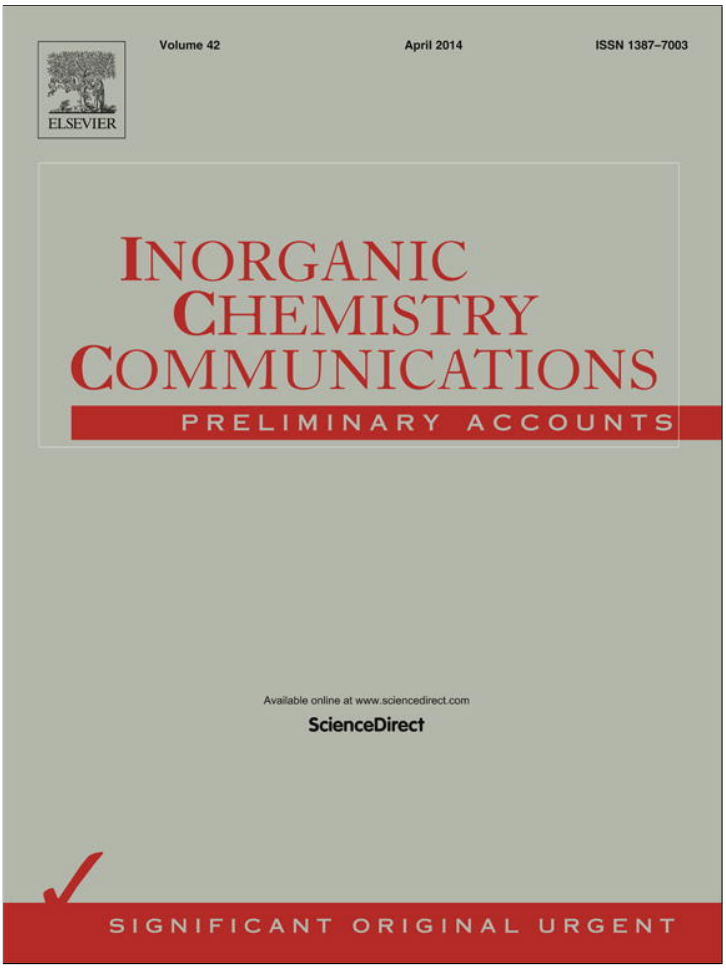

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Highly selective fluorescent chemosensor for Fe^{3+} detection based on diaza-18-crown-6 ether appended with dual coumarins

Hongda Li, Liangliang Li, Bingzhu Yin *

Key Laboratory of Natural Resources of Changbai Mountain & Functional Molecules, Ministry of Education, Department of Chemistry, Yanbian University, Yanji, Jilin 133002, PR China

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ABSTRACT

A new fluorescent chemosensor based on diaza-18-crown-6 ether, which was appended with dual coumarins, exhibited high selectivity and anti-disturbance for Fe^{3+} among environmentally and biologically relevant metal cations. Fe^{3+} sensing was performed via the complexation of Fe^{3+} ions with the chemosensor. In addition, the detection limit of the fluorescence response of the sensor to Fe^{3+} was 0.31 μM with a rapid response of less than 10 s.

Fe^{3+} is one of the most essential trace elements in biological systems and performs a major function in the growth and development of living systems as well as in various cellular biochemical processes [1]. It provides the oxygen-carrying capacity of heme and acts as a cofactor in various enzymatic reactions involved in the mitochondrial respiratory chain [2]. Thus, the presence of Fe^{3+} should be efficiently monitored. Numerous studies have developed selective chemosensors for Fe^{3+}, such as the fluorescent chemosensor that exhibits high sensitivity, specificity, and simplicity. To date, successful fluorescent Fe^{3+} sensor designs are based on two main sensing mechanisms. One design, which can be regarded as a chemosensor, is based on the complexation and ionizable chelation of podands or crown ethers that covalently link the fluorescent dyes with Fe^{3+} [3]. The other design is based on irreversible chemical reactions (such as the coordination-triggered ring-open of rhodamine, Fe^{3+}-promoted Schiff base hydrolysis, and Fe^{3+}-induced hydroxylamine oxidation), which are regarded as chemodosimeters [4,5]. Significant contributions to the development of spectroscopic sensing for Fe^{3+} have been made over the past few decades. However, relatively few fluorescent chemosensors with high selectivity are used for Fe^{3+} sensing, primarily because of the lack of a proper selective ligand system for Fe^{3+}. Furthermore, Fe^{3+} is easily interfered by other transition-metal ions, such as Cu^{2+}, Co^{2+}, Cr^{3+}, and Pb^{2+}. Therefore, the development of a highly selective and highly sensitive fluorescent chemosensor for Fe^{3+} remains a challenge. Given the broad scope of Fe^{3+} chemosensors, only one crown ether-containing fluorescent chemosensor for Fe^{3+} is noted regardless of its excellent coordination ability for metal ions. Thus, fluorophore-attached diazacrown ethers have attracted much interest. Upon binding, the positive charge of the metal ion leads to a reduction in electron density on the coordinating nitrogen atom, which may change the optical properties [6,7]. In addition, metal ion complexation ability and selectivity can be greatly improved when a ligating group is attached to the crown ethers [8]. Ueno et al. previously reported that a diaza-18-crown-6 ether with two 7-hydroxy-4-methyl-coumarins selectively extracts calcium ions [9]. Furthermore, two 8-hydroxyquinoline-attached diaza-18-crown-6 ether derivatives have been proposed as effective highly selective chemosensors for Mg^{2+}, Cd^{2+}, and Hg^{2+} [10–14]. Wolf et al. recently found that diaza-18-crown-6 with two 7-hydroxyquinoilines is suitable for detecting intracellular Mg^{2+} distribution and real-time movements of this cation [15].

Based on the abovementioned findings, we selected 7-amino-4-trifluoromethylcoumarins as fluorophores and introduced this substance to diaza-18-crown-6 ionophore via two urea linkers to synthesize a novel fluorescent chemosensor (**3**). We expected that the chemosensor can selectively coordinate Fe^{3+} while considering the high acidity of Fe^{3+} and high basicity of diaza-18-crown-6 [16]. In the current study, we report the synthesis and metal-recognition properties of the fluorescent chemosensor (**3**), which exhibited high sensitivity and selectivity for Fe^{3+} in aqueous media.

The synthetic route of target **3** is depicted in Scheme 1. Intermediate **2** was synthesized via treatment of 7-diethylamino-4-trifluoromethylcoumarin with triphosgene in dry methylene chloride with triethylamine in good yield (93%). Aminolysis of **2** with 0.5 equiv. diaza-18-crown-6 ether at room temperature in dry methylene chloride produced **3** in 89% yield. **3** was fully characterized through ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR, and matrix-assisted laser desorption/ionization–time of light mass spectra and elemental analysis (see Supplementary Data).

* Corresponding author. Tel.: +86 433 2732298; fax: +86 433 2732456.
E-mail address: zqcong@ybu.edu.cn (B. Yin).

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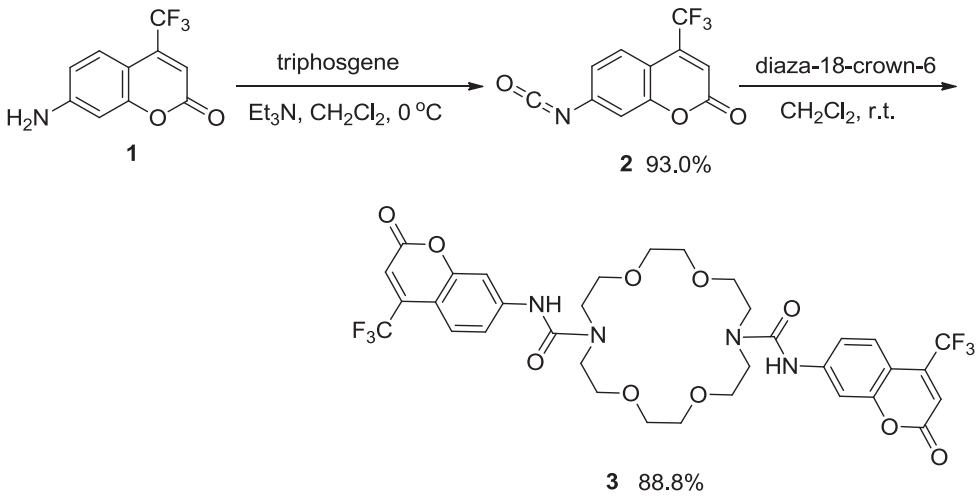

Scheme 1. Synthetic pathway of target compound **3**.

White crystals suitable for X-ray diffraction were obtained by slowly evaporating a methylene chloride–methanol solution of **3** at room temperature. Single-crystal X-ray diffraction structural analysis indicated that **3** crystallized in triclinic system, P-1 space group. The asymmetric unit of **3** contained a half molecule, with the other half generated by a center of inversion. In the centrosymmetric **3**, $C_{34}H_{34}F_6N_4O_{10}$, two coumarin moieties were located oppositely and perpendicular to the macrocycle ring with a chair-like conformation, which was due to the strong intramolecular N(1)–H(1)–O(4) hydrogen bond with an O(4)–N(1) distance of 2.836(2) Å, that originated from urea and the macrocycle ring (Fig. 1). This result is different from those found in the other 18-crown-8-ether-based crystal structures, in which the molecules adopt a pocket-like geometric conformation [17]. A summary of the crystallographic data and structural refinements for **3** is listed in Table S1.

Spectroscopic studies of **3** in the absence or presence of various metal cations were conducted using dimethylformamide (DMF)/H_2O solution (v/v, 4:1) at ambient temperature. **3** (20 μM) exhibited an intense and broad absorption band at 350 nm ($\varepsilon = 1.77 \times 10^5\ M^{-1}\ cm^{-1}$), which can be assigned as a coumarin π — π* transition [18]. However, the UV–vis spectral studies of **3** did not provide meaningful information through Fe^{3+} addition because of the interference that occurred from Fe^{3+} self-absorption around 350 nm (Figs. S1 and S2), which has been reported in the literature [19]. The fluorescence spectrum of **3** (2 μM) in the same medium was characterized by a strong emission of the coumarin moiety at 456 nm. Upon interaction of various metal ions, **3** exhibited significant changes in fluorescence intensity (Fig. 2a). Among the tested metal ions, Fe^{3+} (100 equiv.) induced the most pronounced fluorescence quenching. The fluorescence of **3** was effectively quenched because of its coordination with a paramagnetic Fe^{3+} center and/or coumarin to Fe^{3+} charge transfer (LMCT) [19]. In contrast to Fe^{3+}, other metal ions, such as 500 equiv. of Ag^+, Al^{3+}, Ba^{2+}, Ca^{2+}, Cd^{2+}, Co^{2+}, Cr^{3+}, Cu^{2+}, Fe^{2+}, Hg^{2+}, K^+, Mg^{2+}, Na^+, Ni^{2+}, Pb^{2+}, and Zn^{2+}, did not induce apparent fluorescence changes. Only Fe^{2+} induced a slight quenching of fluorescence. Importantly, Ca^{2+}, Cd^{2+}, Hg^{2+}, and Mg^{2+}, which showed a strong interaction with other diaza-18-crown-6-ether-based chemosensors, [9–14] did not show the fluorescence response toward **3**. In addition, competition experiment of **3** was conducted. As shown in Fig. 2b, all relevant cations tested did not influence the Fe^{3+} fluorescence detection even in the presence of other paramagnetic interfering cations, such as Co^{2+}, Cr^{3+}, and Cu^{2+}. More significantly, the coexistent Fe^{2+}, which induced a slight fluorescence response in the selectivity evaluation for Fe^{3+} (Fig. 2a), did not interfere with Fe^{3+} fluorescence detection. The Fe^{3+} chemosensor design with good discrimination between the iron valence states (Fe^{2+} and Fe^{3+}) is necessary for better understanding various biological processes and Fenton reaction [20]. **3** was clearly shown to be a selective Fe^{3+} chemosensor with good discrimination for iron valence states.

Based on its excellent selectivity, quantitative analysis of **3** toward Fe^{3+} was investigated through fluorescent titration. Titration experiment resulted in good concentration-dependent fluorescence changes. As shown in Fig. 3, with increasing Fe^{3+} concentrations, the fluorescence emission intensity of compound **3** at λ_{max} 456 nm gradually decreased. With an increase in Fe^{3+}concentration up to 120 μM (60 equiv.), the fluorescence emission intensity became saturated (Fig. S3). In addition, a good linear dependence of fluorescence intensity

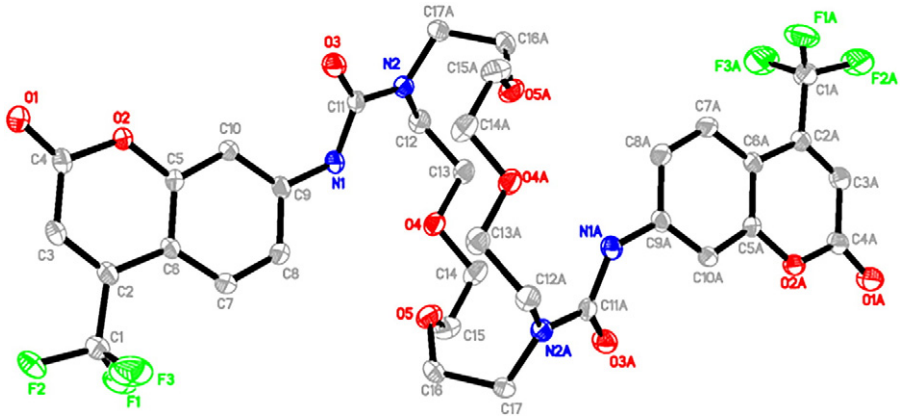

Fig. 1. Crystal structures of **3**. All hydrogen atoms are omitted for clarity. Thermal ellipsoids are shown at the 50% probability level.

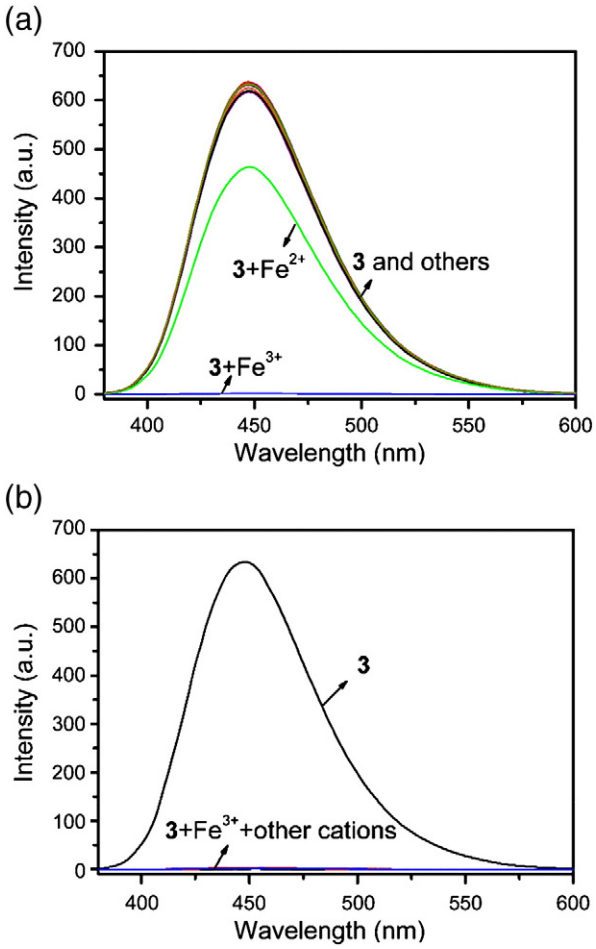

Fig. 2. Fluorescence spectra (λ_{ex} = 355 nm) of **3** (2 μM) upon the addition of different metal ions (a) and competitive fluorescent selectivity toward Fe^{3+} in the presence of different cations (b) (100 equiv. of Fe^{3+} and 500 equiv. of Al^{3+}, Ag^{+}, Ba^{2+}, Ca^{2+}, Cd^{2+}, Co^{2+}, Cr^{3+}, Cu^{2+}, Fe^{2+}, Hg^{2+}, K^{+}, Mg^{2+}, Na^{+}, Ni^{2+}, Pb^{2+} and Zn^{2+}).

was noted on Fe^{3+} concentration (0 μM → 30 μM). The detection limit based on the fluorescence titration data was calculated to be 0.31 μM according to a reported method (Fig. S4) [21]. To determine the stoichiometry of **3**–Fe^{3+} complex, a Job plot experiment was performed at room temperature using the same media. A Job plot in Fig. S5 indicates that **3** chelated with Fe^{3+} in a 1:1 stoichiometry. In terms of both the 1:1 stoichiometry and fluorescence titration data from Fig. 3, the binding constant of **3** for Fe^{3+} was calculated to be 3.9×10^4 M^{-1} (R^2 = 0.9995) (Fig. 3, inset) [22]. By contrast, as a probe for the assigned analyte, response time is important in practical detection. Fig. 4 shows the fluorescence intensity changes at 456 nm for **3** (2 μM) after the addition of 60 equiv. Fe^{3+}. Fe^{3+} signaling by **3** was very fast, which was actually completed in a few seconds.

Mass spectral study was conducted to elucidate the fluorescence-sensing mechanism. First, the 1:1 binding mode between **3** and Fe^{3+} (as observed in a Job plot experiment) was supported by electronic supplementary information (ESI) mass data. ESI mass spectrum of a mixture of **3** and 2 equiv. $FeCl_3 \cdot 6H_2O$ in a mixture of MeOH-DMF showed a molecular mass of 925.5, which corresponded to the formula of $[\mathbf{3}\text{-}FeCl(OCH_3)_2]^+$ (Fig. S6). Furthermore, since Fe^{3+} has a substantial absorbance in the UV and near-visible range, [19] the presence of Fe^{3+} may interfere with the excitation of the sensor fluorophores. To confirm the effect of absorbance by Fe^{3+}, excess EDTA was added to the solution of **3**–Fe^{3+} complex, which instantly resulted in nearly complete regeneration of the fluorescence intensity and maximum emission peak. Apparently, the fluorescence sensing of **3** toward Fe^{3+} was induced completely by Fe^{3+} complexation with **3** (Scheme S1). In addition, the Fe^{3+} absorbance did not influence the Fe^{3+} detection by a quenching effect of Fe^{3+}, which was probably due to the fact that **3** has a longer excitation wavelength (Fig. 5).

To test the potential applicability of **3** for Fe^{3+} analysis in environmental samples with a wide range of pH or in unbuffered media, the pH-dependent fluorescence behavior of compound **3** both in the absence and in the presence of Fe^{3+} was investigated (Fig. S7). In aqueous DMF solution (DMF: H_2O = 4:1), in the absence of Fe^{3+}, although fluorescence quenching at 456 nm was observed for **3** when pH > 8, no substantial changes in the fluorescence intensity at 456 nm was observed when pH ranged from 3 to 8. Similarly, in the presence of 200 μM Fe^{3+}, although slight fluorescence enhancement was observed for **3** when the pH > 8, no substantial change was observed when the pH ranged from 5 to 8 without interference by protons. The results showed that **3** allows Fe^{3+} sensing in a wide pH range. The fluorescence sensing of **3** at approximately pH 7.4 is favorable for Fe^{3+} assays in physiological and environmental samples.

In summary, we have developed a new fluorescent chemosensor for Fe^{3+} detection based on 7-amino-4-trifluoromethylcoumarins and diaza-18-crown-6 moieties, as fluorophore and ionophore, respectively. The sensor exhibits high selectivity and anti-disturbance property for Fe^{3+} ions among environmentally and biologically relevant metal ions including other paramagnetic metal ions. Fe^{3+} sensing was performed completely via the complexation of Fe^{3+} with the chemosensor with a 1:1 binding stoichiometry. The detection limit on fluorescence response

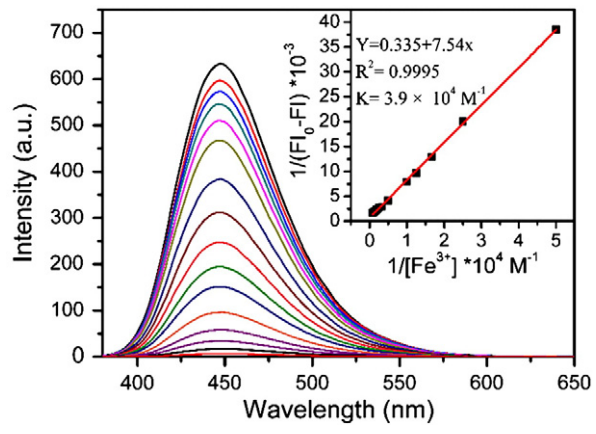

Fig. 3. Fluorescence spectra changes of **3** (2 μM) upon addition of Fe^{3+} (0–200 μM), λ_{ex} = 355 nm. Inset: plots of fluorescent emission 456 nm versus the equivalents of Fe^{3+} added.

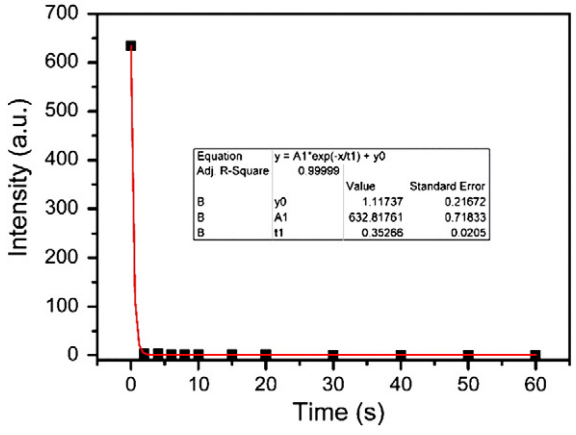

Fig. 4. Time course of the fluorescence response of **3** (2 μM) in the presence of 60 equiv. of Fe^{3+}. The fluorescence intensity was recorded at 456 nm, with an excitation at 355 nm at room temperature.

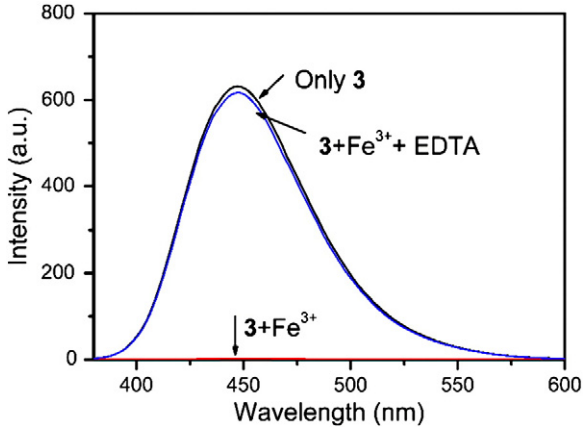

Fig. 5. Fluorescent spectra of **3** (2 μM) in the absence and presence of Fe^{3+} (100 equiv.) and/or EDTA (100 equiv.).

of the sensor to Fe^{3+} is 0.31 μM with rapid response. This sensor can be applied to Fe^{3+} detection in aqueous media with a wide pH range.

Acknowledgments

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Appendix A. Supplementary material

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.inoche.2014.01.008.

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