A new dual chromo- and fluorogenic chemosensor for Fe^{3+} in aqueous solution

Lijun Tang*, Ye Li and Jianhua Qian

College of Chemistry and Chemical Engineering, Liaoning Key Laboratory for the Synthesis and Application of Functional Compounds, Bohai University, Jinzhou 121013, P. R. China

A new rhodamine-based chemosensor **2**, which shows a reversible dual fluorogenic and chromo-response to Fe^{3+} in MeOH-HEPES buffer (10 mM, pH 7.4) (3:1 v/v), has been developed. The free solution of **2** is colourless and nonfluorescent which changes to pink with a strong fluorescence in the presence of Fe^{3+}. Other metal ions (Hg^{2+}, Ag^{+}, Pb^{2+}, Sr^{2+}, Ba^{2+}, Cd^{2+}, Ni^{2+}, Co^{2+}, Fe^{2+}, Mn^{2+}, Cu^{2+}, Zn^{2+}, Ce^{3+}, Cr^{3+}, Mg^{2+}, K^{+} and Na^{+}) had no significant effect.

Keywords: fluorescence, colourimetric, chemosensor

The design and development of fluorescent chemosensors which have advantages of simplicity, high sensitivity and instantaneous response[1–5] for a variety of metal ions, especially heavy, transition metal ions, have received increasing attention. Among these metal ions, Fe^{3+} is of importance. Fe^{3+} plays an indispensable role in the growth and development of living systems. For example, numerous enzymes use iron as a catalyst for oxygen metabolism, electron transfer, and DNA and RNA synthesis,[6–8] both its lack and excess in the body can cause serious diseases.[9] Therefore, design of fluorescent chemosensors for detecting Fe^{3+} is of great importance. However, the reported fluorescent chemosensors for Fe^{3+} in aqueous medium are still rare[10–18] and most of them are signalled by fluorescence quenching due to the paramagnetic nature of Fe^{3+}.[16–18] Thus, there is an urgent need to develop selective fluorescent chemosensors for Fe^{3+} with fluorescence enhancement, which is more sensitive than that with fluorescence quenching because of high signal-to-noise ratio.[4]

Rhodamine-based fluorogenic and chromogenic probes have received increasing interest in recent years by virtue of their properties of long-wavelength emission, high fluorescence quantum yield and large molar extinction coefficient, and many fluorescent probes based on metal induced spirolactam ring opening have been developed,[19–24] because they can perform not only great fluorescence intensity enhancement toward some specific cations, but also a strong colour development against the colourless blank during the sensing event.

We report here a new rhodamine-based and dual chromo- and fluorogenic chemosensor **2** (Scheme 1), which exhibited highly selectivity and sensitivity toward Fe^{3+} based on the metal induced ring-opening (fluorescent and pink colour) of the corresponding spirolactam (non-fluorescent and colourless) of rhodamine in MeOH–HEPES buffer (10 mM, pH 7.4) (3:1 v/v).

Results and discussion

Chemosensor **2** was synthesised by treating compound **1**[25] with thiophene-2-carboxaldehyde, which was followed by $NaBH_4$ reduction. After column chromatography, chemosensor **2** was obtained in a 66% yield (Scheme **1**). The structure of **2** was confirmed by ^1H NMR spectroscopy and ESI mass spectrometry.

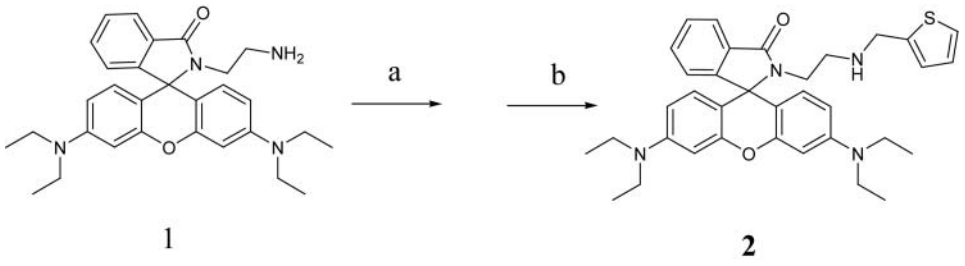
The selective coordination studies of **2** were firstly conducted by fluorescence spectroscopy. Fig. 1 shows the representative behaviour of **2** (20 μM) toward metal ions in MeOH-HEPES buffer (10 mM, pH 7.4) (3:1 v/v). Interestingly, upon addition of 15 equiv. of Fe^{3+} into the colourless solution of **2** leads to a prominent enhancement of fluorescence emission at 580 nm accompanying the colour of the solution changed to pink, while Hg^{2+}, Ag^{+}, Pb^{2+}, Sr^{2+}, Ba^{2+}, Cd^{2+}, Ni^{2+}, Co^{2+}, Fe^{2+}, Mn^{2+}, Cu^{2+}, Zn^{2+}, Ce^{3+}, Cr^{3+}, Mg^{2+}, K^{+} and Na^{+} (15 equiv. of each) did not induce significant fluorescence enhancement under identical conditions. Thus, compound **2** shows a remarkable selectivity for Fe^{3+}.

The fluorescence enhancement effects of various amounts of Fe^{3+} on compound **2** were investigated under excitation at $\lambda_{ex} = 530$ nm (Fig. 2). No obvious fluorescence emission was observed in solution of **2** in the absence of Fe^{3+}. When an incremental amount of Fe^{3+} was added into a 20 μM solution of **2**, it resulted in a remarkable fluorescence peak centred at 580 nm. The fluorescence intensity increase was saturated upon addition of 75 equiv. of Fe^{3+} to the solution of **2**. The absorption spectra of **2** with varying Fe^{3+} concentration were also recorded. The colourless solution of free **2** presented almost no absorption peak in the visible wavelength range (>400 nm). However, addition of Fe^{3+} to the MeOH-HEPES buffer solution of **2** induced a clear colour change from colourless to pink with a distinctive absorption peak at 557 nm. The change is readily detected visually for Fe^{3+} (Fig. 2, inset).

The binding stoichiometry of **2** and Fe^{3+} was confirmed by non-linear fitting of the absorption titration curve.[20] When assuming a 1:1 association between **2** and Fe^{3+}, the following equation was used.

$$A = A_0 + \frac{A_{lim} - A_0}{2}\left\{1 + \frac{C_M}{C_L} + \frac{1}{K_s C_L} - \left[\left(1 + \frac{C_M}{C_L} + \frac{1}{K_s C_L}\right)^2 - 4\frac{C_M}{C_L}\right]^{\frac{1}{2}}\right\}$$

where A is the recorded absorbance, A_0 is the start value without addition of Fe^{3+}, A_{lim} is the limiting value, C_M is the Fe^{3+}



Scheme 1 Synthesis of chemosensor **2**. Condition and reagent: (a) thiophene-2-carboxaldehyde, MeOH; (b) $NaBH_4$.

* Correspondent. E-mail address: lijuntang@tom.com

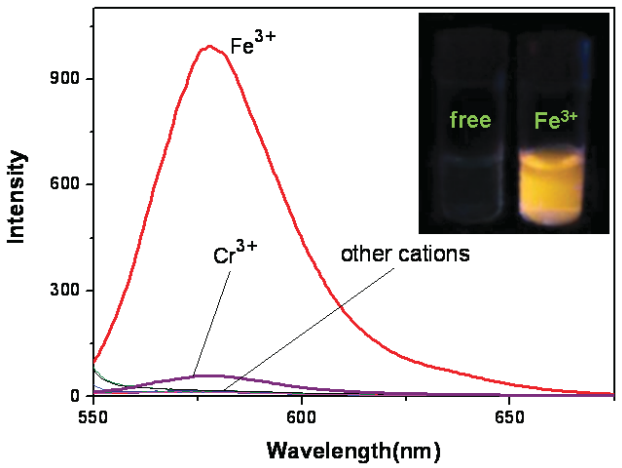


Fig. 1 Fluorescence spectra (λ_{ex} = 530 nm) of **2** (20 μM) measured in MeOH-HEPES buffer (10 mM, pH 7.4). (3:1 v/v) in the presence of 15 equiv. of Hg^{2+}, Fe^{3+}, Ag^{+}, Pb^{2+}, Sr^{2+}, Ba^{2+}, Cd^{2+}, Ni^{2+}, Co^{2+}, Fe^{2+}, Mn^{2+}, Cu^{2+}, Zn^{2+}, Ce^{3+}, Cr^{3+}, Mg^{2+}, K^{+} and Na^{+}. (excitation slit: 2.5 nm; emission slit: 5.0 nm). Inset: Change in fluorescence colour.

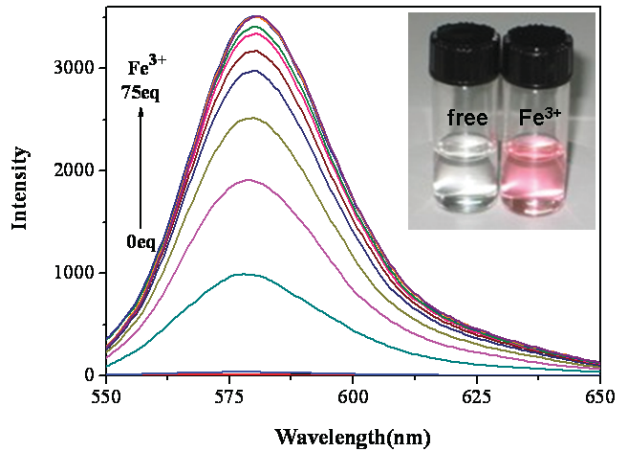


Fig. 2 Fluorescence titration spectra of **2** (20 μM) in MeOH-HEPES buffer (10 mM, pH 7.4) (3:1 v/v) upon gradual addition of Fe^{3+}. Excitation wavelength was 530 nm. (excitation slit: 2.5 nm; emission slit: 5.0 nm). Inset: Change in solution colour.

concentration, and C_L is the sensor concentration. As shown in Fig. 3, the plot of absorbance against $C_{Fe^{3+}}$ indicates that **2** indeed associates with Fe^{3+} in a 1:1 stoichiometry. The association constant, *K*, between **2** and Fe^{3+}, is determined to be $(1.55 \pm 0.8) \times 10^4$ M^{-1}.

For a chemosensor, the reversibility is an important requirement. Thus, the reversibility of this system was verified by use of ethylenediamine (EDA). As shown in Fig. 4, when increasing amounts of EDA was added to a solution containing **2** (20 μM) and Fe^{3+} (1.5 mM) in MeOH-HEPES buffer (10 mM, pH 7.4) (3:1 v/v), the pink colour gradually faded and the intensity of fluorescence decreased. When 100 equiv. of EDA (relative to **2**) was added, the solution changed to colourless and the fluorescence completely disappeared. Whereas, when Fe^{3+} was added to the system again, the pink colour and fluorescence could be reproduced. These results indicated that **2** was a reversible chemosensor for Fe^{3+}.

According to some rhodamine-based chemosensors reported in the literatures,[10,12,20,25] the possible mechanism for metal-induced fluorescence enhancement and colour changes of chemosensor **2** is proposed in Scheme 2. It may be that Fe^{3+}

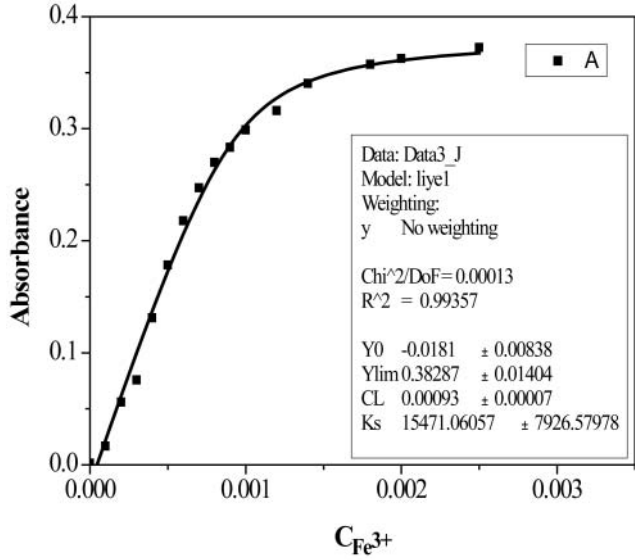


Fig. 3 Non-linear fitting of the absorption titration curve of **2** (20 μM) with Fe^{3+} in MeOH-HEPES buffer (10 mM, pH 7.4) (3:1 v/v). Absorbance was recorded at 557 nm.

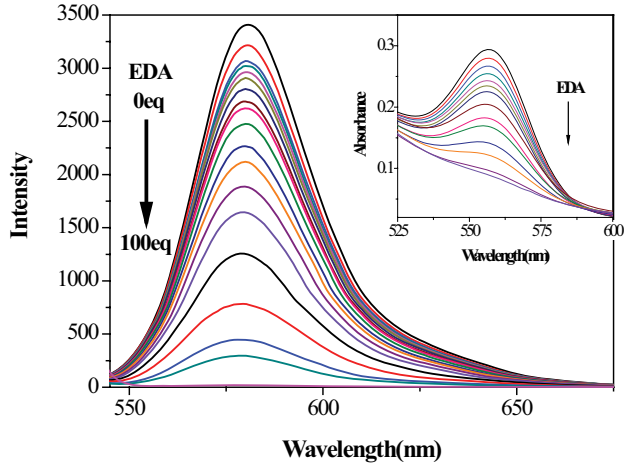


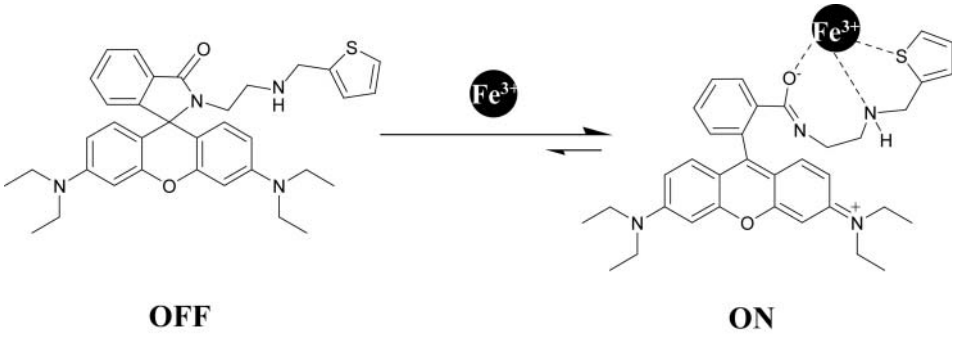
Fig. 4 Fluorescence titration of ethylenediamine (EDA) (top to bottom: 0 equiv. to 100 equiv.) in the presence of **2** (20 μM) and Fe^{3+} (1.5 mM) in MeOH-HEPES mixed buffer solution. Excitation wavelength was 530 nm. (excitation slit: 2.5 nm; emission slit: 5.0 nm). Inset: Absorption titration of ethylenediamine (EDA) (top to bottom: 0 equiv. to 90 equiv.) in the presence of **2** (20 μM) and Fe^{3+} (1.5 mM) in MeOH-HEPES mixed buffer solution.

coordinated with the carbonyl "O", "N" and thiophene "S", allowing the spirocycle to be opened, thus resulting in a dual chromo- and fluorogenic observation.

In summary, we have synthesised a new rhodamine-based and dual chromo- and fluorogenic sensor **2**, which behaves with a high selectivity toward Fe^{3+} over other metal ions in MeOH-HEPES buffer (10 mM, pH 7.4) (3:1 v/v). This chemosensor binds with Fe^{3+} in a 1:1 stoichiometric manner to induce a large increment in the fluorescence intensity and marked colour change. In addition, the sensing of compound **2** to Fe^{3+} proved to be reversible by the EDA-titration experiments.

Experimetal

All reagents obtained from commercial sources were of AR grade. NMR spectra were recorded on a Bruker 300 MHz NMR spectrometer with TMS as internal standard and $CDCl_3$ as solvent. HRMS was carried out on a UPLC/Q Tof mass spectrometer. UV spectra were measured on a SP-1900 spectrophotometer. Fluorescence spectra



Scheme 2 The proposed mechanism for the fluorescent and colour changes of **2** upon addition of Fe^{3+}.

were obtained with a Hitachi F-4500 FL spectrophotometer at room temperature for aerated solutions.

Preparation of compound **1** *and* **2***; general procedure*

Compound **1** was prepared according to literature procedure.[25] Compound **1** (0.6 mmol, 0.291 g) and thiophene-2-carboxaldehyde (0.6 mmol, 0.067 g) were stirred in anhydrous methanol with three drops of acetic acid at room temperature. After 3h, $NaBH_4$ (0.6 mmol, 0.023 g) was added into mixture under ice bath. When the reactant disappeared on TLC, the solvent was removed by rotatory evaporation. The crude product was purified by column chromatography using ethyl acetate/petroleum ether (3:4) as eluent to give 0.23 g of pale yellow oil of compound **2** (66%). ^{1}H NMR (300 MHz, $CDCl_3$): δ:1.16 (t, 12H), 2.02 (m, 1H), 2.49 (t, 2H), 3.33 (q, 8H), 3.81 (s, 2H), 4.09 (d, 2H), 6.24 (dd, 2H), 6.36 (d, 2H), 6.41 (d, 2H), 6.87 (t, 1H), 7.07 (t, 1H), 7.13 (d, 1H), 7.26 (t, 1H), 7.43 (q, 2H), 7.89 (m, 1H). HRMS (ESI+) $[M+H]^+$, Calcd for $C_{35}H_{41}N_4O_2S$ 581.2950. Found 581.2947.

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