 cm^{-1} region. The melting points of the compounds were determined on a Beijing XT4-100x microscopic melting point apparatus. Molar conductivity measurements were performed in DMF solution with a DDS-11C conductometer. The metal contents of the complexes were determined by titration with EDTA.

Preparation of Ligand (L)

The synthetic routes of ligand was shown in Figure 1. Ligand was synthesized as following. Diethylenetriamine pentaacetic bianhydride (DTPAA) has been prepared according to references.[27,28]

5-Fluorouracil-1-aceticether

5-Fluorouracil (1.56 g) was dissolved in a solution of KOH (2.56 g) in water (8 mL), then a solution of chloroacetic acid (1.7 g) in water (4 mL) was added dropwise at 60°C. The reaction mixture was stirred at 60°C for 5 h. After that, an excess of concentrated hydrochloric acid was added to make the solution acidic and a white precipitate appeared at the same time, then cooled in the refrigerator for 2 h to get more white precipitate. The white precipitate was collected and dissolved in excessive ethanol. A few drops of concentrated sulfuric acid was added as a catalyst and the mixture was refluxed for 10 h. the solvent was evaporated and the residue was taken up in a mixture of ethyl acetate/water (1:1; 300 mL). The organic layer was isolated, and washed with several portions of water. Evaporation of the organic layer gave the product as a white solid. Yield: 53.6%. m.p. 162°C. ^{1}H NMR (200 MHz CD_3COCD_3): 1.25–1.32 (t, J = 7.2Hz, 3H, —CH_3), 4.19–4.29 (q, J = 7.0 Hz, 2H, —CH_2—), 4.58 (s, 2H, —CO—CH_2—N—), 7.90–7.93 (d, J = 6.0 Hz, 1H, Flu—H).

5-Fluorouracil-1-N-(2-aminoethyl)acetamide

5-Fluorouracil-1-aceticether (1.0 g) was dissolved in ethnol and excessive ethylenediamine was added. The mixture was refluxed for 10 h and a large amount of white precipitate appeared. The white precipitate obtained was filtered off, washed with ethnol, and dried. No further purification was necessary to yield pure product. Yield: 91.6%. m.p. 224–226°C. ^{1}H—NMR (400 MHz, D_2O): δ (ppm): 3.13–3.17 (t, J = 7.6Hz, 2H, —CH_2—), 3.53–3.57 (t, J = 7.6Hz, 2H, —CH_2—), 4.44 (s, 2H, —CO—CH_2—N—), 7.58–7.60 (d, J = 6.0Hz, 1H, Flu-H).

N^1,N^7-di(5′-fluorouracil-1′-acetyl) aminoethyleneaminocarboxymethyl-diethylenetriamine-N^1,N^4, N^7-triacetic acids

0.357 g DTPAA was dissolved in DMF and 0.460 g 5-Fluorouracil-1-N-(2-Aminoethyl)acetamide was added. The mixture was stirred at room temperature for 10 h. The solvent was evaporated, a large amount of ethnol was added and a white precipitate was obtained. Filtration of the white precipitate gave the product as a white solid. Yield: 85.6%. ^{1}H-NMR (400 MHz, D_2O): δ (ppm): 3.36, 3.41 (br s, J = 4.0,8.0Hz, each 8H, —NCH_2CH_2N—), 3.71 (s, 4H, —CO—CH_2—N—), 3.82 (s, 4H, —CO—CH_2—N—), 3.92 (s, 2H, —CO—CH_2—N—), 4.48 (s, 4H, —CO—CH_2—N—), 7.84 (d, J = 6.0Hz, 2H, Flu—H). FAB—MS: m/z = 818[M+H]$^+$. IR (KBr) cm^{-1}: $\nu_{(imide)C=O}$: 1698, $\nu_{(carboxyl)C=O}$: 1666, $\nu_{C—N}$: 1346.

A quite clean mass spectrum provided a strong evidence for the synthesis of the ligand as shown in Figure 2.

Synthesis of Complexes

Gd(III)L: First, 1 mmol ligand **L** was dissolved in 10 mL distilled water to form a homogeneous solution whose pH is approximately 3. Then, an excess of $Gd_2(CO_3)_3$ was added to the system which was stirred on a water bath until the pH of the system is approximately 7. The excess $Gd_2(CO_3)_3$ was filtered off. Then the filtrate was concentrated on a water bath until it is nearly dry. The light yellow powder was then obtained after the mother liquor was removed. Finally, it was dried in vacuum with P_4O_{10}. Yield: 98.1%. Anal. Calcd. (%) for $C_{30}H_{48}N_{11}O_{19}F_2Gd$:

Table 2. Some main IR data of the ligand and its complexes

Compound	$\nu_{(imide)}$ C=O (cm^{-1})	$\nu_{(carboxyl)}$ C=O (cm^{-1})	ν_{C-N} (cm^{-1})	$\nu_{(M-O)}$ (cm^{-1})
L	1698	1666	1346	—
Gd(III)L	1664	1598	1328	582
Mn(II)L	1663	1589	1333	560

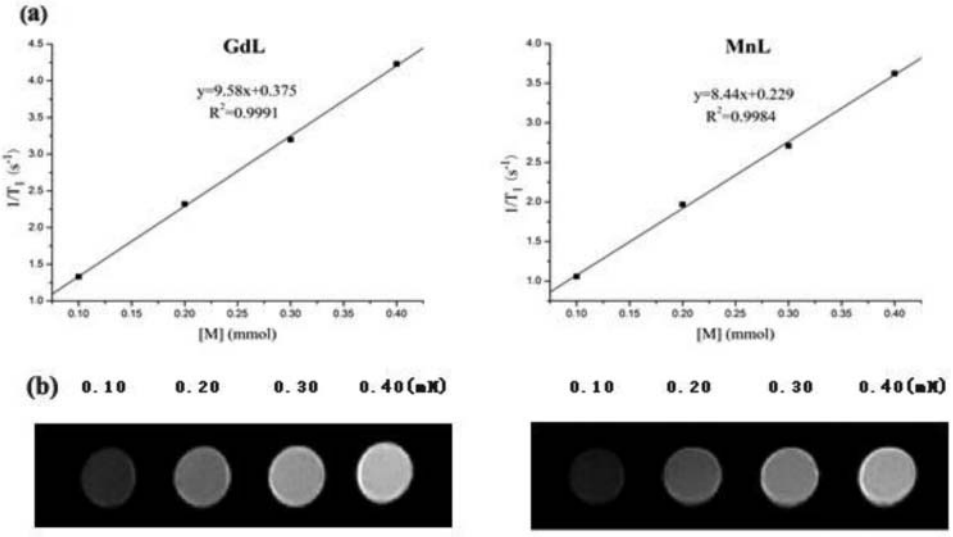

Fig. 3. (a) Solution of R_1 relaxivity and (b) T_1-weighted MRI images.

C, 33.93; H, 4.52; N, 14.51; Gd, 14.80. Found: C, 34.01; H, 4.50; N, 14.47; Gd, 14.72. FAB-MS: m/z = 973 $[M+Gd+H]^+$; m/z = 995$[M+Gd+Na]^+$. IR (KBr) cm^{-1}: $\nu_{(imide)C=O}$: 1664, $\nu_{(carboxyl)C=O}$: 1598, ν_{C-N}: 1328.

Mn(II)L: Mn complex was synthesized in the same way as that of Gd(III)**L**. Yield: 97.5%. Anal. Calcd. (%) for $C_{30}H_{45}N_{11}O_{17}F_2Mn$: C, 38.96; H, 4.87; N, 16.67; Mn, 5.95. Found: C, 38.91; H, 4.91; N, 16.60; Mn, 5.88. FAB-MS: m/z = 871$[M+Mn+H]^+$; m/z = 893$[M+Mn+Na]^+$. IR (KBr) cm^{-1}: $\nu_{(imide)C=O}$: 1663, $\nu_{(carboxyl)C=O}$: 1589, ν_{C-N}: 1333.

Results and Discussion

The Composition and General Character of Complexes

Complex of Gd(III)**L** is soluble in water, dimethylformamide, and dimethylsulfoxide; insoluble in acetone, chloroform, and ether; quite stable at room temperature and normal pressure; and not sensitive to light. The molar conductivity of Gd(III)**L** in dimethylformamide was 9.1 $s{\cdot}cm^2{\cdot}mol^{-1}$, which shows the nonelectrolytic nature of the complex. Elemental analyses showed that the complex is composed of metal ions and ligand in a proportion of 1:1 and the empirical formula is Gd(III)**L**$\cdot 5H_2O$.

Complex of Mn(II)**L** is also soluble in water, dimethyl formamide, and dimethyl sulfoxide; insoluble in acetone, chloroform, and ether; quite stable at room temperature and normal pressure; and not sensitive to light. The molar conductivity was 17.9 $s{\cdot}cm^2{\cdot}mol^{-1}$ in dimethylformamide, indicating the nonelectrolytic nature of Mn(II)**L**. Elemental analyses demonstrated that the complex is composed of metal ions and ligand in a proportion of 1:1 and the empirical formula is Mn(II)**L**$\cdot 3H_2O$.

To get a clean data set, some general character of the two complexes are shown in Table 1.

IR Spectra

IR spectra usually provide lots of valuable information on coordination. Here, we use it to find out the binding sites of the ligand.

For the Gd(III) complex, the main stretching frequencies of the IR spectra of the ligand and its complex are tabulated in Table 2. The $\nu_{(imide)C=O}$ and $\nu_{(carboxyl)C=O}$ vibrations of the free ligand appear at 1698 and 1666 cm^{-1}, respectively; for the complex these peaks shift to 1664 and 1598 cm^{-1}, and $\Delta\nu$ (ligand-complex) is equal to 34 and 68 cm^{-1}. It demonstrates that the oxygen of carbonyl has formed a coordinative bond with the metal ion. The band at 1346 cm^{-1} for the free ligand is assigned to the ν_{C-N} stretch, which shifts to about 1328 cm^{-1} for its complex, and $\Delta\nu$ (ligand-complexes) is equal to 18 cm^{-1}, indicating that the Gd-N bond is really formed but weak. A new peak for the complex at 582 cm^{-1} is assigned to ν_{M-O}, which further confirms formation of a coordinative bond between gadolinium and oxygen.

For the Mn(II) complex, Table 2 shows that the $\nu_{(imide)C=O}$ and $\nu_{(carboxyl)C=O}$ vibrations of the Mn(II) complex shift to 1663 and 1589 cm^{-1}, and $\Delta\nu$ (ligand-complexes) is equal to 35 and 77 cm^{-1}. It indicates that the oxygen of carbonyl has formed a coordinative bond with the metal ion. The ν_{C-N} stretch shifts to about 1333 cm^{-1} for the Mn(II) complex, and $\Delta\nu$ (ligand-complexes) is equal to 13 cm^{-1}, suggesting that the Mn-N bond is really formed but weak. A new peak for the complex at 560 cm^{-1} is assigned to ν_{M-O}, which further confirms formation of a coordinative bond between manganese and oxygen.

Table 3. Relaxivity of the complexes

Compound	Gd-DTPA	Gd(III)**L**	Mn(II)**L**
R_1 ($mM^{-1}{\cdot}s^{-1}$)	4.34	9.58	8.44
R_2 ($mM^{-1}{\cdot}s^{-1}$)		10.70	32.99

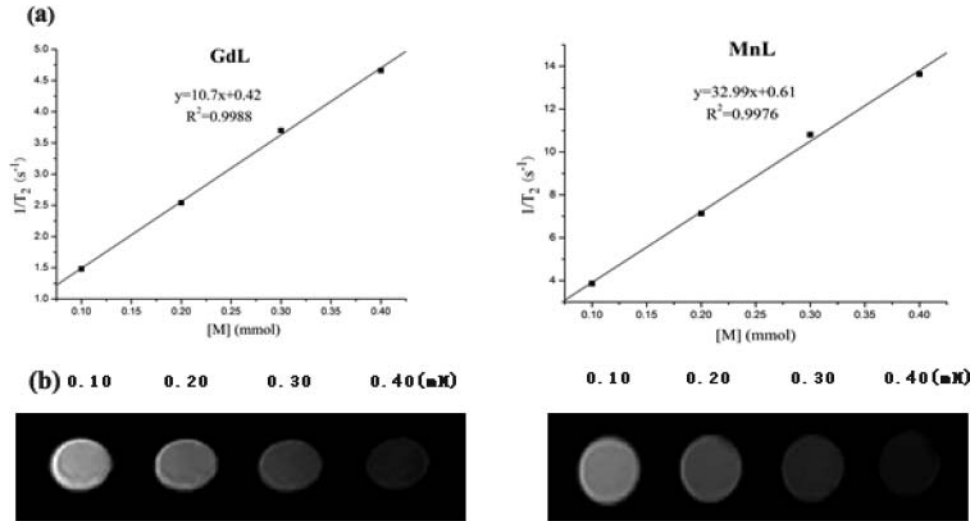

Fig. 4. (a) solution of R_2 relaxivity and (b) T_2-weighted MRI images.

It is common knowledge that the DTPA-derivative ligands always provide three nitrogen atoms and five carbonyl oxygen atoms bonding to metal, and the IR spectra of **L** and its complexes accord with the conclusion.

Thermodynamic Stability Constant of the Complexes

As free metal ion and free ligand are both toxic for the organism, the complexes must have a sufficient thermodynamic stability. It is necessary to carry out the experiment about thermodynamic stability constants. The normal chelate of thermodynamic stability constants is expressed as in the following equation[29]:

$$K = [ML]/[M^{n+}][L^{n-}]$$

Where M^{n+} represents the free, unhydrolyzed aqua-metal ion, L^{n-} represents the uncomplexed, totally deprotonated form from the ligand and ML is the normal unprotonated and unhydrolyzed complex. Thermodynamic stability constant of Gd(III)**L** ($K_{Gd(III)L} = 10^{21.83}$) was a few larger than that of $Gd(DTPA)^{2-}$ ($K_{Gd\text{-}DTPA} = 10^{20.73}$), which suggested that the ligand can enwrap the metal ions tightly and prevent the release of free metal ions in the body, and thus improve the clinical safety. Related to the lower charge of the Mn^{2+} ion, the thermodynamic stability of Mn(II)**L** ($K_{Mn(II)L} = 10^{18.31}$) is lower in comparison to that of Gd^{3+} complexes. As manganese owns much lower toxicity and the role of a biogenic element, the thermodynamically stable Mn^{2+} complexes are also treated to be labile.

Relaxivity of the Complexes

To evaluate the effectiveness of the complexes as MRI agents, experiments about relaxivities were carried out. The enhancement value of the relaxation rate of the complex for water protons is calculated by the following equation[30]:

$$1/T_{1,2} = 1/T^0_{1,2} + R_{1,2}[M]$$

where $1/T_{1,2}$ is the observed relaxation rate in the presence of paramagnetic metal complex, $1/T^0_{1,2}$ is the relaxation rate of pure water, [M] is the concentration of paramagnetic metal complex, and R_1 and R_2 are the longitudinal and transverse relaxivities, respectively. R_1 and R_2 are the relaxivities in units of $mM^{-1}\cdot s^{-1}$, which reflects the relaxation enhancement ability of a paramagnetic compound.

From the equation, we can see that R_1 and R_2 can be calculated from the linear correlation between $1/T_{1,2}$ and [M]. As shown in Figure 3, the Gd(III)**L** complex ($R_1 = 9.58$ $mM^{-1}\cdot s^{-1}$) exhibited higher R_1 relaxivity than that of Mn(II)**L** complex ($R_1 = 8.44$ $mM^{-1}\cdot s^{-1}$), and are both higher than the values recorded for commercial contrast agent Gd-DTPA ($R_1 = 4.34$ $mM^{-1}\cdot s^{-1}$) as shown in Table 3. The relaxation theory predicts that higher relaxation rates are obtained upon increase of the rotational correlation time of complexes. As the molecular rotation correlation time is proportional to the molecular size, the attachment of 5-fluorouracil derivatives to DTPA can considerably enhance the relaxivity. Thus, the two complexes are potential candidates to act as T_1-weighted MRI contrast agents. For T_2-weighted images (Figure 4), the R_2 relaxivity of Mn(II)**L** complex ($R_2 = 32.99$ $mM^{-1}\cdot s^{-1}$) are much stronger than that of Gd(III)**L** complex ($R_2 = 10.70$ $mM^{-1}\cdot s^{-1}$), which owns to the nature of Mn ion. Moreover, the high R_2 relaxivity of Mn(II)**L** complex is consistent with a recent study that transverse relaxivities of a Mn^{2+} ion are much higher than its longitudinal relaxivities.[31] Brightening of T_1-weighted images and darkening of T_2-weighted images (as shown in Figure 3b and Figure 4b) suggest dual contrast enhancement by the two complexes, and they have potential utility as T_1-weighted MRI contrast agents compared to Gd-DTPA.

Conclusion

In this work, DTPA, a strong chelating ligand, was modified by bis-amide 5-fluorouracil derivatives to get the neutral Gd complex as contrast agent for low osmolality. For the high toxicity of free Gd^{3+} ion, the Mn(II) complex was synthesized for further study and showed good T_2-weighted images. Taken together, the neutral Gd(III) and Mn(II) complexes derivative from modification of DTPA may be a prospective MRI contrast agent with good stability, superb solubility, low cost, low osmotic pressure due to nonion complex, and high relaxivity.

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