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A gadolinium(III)-coumarin complex based MRI/Fluorescence bimodal probe for the detection of fluoride ion in aqueous medium

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ABSTRACT

By virtue of high affinity of Gadolinium(III) with fluoride, a novel MRI/fluorescence bimodal probe was prepared by self-assembly of Gd(III) based contrast agent with the coumarin-based fluorophore (**CL**). Upon addition of fluoride ion (F^-) to the aqueous solution of EDTA-Gd(III)-**CL**, the replacement of coordination **CL** occurs, realizing switch-on both the longitudinal relaxivity (r_1) and fluorescence responses, simultaneously. The fluorescence detection limit for fluoride ions was established at 0.15 μM. EDTA-Gd(III)-**CL** features of favorable selectivity towards F^- for both relaxivity and fluorescence, reliability at physiological pH allow its potential application in biomedical diagnosis fields.

1. Introduction

The design of molecular probes is the key point and prerequisite for molecular imaging technique. Probes are molecules of abiotic origin that bind selectively to the analyte of interest with concomitant change in one or more properties of the system, such as fluorescence, redox potential, or magnetic property.[1–3] Among various types of molecular probes, fluorescent probe, due to its high sensitivity, operational simplicity, cost effective and rapid, has become a hot research topic.[4–9] Combined with micro-imaging technology, fluorescent probes are capable of imaging and visualizing the intracellular molecular events.[10,11] Magnetic resonance imaging (MRI) is another powerful imaging modality that is often coupled with paramagnetic contrast agents (aka probe) to enhance sensitivity and image quality. MRI can provide images of intact, opaque organisms in three dimensions, even deep within a specimen.[12,13] Hence, it has become a powerful diagnostic tool to visualize deep regions of animal bodies, realizing monitoring the course of diseases *in vivo*. However, amongst molecular imaging techniques, no single modality is perfect and sufficient to gain all the necessary information. For instance, fluorescence imaging is difficult to quantify-especially in tissue more than a few millimetres in depth within a subject[14]; magnetic resonance imaging (MRI) has superb resolution but low sensitivity.[15] Therefore, dual-modal or multi-modal contrast agents or imaging probes have been developed to solve this problem.[16] For example, the combination of magnetic resonance imaging (MRI) and fluorescence imaging offers synergistic advantages over either modality alone, complements each weakness and maximizes strengths.[17–19] As the field matures there is an increasing emphasis on synthetic MRI/fluorescent bimodal probes for the sensing and imaging of metal ions, biological molecules in aqueous medium and in living cells.[20–23] However, anion recognition in aqueous media or in biological system is still an extremely challenging task for a number of reasons, such as strong hydration nature, large ionic radius and complicated geometries of the anions.[24–26] Therefore, the development of simple and effective MRI/fluorescent bimodal imaging probes for the rapid and sensitive detection of anions in aqueous solution, and especially in biological systems are of great importance.

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Fluoride ion (F^-) is one of the most important anions because of its special roles in health and environmental issues.[27,28] For example, the low level of F^- in toothpaste and in drinking water is beneficial to the dental health and treatment of osteoporosis.[29] On the other hand, a high intake of F^- has adverse effect on human health, causing urolithiasis, stomach ulcers, or even cancer.[30,31] The World Health Organization (WHO) guideline reports that more than 100 million people worldwide drink water with F^- concentrations exceeding a value of 1.5 mg per litre, causing severe dental problems, crippling skeletal fluorosis and cancer.[32] Accordingly, sensing and characterization of F^- is an important part of understanding the benefits as well as the potential toxicity of fluoride in biotic and abiotic natural sources.[33]

Among numerous F^- probes,[34,35] self-assembly at lanthanide centres has been widely used as responsive probes for F^- sensing with associated displacement of water or ligand molecules.[36–38] Gd(III) is a typical lanthanide ion, which has high magnetic moment and a symmetric electronic ground state.[39] Accordingly, Gd(III) chelates have long been used as responsive MRI contrast agent. The relaxivity of Gd(III)-based contrast agents can flexibly governed by adjusting the bound water molecules (q) triggered by particular analyte.[40–42] In this work, we report a novel MRI/fluorescence bimodal F^- probe by self-assembly of EDTA-Gd(III) complex based contrast agent with a coumarin-based fluorophore (**CL**). We chose coumarin to construct fluorescent unit since its excellent photophysical properties, such as long-wavelength absorption and emission, high fluorescence quantum yield and good biological compatibility.[43] Ethylenediaminetetraacetic acid (EDTA) provides four oxygen donors and two nitrogen donors to sequester the Gd(III) to form a high dynamical stability complex EDTA-Gd(III), preventing the toxic effects of the free Gd(III).[44] Upon addition of fluoride ion to the aqueous solution of EDTA-Gd(III)-**CL**, the added fluoride ion led to the liberation of **CL** and bonded to Gd(III). In addition, strong hydrogen bond formed between fluoride and water molecule leading to the increase of the second-sphere hydration access Gd(III) center, resulting in the enhancement of the longitudinal relaxivity (r_1), by which fluorescence/MRI bimodal fluoride ion sensing was achieved.

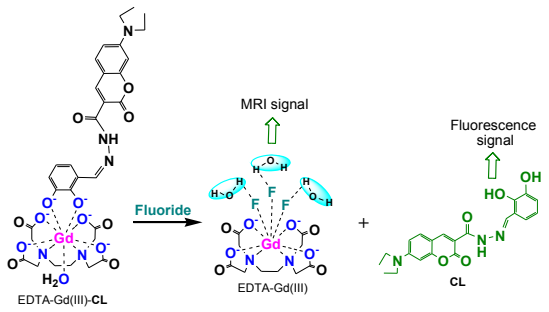
2. Results and discussion

2.1. Synthesis and spectroscopic characterization of EDTA-Gd(III)-CL in aqueous solution

The coumarin-based fluorophore (**CL**) has been reported in our previous work.[45] Synthetic route of bimodal probe, EDTA-Gd(III)-**CL** and proposed sensing mechanism towards fluoride ions was depicted in Scheme 1. EDTA-Gd(III)-**CL** stock solution for anions sensing was prepared *in situ* by addition of 10.0 equiv. of [EDTA-Gd(III)]Na to **CL** solution (10 μM) in CH_3CN-H_2O (3:7, v/v, pH = 5.5). The formation of EDTA-Gd(III)-**CL** and its spectroscopic characterizations were firstly investigated by recording the changes in UV–Vis absorption spectrain aqueous medium. As showed in Fig. 1A, **CL** displays a major absorption peak at around 445 nm, which could be assigned to the charge transfer (CT) absorbance.[46] Upon an increase in the concentration of $[EDTA\text{-}Gd(III)]^-$ (0–0.15 mM), the maximum absorption peak of **CL** was gradually reduced with a continuous hypochromatic shift of about 5 nm, implicating the formation of aEDTA-Gd(III)-**CL** complex. The complexation of **CL** with EDTA-Gd(III) was further verified by fluorescence spectra titration. **CL** displayed a strong fluorescence emission ($\Phi_1 = 0.68$). As expected, upon incremental addition of EDTA-Gd(III), the fluorescence intensity and fluorescence color of **CL**solution quenched gradually when 0.15 mM was added ($\Phi_2 = 0.11$) (Fig. 1B and C), which further confirmed the complexation of EDTA-Gd(III) toward **CL**. The plot of $1/(F_0-F)$ versus $1/[EDTA\text{-}Gd(III)]$ showed a linear relationship ($R^2 = 0.9907$), from which one can estimated that **CL** was bound with EDTA-Gd(III) in a 1:1 stoichiometry, and the association constant (K_a) was calculated to be $2.53 \times 10^5\ M^{-1}$ according to the B–H plot (Fig. 1D).[47,48]

2.2. UV–vis spectra responses of EDTA-Gd(III)-CL towards anions

Lanthanide(III) ions are strong Lewis acid, while fluoride ion as a Lewis base. By virtue of the high affinity of F^- with Gd(III), the specific interaction with EDTA-Gd(III)-**CL** led to the liberation of the coordinated fluorophore (**CL**) results in increasing the longitudinal relaxivity (r_1) as well as the distinct spectroscopic responses.[49] The proposed sensing process of EDTA-Gd(III)-**CL** towards F^- in aqueous solution (CH_3CN: H_2O = 3:7, pH = 5.5) was firstly supported by the UV–vis absorption spectra measurements. As shown in Fig. 2, continuously addition of tetrabutylammonium fluoride ($n\text{-}Bu_4NF$) into the solution of EDTA-Gd(III)-**CL** led to a increase in the absorption band intensity at 445 nm accompanied by two well-defined isosbestic points centred at 410 nm and 460 nm, indicating that the regeneration of the absorption bands of **CL** (Fig. S5), triggered by the decomplexation of EDTA-Gd(III)-**CL**.[50] The addition



Scheme 1. The structure of EDTA-Gd(III)-**CL** and proposed bimodal responses mechanism towards fluoride ion.

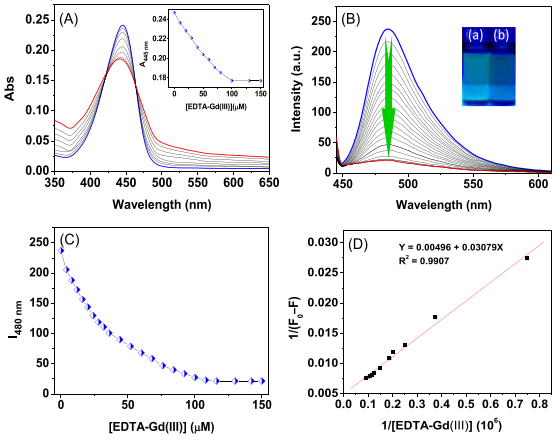


Fig. 1. (A) UV–vis absorption spectra of **CL** (10 μM) in the presence of increasing amount of EDTA-Gd(III) in aqueous solution (CH_3CN: H_2O = 3:7, pH = 5.5). Insert: UV–vis absorption of **CL** at 445 nm as a function of $[EDTA\text{-}Gd(III)]^-$ (0–0.15 mM). (B) Fluorescence spectra and corresponding fluorescence colors of **CL** (10 μM) the exposure to different concentrations of EDTA-Gd(III). Final titration spectra in A and B are shown in red. (C) The plot of the emission intensity of **CL** at 480 nm versus EDTA-Gd(III) concentration. (D) Benesi-Hildebrand plot (emission at 480 nm) of **CL** (10 μM) based on 1:1 binding stoichiometry with EDTA-Gd(III). Excitation was performed at 430 nm.