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A Novel Coumarin-based Fluorescence Chemosensor for Fe^{3+}

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Abstract A novel coumarin derivative[7-diethylamino-2-oxo-2*H*-chromene-3-carboxylic acid(6-amino-pyridin-2-yl)-amide, CFe**1**] has been synthesized and its potential application as a chemosensor for the detection of metal ions has been further investigated. The responses of CFe**1** to Fe^{3+} were studied by fluorescence emission spectrometry in the presence of other metal ions such as Al^{3+}, Ba^{2+}, Ca^{2+}, Co^{3+}, Cr^{3+}, Cu^{2+}, Fe^{2+}, Hg^{2+}, Mg^{2+}, Mn^{2+}, Na^{+}, Ni^{+}, Pb^{2+}, Zn^{2+}, K^{+}, and Ag^{+}. CFe**1** showed a good selectivity for Fe^{3+} with fast response, a wide pH span of 3.3—9.18, and a large Stocks shift. CFe**1** in the presence of Fe^{3+} and ethylene diamine tetraacetic acid(EDTA) makes the blue solution fade to colorless, which is due to the formation of CFe**1**-Fe^{3+} complex instead of any catalytic action of Fe^{3+}. Furthermore, the imaging of Fe^{3+} in cultured single mice microglia cells was realized with the aid of CFe**1**, indicating that CFe**1** has a great potential to be used as promising models for the future design of novel and robust chemosensor for metal ion detection in the field of biomedical and environmental analyses.

Keywords Coumarin; Fe^{3+}; Fluorescence; Selectivity

1 Introduction

Metal ions detection is of great importance for biomedical analysis and environmental monitoring. Among them, the iron ion(Fe^{3+}) is an essential metal ion in humans and plants, which acts as a cofactor for many proteins in a wide range of biochemical processes such as cellular metabolism[1] and enzyme catalysis[2]. Moreover, Fe^{3+} is recognized as a valuable biomarker for various diseases, and the disruption of Fe^{3+} is commonly associated with a great many disease states including neurodegenerative diseases, hereditary hemochromatosis, alzheimer disease, iron-deficiency anaemia, and so on[3—7]. Obviously, the analysis of Fe^{3+} content has great significance not only for fundamental but also for some disease diagnosis. To date, researches have been focused on the development of technologies for Fe^{3+} detection and some assays have been built up, including atomic absorption spectrometry[8,9], inductively coupled plasma-atomic emission spectrometry[10], inductively coupled plasma-mass spectrometry[11,12], spectrophotometry[13,14], and so on. However, some disadvantages such as costly instrumentations and complicated pretreatment process make those methods unsuitable for on-line or field monitoring.

As well known, fluorescence chemosensors have several advantages including low cost, simplicity, portability, high selectivity and sensitivity, real-time monitoring and so on[15—18]. Thereby, the design of fluorescent chemosensors to detect Fe^{3+} is of great importance in biological and environmental studies. Recently, Lin *et al.*[19,20] described two fluorescence chemosensors for Fe^{3+} based on metal-promoted hydrolysis of (coumarinyl)Schiff base with long responsive time. Chen *et al.*[21] reported a new chemosensor for Fe^{3+} with a high sensitivity(0.36 μmol/L) and wider linear range as well as a narrow pH span(3.6—4.6). Li *et al.*[22] developed an "Off-On" chemosensor for Fe^{3+} with a detection limit of 5.0 μmol/L. Although significant researches have been done, the properties of these chemosensors still need to improve. Thus, we focused on developing a chemosensor for Fe^{3+} that meets particular criteria: easy synthesis, a wide range of pH and fast response as well as high sensitivity.

Coumarin dyes are an important class of fluorescent compounds that are widely used in chemosensors because of their excellent photophysical properties, such as strong fluorescence, high light quantum stability and photoluminescence efficiency. To date, coumarin derivatives have already been applied to the monitoring of Cu^{2+}[23,24], Zn^{2+}[25], Fe^{2+}[11], Mg^{2+}[26,27], fructose[28], NO[29] and CN^{-}[30]. Given the coumarin derivatives some enhanced advantages such as good water solubility, high selectivity, fast response time, low toxicity and simple synthesis, they have huge potential application in fluorescence chemosensors for Fe^{3+}. Herein, we synthesized 7-diethylamino-2-oxo-2*H*-chromene-3-carboxylic acid(6-amino-pyridin-2-yl)-amide(CFe**1**) by combining pyridine-2,6-diamine, which shows good binding ability to Fe^{3+}, with coumarin derivatives by one-pot procedure. Thus, we obtained a new Fe^{3+}-selective fluorescence chemosensor with fast response, a pH span of 3.3—9.18, a large Stocks shift of 124 nm, and high selectivity

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over other metal ions. Furthermore, we presented the biological application of CFe**1** to the monitoring of Fe^{3+} in cultured mice microglia cells.

2 Experimental

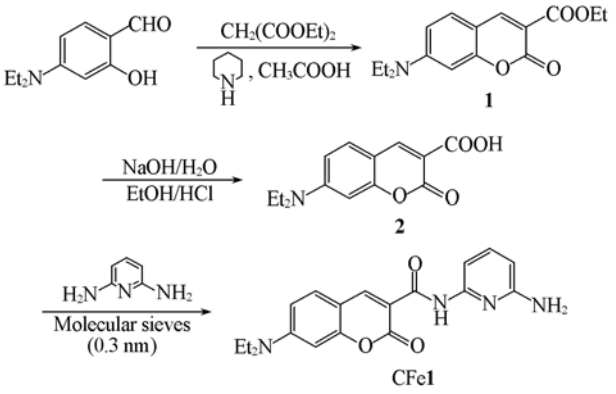
2.1 Apparatus and Reagents

Fluorescence spectra were measured on a HITACHI F-2500 spectrofluorimeter(Hitachi High-Technologies Co., Tokyo, Japan) at an excitation wavelength of 343 nm and an emission wavelength of 467 nm, equipped with a xenon discharge lamp and 1.0 cm quartz cells. The UV-Vis spectra were recorded on an UV-2450 spectrophotometer equipped with quartz curves(Shimadzu, Tokyo，Japan). NMR spectra were recorded with an AC-P 400 spectrometer(Bruker, German) operated at 400 MHz in DMSO-d_6 with tetramethylsilane as the internal standard. Electronic spray ionization(ESI) mass spectra were obtained on an Orbitrap Discovery(Thermo, England) mass spectrometer with a Micromass Z-spray ESI ion source, and Fourier transform infrared(FTIR) spectra were obtained on a Perkin-Elmer model FTIR-682 infrared spectrophotometer with KBr discs. Live cell microscopy images were collected on a fluorescence microscope(Olympus-dp71, Japan). The pH value of the solution was determined by a Thermo model 410A plus pH meter(Thermo Orion Inc., USA), with a combined glass-calomel electrode. All the measurement experiments were operated at room temperature.

A stock standard solution of Fe^{3+}(0.1 mol/L) was prepared from ferric nitrate. A working solution of Fe^{3+}(10.0 mmol/L) was prepared by diluting the stock solution. The stock standard solution of CFe**1**(0.17 mmol/L) was prepared in ethanol/H_2O (95:5, volume ratio). A working solution of CFe**1**(17.0 μmol/L) was prepared by diluting the stock solution with the solution of ethanol/H_2O. All the reagents were purchased from commercial sources and used without further purification. Mice microglia cells were obtained from the Institute of Brain Science, Datong University, China. Unless otherwise stated, all the chemicals were of A. R. grade. Double distilled water was used for all experiments.

2.2 Synthesis of CFe1

CFe**1** was obtained by three-step reaction, as shown in Scheme 1. Firstly, a solution of 4-diethylamino-2-hydroxybenzaldehyde(4.8 g) and diethyl malonate(4.8 mL) in ethanol(25.0 mL) was treated with an appropriate amount of piperidine and glacial acetic acid and refluxed for 3 h. After 25.0 mL of H_2O was added to the reaction mixture, the mixture was cooled to 0 °C. The crystalline solid was filtered and washed with the cold solution of ethanol/H_2O(1:1, volume ratio). Recrystallization from the solution of ethanol/H_2O gave compound **1** as a yellow solid. Yield 43.4%(3.14 g). m. p. 79—83 °C. ^{1}H NMR($CDCl_3$, 400 MHz), *δ:* 8.41(s, 1H), 7.34(m, 1H), 6.59(d, *J*=8.9 Hz, 1H), 6.44(d, *J*=2.1 Hz, 1H), 4.35(d, *J*=7.1 Hz, 2H), 3.43(q, *J*=7.1 Hz, 4H), 1.37(t, *J*=7.1 Hz, 3H), 1.21(t, *J*=7.1 Hz, 6H). FTIR(KBr), $\tilde{\nu}$/cm^{-1}: 3027, 2975, 1755, 1701, 1615, 1592, 1513, 1422, 1222. Elemental anal.(%) calcd. for compound **1**: C 67.96, N 5.00, H 6.528; found: C 66.42, N 4.84, H 6.62.



Scheme 1 Synthetic route of CFe1

Furthermore, 15.0 mL of NaOH(10%, mass fraction) was added to the compound **1**(2.89 g, 0.01 mol) in 15.0 mL of ethanol, and the mixture was heated under reflux for 15 min. Acidification to pH=2 with concentrated hydrochloric acid and cool of it to 0 °C gave compound **2** as a red solid. Yield 71.2%(1.68 g). m. p. 222—226 °C. ^{1}H NMR(400 MHz, $CDCl_3$), *δ:* 12.52(s, 1H, OH), 8.57(s, 1H, C═CH), 7.62(d, *J*=9.0 Hz, 1H, ArH), 6.78(d, *J*=8.9 Hz, 1H, ArH), 6.55(s, 1H, ArH), 3.46(q, *J*=6.81 Hz, 4H, $2CH_2$), 1.11(q, *J*=6.9 Hz, 6H, $2CH_3$). FTIR(KBr), $\tilde{\nu}$/cm^{-1}: 3110, 2986, 2924, 1735, 1667, 1620, 1566, 1511, 1420, 1357, 1263. Elemental anal.(%) calcd. for compound **2**: C 64.92, N 5.44, H 5.876; found: C 64.35, N 5.36, H 5.78.

CH_2Cl_2 was freshly distilled in the presence of calcium hydride. To the solution of compound **2**(1.0 mmol, 0.26 g) and pyridine-2,6-diamine(1.2 mmol, 0.13 g) in CH_2Cl_2(15.0 mL) was added the molecular sieve(0.3 nm). After the mixture was stirred for 6 h at room temperature, the solvent was removed *in vacuo*. The residue was further purified by column chromatography over silica gel[eluant: *V*(methanol)/*V*(dichloromethane)=1/10] to afford CFe**1** as a yellow solid. Yield 65.9%(0.22 g). m. p. 198—200 °C. ^{1}H NMR(400 MHz, DMSO-d_6), *δ:* 8.58(s, 1H, NH), 7.64(d, *J*=9.0 Hz, 1H, ArH), 7.02(t, *J*=7.8 Hz, 1H, ArH), 6.80(d, *J*=9.0 Hz, 1H, ArH), 6.58 (s, 1H, ArH), 5.61(d, *J*=7.8 Hz, 2H, 2PyH), 5.39(s, 3H, NH, NH_2), 3.49(q, *J*=6.9 Hz, 4H, $2CH_2$), 1.14(d, *J*=7.0 Hz, 6H, $2CH_3$). ^{13}C NMR(200 MHz, DMSO-d_6), *δ:* 12.70, 44.76, 95.55, 96.32, 107.77, 107.79, 110.41, 132.16, 138.77, 149.64, 153.23, 158.24, 158.88, 159.90, 165.02; FTIR(KBr), $\tilde{\nu}$/cm^{-1}: 3430, 3335, 3130, 1708, 1612, 1509, 1400. ESI-MS, *m/z*: calcd. for $C_{19}H_{24}N_4O_3[M+H]^+$: 357.1921; found: 357.1905.

2.3 Analytical Procedure

A proper amount of Fe^{3+} working solution(10.0 mmol/L) and 3.0 mL of CFe**1** working solution(17.0 μmol/L) were added in a 1.0 cm quartz cell subsequently. The solutions were well mixed before the fluorescence measurement was carried out by excitation/emission at $\lambda_{ex}/\lambda_{em}$=343 nm/467 nm. For the determination of Fe^{3+} at low concentrations, Fe^{3+} working solution(1.0 mmol/L) was prepared by diluting the original stock solution, and proper amounts of these solutions were used in

the analytical procedure.

3 Results and Discussion

As is shown in Fig.1, UV-Vis spectra of CFe**1**(17.0 μmol/L) in the solution of ethanol/H_2O(95:5, volume ratio) reveal two maxima at λ=401 nm and λ=250 nm, respectively. With the increase of the concentration of Fe^{3+}, the band position(λ=250 nm) did not change. Upon complexation of it with Fe^{3+}, the characteristic strong absorption band of CFe**1** shifted from 401 nm to 428 nm, and its intensities increased gradually. Notably, weak absorption band(λ=308 nm) was turned inversely into strong absorption band and red-shifted by ultimate 27 nm in the presence of 25 μmol/L Fe^{3+}.

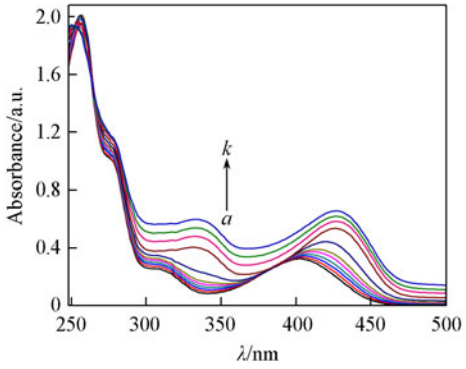


Fig.1 Absorption spectra of chemosensor CFe1 (17.0 μmol/L) in a solution of ethanol/H_2O (95:5, volume ratio)

Concentration of Fe^{3+}/(μmol·L^{-1}) from *a* to *k*: 0, 2.0, 4.0, 6.0, 8.0, 10.0, 15.0, 25.0, 35.0, 45.0, 55.0.

Good selectivity is an essential part of fluorescence chemosensors. Therefore, the selectivity of CFe**1** as a chemosensor for Fe^{3+} was tested in ethanol/H_2O(95:5, volume ratio) by incubating CFe**1**(17.0 μmol/L) with a range of environmentally and biologically important metal ions(47.0 μmol/L) as their nitrate salts. The addition of Al^{3+}, Ba^{2+}, Ca^{2+}, Co^{2+}, Cr^{3+}, Cu^{2+}, Fe^{2+}, Hg^{2+}, Mg^{2+}, Mn^{2+}, Na^{+}, Ni^{2+}, Pb^{2+}, Zn^{2+}, K^{+} and Ag^{+} caused virtually no change to the fluorescence emission spectrum of CFe**1**. However, the addition of Fe^{3+} resulted in a significant decrease of 72.3% in the fluorescence intensity of the band at 467 nm[Fig.2(A)]. F/F_0 at 467 nm was calculated for each metal ion, and excellent selectivity was observed for Fe^{3+} over all the other tested ions as shown in Fig.2(B).

The effects of pH on the fluorescence intensities of CFe**1** and CFe**1**-Fe^{3+} were investigated by recording the fluorescence spectra over a range of different pH values. The fluorescence intensity at 467 nm was plotted as a function of pH, as shown in Fig.3. These results illustrate that the fluorescence intensity didn't change in the pH range of 3.3—9.18, but decreased dramatically from pH 9.18 to 12. This large decrease in fluorescence intensity might be caused by the structural damaging of CFe**1** in a strong alkali solution. Importantly, the fluorescence-pH titration shows that the fluorescence intensity of CFe**1** remains constant in the physiological range.

To investigate the stability of chemosensor CFe**1** and the dynamic experiment of the reaction of chemosensor CFe**1**, we recorded the fluorescent signals of CFe**1** and CFe**1**-Fe^{3+} at 467 nm (λ_{ex}=343 nm) in 200 s. As shown in Fig.4, the fluorescence intensity of chemosensor CFe**1** did not change over time, which illustrates that CFe**1** is stable in air and light. Notably,

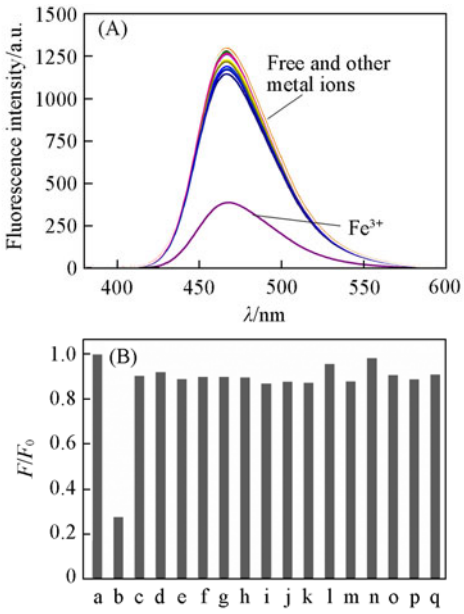


Fig.2 Fluorescence spectra(λ_{ex}=343 nm) of 17.0 μmol/L CFe1 in the presence of different metal ions(47.0 μmol/L) in ethanol/H_2O solution(95:5, volume ratio)(A) and F/F_0 at 467 nm for each metal ion(B)

(B) a. Blank; b. Fe^{3+}; c. Ag^{+}; d. Ca^{2+}; e. Cd^{2+}; f. Co^{3+}; g. Cr^{3+}; h. Cu^{2+}; i. Fe^{2+}; j. Hg^{2+}; k. K^{+}; l. Mg^{2+}; m. Mn^{2+}; n. Na^{+}; o. Ni^{+}; p. Pb^{2+}; q. Zn^{2+}. F_0 is the fluorescence intensity of 17.0 μmol/L CFe**1** and F the fluorescence intensity of 17.0 μmol/L chemosensor **1** with the addition of metal ions.

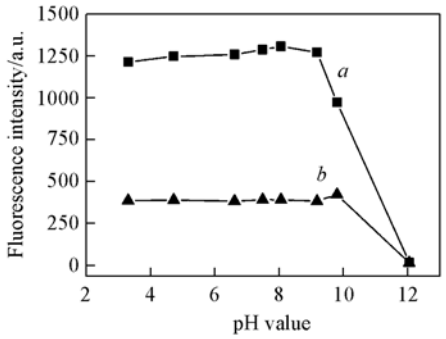


Fig.3 Effect of pH on the fluorescence intensity of 17.0 μmol/L CFe1(*a*) or 17.0 μmol/L CFe1 with the addition of 47.0 μmol/L Fe^{3+}(*b*)

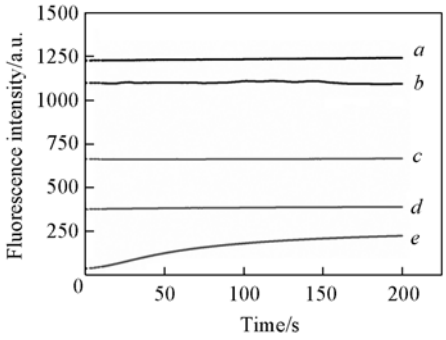


Fig.4 Reaction-time profile of chemosensor CFe1 (17.0 μmol/L) in the absence(*a*) and presence of Fe^{3+} of 3.3 μmol/L(*b*), 23.3 μmol/L(*c*), 47.0 μmol/L(*d*) and 63.3 μmol/L(*e*)

the fluorescence intensity of CFe**1** changed rapidly after the addition of Fe^{3+} and then approached to a constant over the time. The only exception was the reaction of CFe**1** with Fe^{3+} at a high concentration. It was indicated that the interaction between CFe**1** and Fe^{3+} at a low concentration was fully completed rapidly.

To further investigate the utility of CFe**1** in ethanol/H_2O (95:5, volume ratio) as a "Sign-off" chemosensor for Fe^{3+}, the competition experiments were conducted[Fig.5(A)]. F/F_0 at 467 nm was calculated for each metal ion with Fe^{3+} added. Fig.5(B) shows moderate interference with the fluorescence responses of CFe**1**-Fe^{3+} complex in the presence of excess metal ions of one kind, such as Al^{3+}, Ba^{2+}, Ca^{2+}, Co^{2+}, Cr^{3+}, Cu^{2+}, Fe^{2+}, Hg^{2+}, Mg^{2+}, Mn^{2+}, Na^{+}, Ni^{2+}, Pb^{2+}, Zn^{2+}, K^{+} and Ag^{+}, with only a little interference by Cr^{3+} and Fe^{2+}. Thus, it is notable that CFe**1** could be used as a Fe^{3+}-selective fluorescent probe in the presence of tested competing cations.

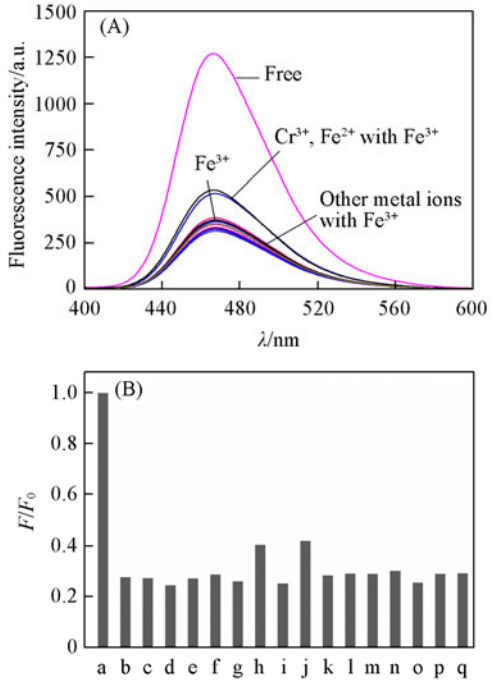


Fig.5 Fluorescence spectra(λ_{ex}=343 nm) of CFe1 in ethanol/H_2O solution(95:5, volume ratio) in the presence of each of different metal ions(670.0 μmol/L) upon the addition of 47.0 μmol/L Fe^{3+}(A) and F/F_0 of CFe1 in the presence of 670.0 μmol/L different metal ions upon the addition of 47.0 μmol/L Fe^{3+}(B)

(B) a. Blank; b. Fe^{3+}; c. Ag^{+}; d. Ca^{2+}; e. Cd^{2+}; f. Co^{3+}; g. Cr^{3+}; h. Cu^{2+}; i. Fe^{2+}; j. Hg^{2+}; k. K^{+}; l. Mg^{2+}; m. Mn^{2+}; n. Na^{+}; o. Ni^{+}; p. Pb^{2+}; q. Zn^{2+}. F_0 is the fluorescence intensity of 17.0 μmol/L CFe**1** and F the fluorescence intensity of 17.0 μmol/L CFe**1** with the addition of Fe^{3+} in the presence of 670.0 μmol/L different metal ions.

To determine the sensitivity of CFe**1** to measure Fe^{3+}, a series of solutions was prepared in which the concentration of CFe**1** was kept constant but the concentration of Fe^{3+} was gradually increased. The fluorescence emission spectrum of each solution was measured[Fig.6(A)] and the plot of $(F_0–F)/F_0$ against the concentration of Fe^{3+} is shown in Fig.6(B). A linearity of $(F_0–F)/F_0$ was found in a range of 3.3—16.7 μmol/L with a correlation coefficient of R^2=0.9927(n=5). The detection limit was then calculated as 0.33 μmol/L according to the definition by IUPAC($C_{DL}=3S_b/m$). Good linearity in a range of 3.3—16.7 μmol/L indicates that CFe**1** could act as a "Sign-off" fluorescence chemosensor in this range.

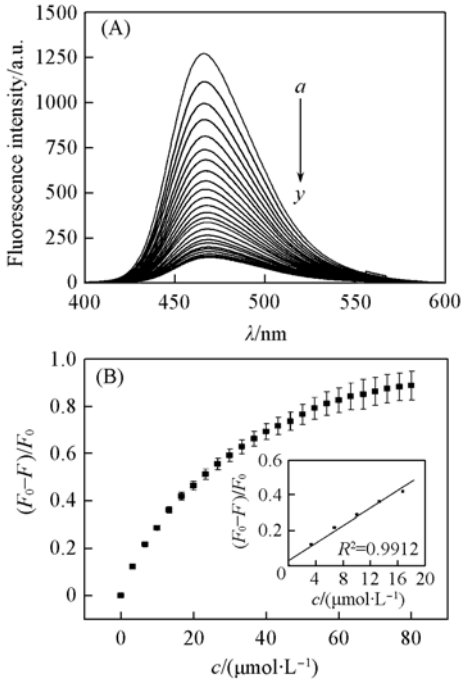
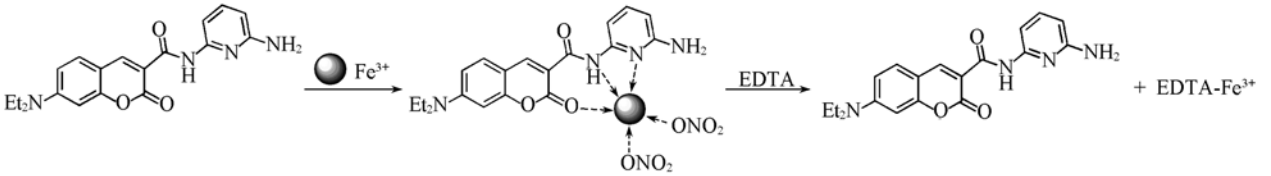


Fig.6 Fluorescence spectra(λ_{ex}=343 nm) of CFe1 (17.0 μmol/L) with increasing the concentration of Fe^{3+}(A) and plot of $(F_0-F)/F_0$ at 467 nm against the concentration of Fe^{3+}(B)

(A) Concentration of Fe^{3+}/(μmol·L^{-1}) from a to y: 0, 3.3, 6.7, 10.0, 13.3, 16.7, 20.0, 23.3, 26.7, 30.0, 33.3, 36.7, 40.0, 43.3, 46.7, 50.0, 53.3, 56.7, 60.0, 63.3, 66.7, 70.0, 73.3, 76.7, 80.0. Inset of (B) shows the standard curve for Fe^{3+} detection. F_0 is the fluorescence intensity of 17.0 μmol/L CFe**1** and F the fluorescence intensity of 17.0 μmol/L CFe**1** with the addition of Fe^{3+}.

The investigation of CFe**1** in the presence of ethylene diamine tetraacetic acid(EDTA) was assessed(Fig.S1, see the Electronic Supplementary Material of this paper). The blue color of CFe**1** faded to colorless upon the addition of Fe^{3+}. And the colorless of complex was restored to the original blue upon the addition of EDTA. After the solution was quenched by Fe^{3+}, the fluorescence intensity returned to 55.3% of its initial value within 5 min when EDTA, a metal ion chelator, was added and allowed to equilibrate. The fluorescence intensity did not return to 100% of its initial value due to the precipitating of CFe**1** out of the solution. The colorless solution regained its blue color upon the addition of EDTA, suggesting that fading is due to the formation of CFe**1**-Fe^{3+} complex but not any catalytic action of Fe^{3+}. The possible mechanism of the changes in the fluorescence characteristics of CFe**1** upon the addition of Fe^{3+} is shown in Scheme 2. All these data imply that a complex formation should involve the carbonyl oxygen atom of benzopyrone, three nitrogen-atoms of pyridine-2,6-diamine, and nitrate radical oxygen in solution.

The position of fluorescence band did not change upon the addition of Fe^{3+}, indicating the charge-transfer emitting of CFe**1**. Jung *et al.*[31] developed a novel cumarin-based



Scheme 2 Possible mechanism of CFe1-Fe^{3+} complex formation

chemosensor for Cu^{2+} by combining the coumarin derivative with 2-picolyl and provided an additional fluorescence quenching pathway, that is, the fluorescence quenching of the ligand may occur by the excitation energy transfer from the ligand to the metal *d*-orbital and/or the charge transfer from the ligand to the metal. Thus, the fact that the position of fluorescence band did not change could be reasonably explaned. Here, we also introduced this fluorescence quenching pathway to explain this phenomenon. The fluorescence quenching of CFe**1** might be due to the excitation energy transfer from the ligand to the metal *d*-orbital and/or the charge transfer from the ligand to the metal. But the reason needs to be further investigated.

Furthermore, we tested the suitability of CFe**1** for the imaging of mice microglia cells exposed to Fe^{3+}. Mice microglia cells were incubated with CFe**1**(17.0 μmol/L) in the culture medium for 12 h at 37 °C, and then washed with phosphate buffer solution(PBS, pH=7.4) to remove unbound CFe**1**. The cells were then incubated with Fe^{3+} in Dulbecco's Eagle Medium(DMEM culture medium) for 5 min at 37 °C, followed by the washing with PBS buffer to remove excess metal ions. Further, the cells were incubated with EDTA(100.0 μmol/L). 10.0 μL of 1.7 mmol/L stock solution of CFe**1** in ethanol/H_2O solution(95:5, volume ratio) was dispersed into 1.0 mL of culture medium to obtain a final concentration of 17 μmol/L (0.95% ethanol in DMEM medium) in order to minimize the effects of ethanol. Mice microglia cells treated with both CFe**1** and Fe^{3+} displayed intense blue fluorescence as shown in Fig.7. The fluorescence images indicate clearly that CFe**1** could be used to detect live mice microglia cells exposed to Fe^{3+} and the suitability of CFe**1** for bio-imaging application.

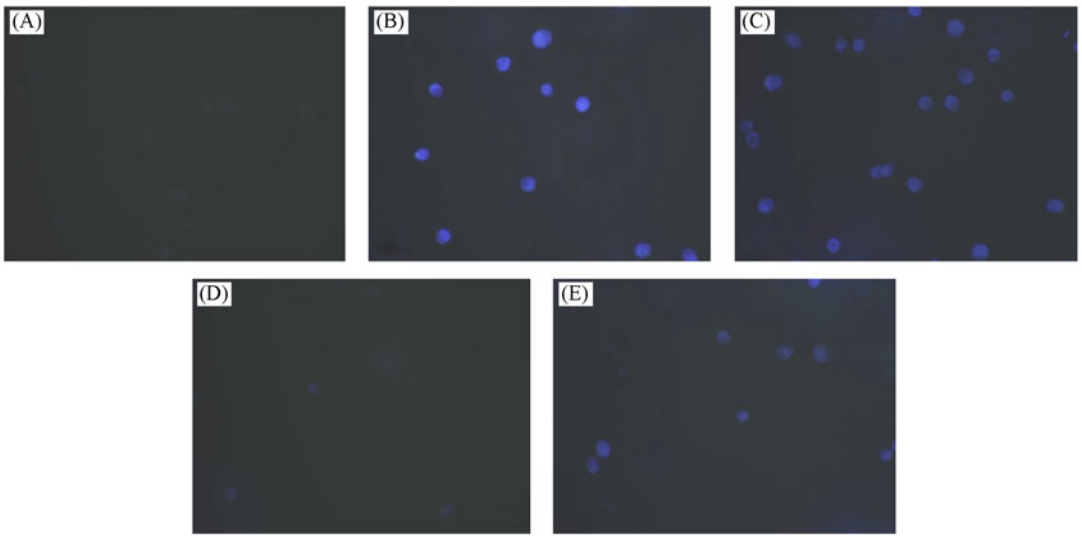


Fig.7 Microscopic images of untreated mice microglia cells(A), cells incubated with CFe1(17.0 μmol/L)(B), cells incubated with CFe1(17.0 μmol/L) and Fe^{3+}(26.7 μmol/L)(C), cells incubated with CFe1(17.0 μmol/L) and Fe^{3+}(47.0 μmol/L)(D) and cells incubated with CFe1(17.0 μmol/L), Fe^{3+}(47.0 μmol/L) and EDTA(100.0 μmol/L)(E)

4 Conclusions

We have synthesized a functional chemosensor CFe**1** for Fe^{3+} detection, which responds to Fe^{3+} with high selectivity in a concentration range of 3.3—16.7 μmol/L, whereas other common metal ions hardly have any effects on the fluorescence emission. The fluorescent reduction upon the addition of Fe^{3+} could be rationally explained by the excitation energy transfer from the ligand to the metal *d*-orbital and/or the charge transfer from the ligand to the metal. The advantages such as fast response, the stability in a wide pH span of 3.3—9.18, a large Stocks shift as well as high selectivity for Fe^{3+} indicate that CFe**1** has great potential application in the detection of Fe^{3+}. To confirm the suitability of CFe**1** for biological application, we employed it for the fluorescence detection of intracellular Fe^{3+} in cultured cells. Therefore, we have expected the present fluorescence chemosensor could serve as a new tool in Fe^{3+}-related chemical, biological and environmental investigations.

Electronic Supplementary Material

Supplementary material is available in the online version of this article at http://dx.doi.org/10.1007/s40242-014-3192-1.

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