



Highly Selective and Sensitive Detection of Fe³⁺ by 1,8-Naphthalimide-Based Fluorescent Sensors

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(Received: 19 July 2012;

Accepted: 6 May 2013)

AJC-13450

Highly selective and sensitive detection of Fe³⁺ by two 1,8-naphthalimide-based fluorescent sensors, 2-(2-(dimethylamino)ethyl)-6-((2-(dimethylamino)ethyl)-amino)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (MMN) and 2-(2-(diethylamino)ethyl)-6-((2-(diethylamino)ethyl)amino)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (EEN) in *N,N*-dimethyl formamide is reported. The fluorescence intensity of MMN and EEN is greatly enhanced by Fe³⁺ ion with the response time of less than 1s. The maximum fluorescence intensity of the sensors is linearly dependent on the concentration of Fe³⁺ within the range of 10-100 μM. The binding stoichiometry indicates that a 2:1 complex is formed between Fe³⁺ and the sensor and the detection limits for MMN and EEN are 180 and 310 nM, respectively. A large number of biologically relevant ions show no obvious interferences with the detection.

Key Words: 1,8-Naphthalimide, Sensors, Fluorescent sensors, Fluorescence sensors, Fe³⁺.

INTRODUCTION

Fluorescent sensors have attracted great interest in detecting various ions because of the distinct advantage of high sensitivity, rapid response, low cost and easy monitoring^{1,2}. 1,8-Naphthalimide is considered as one of the most favorite reporters for fluorescent sensors due to its high photostability, large Stokes shift, strong fluorescence and easy modification³⁻⁵. 1,8-Naphthalimide-based fluorescent sensors for several cations⁶⁻¹⁵ have been developed, but their selectivity, sensitivity and solubility are not very satisfactory. Thus, we synthesized two 1,8-naphthalimide derivatives and investigated their sensing behaviours to cations. It is observed that they can sense H⁺ in aqueous solution and sense Fe³⁺ in DMF. The sensors reported herein are with a simple structure, easily synthesized and water soluble. They are highly selective and sensitive and responding faster, as compared to the earlier fluorescence quenching sensors for Fe³⁺¹⁶⁻²⁴ and the 1,8-naphthalimide²⁵, coumarin²⁶, rhodamine²⁷⁻²⁹, phenanthrene³⁰-based "turn-on" fluorescent sensors.

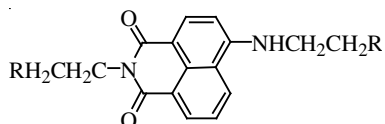
EXPERIMENTAL

5-Nitroacenaphthene, *N,N*-dimethylethylenediamine and *N,N*-diethylethylenediamine were purchased from J & K Chemical Company (China) and were used as received. The metal cation sources, NaCl, KCl, CaCl₂, MgCl₂, FeCl₃·6H₂O,

CuSO₄·5H₂O, ZnSO₄·7H₂O, CrCl₃·6H₂O, Pb(CH₃COO)₂·3H₂O, Ni(CH₃COO)₂·4H₂O, FeCl₂·4H₂O, Mn(CH₃COO)₂·4H₂O, Co(CH₃COO)₂, CdCl₂·2.5H₂O and HgCl₂, were purchased from Sinopharm Chemical Reagent Company (China) and used as obtained. All the solvents were of spectroscopy grade and used without special treatment. 2-(2-(Dimethylamino)ethyl)-6-((2-(dimethylamino)ethyl)-amino)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (MMN) and 2-(2-(diethylamino)ethyl)-6-((2-(diethylamino)ethyl)amino)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (EEN) were dissolved in water or *N,N*-dimethyl formamide (DMF) to form 1 mM stock solutions. Metal salts were dissolved in water or DMF to get 10 mM stock solutions. When examining the sensing behaviours of MMN and EEN to cations in aqueous solution, 500 μL aqueous stock solutions of MMN and EEN were diluted to 10 μM with Britton-Robinson buffer at different pH values. When studying the sensing behaviours in DMF, 500 μL stock solution of the sensors and 25-800 μL stock solution of metal salts in DMF were mixed and diluted with DMF. The concentration of the sensors and metal ions was 10 μM and 5-160 μM, respectively. The fluorescence enhancement (FE) was determined from the ratio of maximum fluorescence intensity *I* (after addition of metal cations) and *I*₀ (before addition of metal cations). ¹H and ¹³C NMR spectra were tested on a Varian Unity Inova spectrometer, operating at 300 and 400 MHz, respectively. LC-MS analysis was done on an Agilent 1200/6220

spectrometer. The elementary analysis was performed on a Carlo-Erba EA1110 CHNO-S. UV-VIS spectra were carried out on a U-3900 spectrophotometer. Fluorescence spectra were taken on a Fluoromax-4 spectrofluorometer (Slit width: 1 nm; T: 25 °C). The pH values were measured on a Mettler-Toledo FE20 pH meter.

General procedure: The structures of the fluorescent sensors are presented in **Scheme-I**. The precursor, 4-nitronaphthalic anhydride, was synthesized according to the literature³¹.



MMN: R = N(CH₃)₂
EEN: R = N(CH₂CH₃)₂

Scheme-I: Structure of the fluorescent sensors

2-(2-(Dimethylamino)ethyl)-6-((2-(dimethylamino)ethyl)amino)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (MMN) and 2-(2-(diethylamino)ethyl)-6-((2-(diethylamino)ethyl)amino)-1*H*-benzo[de]isoquinoline-1,3(2*H*)-dione (EEN) were prepared by one step reaction between 4-nitro-1,8-naphthalic anhydride and *N,N*-dimethylethylenediamine (or *N,N*-diethylethylenediamine) under very mild conditions. To a solution of 4-nitro-1,8-naphthalic anhydride (0.2 g, 822 μM) in DMF (3 mL), *N,N*-dimethylethylenediamine (1.2 mL, 11 mM) or *N,N*-diethylethylenediamine (0.9 mL, 6.4 mM) was added dropwise at room temperature. The solution was stirred for 8 h at 45 °C, after which the solvent was removed under reduced pressure. Silica gel chromatography with methanol/chloroform (1:30 v/v) as eluent afforded 0.22 g (75.0%) of MMN or 0.24 g (70.5 %) of EEN. The present method of synthesis is simpler and more efficient than the literature methods in which MMN was used as a potential DNA-binding antitumor agent³² and EEN was used for the repair of meniscal lesions³³. MMN: m.p. 119-121 °C; ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS) δ: 2.34 (s, 6H), 2.38 (s, 6H), 2.66 (t, 2H, *J* = 12.0 Hz), 2.74 (t, 2H, *J* = 12.0 Hz), 3.38 (m, 2H), 4.32 (t, 2H, *J* = 14.4 Hz), 6.31 (s, 1H), 6.66 (d 1H, *J* = 8.0 Hz), 7.62 (t, 1H, *J* = 8.0 Hz), 8.14 (d, 1H, *J* = 8.0 Hz), 8.45 (d, 1H, *J* = 8.0 Hz), 8.57 (d, 1H, *J* = 7.2 Hz); ¹³C NMR (300 MHz, CDCl₃, 25 °C, TMS) δ: 38.04, 40.32, 45.28, 45.98, 57.07, 57.27, 104.55, 110.06, 120.50, 123.05, 124.75, 126.68, 129.97, 131.30, 134.77, 149.87, 164.34, 164.95; LC-MS *m/z*: 355.2 (*M* + *H*⁺); Anal. (%): calcd. for C₂₀H₂₆N₄O₂: C 67.77, H 7.39, N 15.81; found (%): C 67.38, H 7.27, N 15.46.

EEN: m.p. 51-52 °C; ¹H NMR (400 MHz, CDCl₃, 25 °C, TMS) δ: 1.11 (m, 6H), 1.13 (m, 6H), 2.65 (m, 4H), 2.69 (m, 4H), 2.80 (t, 2H, *J* = 12.0 Hz), 2.87 (t, 2H, *J* = 11.6 Hz), 3.35 (m, 2H), 4.28 (t, 2H, *J* = 15.6), 6.52 (s, 1H), 6.66 (d, 1H, *J* = 8.0 Hz), 7.62 (t, 1H, *J* = 8.8 Hz), 8.09 (d, 1H, *J* = 8.4 Hz), 8.45 (d, 1H, *J* = 8.0 Hz), 8.58 (d, 1H, *J* = 8.0 Hz); ¹³C NMR (300 MHz, CDCl₃, 25 °C, TMS) δ: 12.24, 12.40, 37.76, 40.17, 46.61, 47.85, 50.06, 50.71, 104.69, 109.90, 120.65, 123.09, 124.84, 126.51, 130.02, 131.24, 134.81, 149.99, 164.33, 164.93; LC-MS *m/z*: 411.3 (*M* + *H*⁺); Anal. (%): calcd for C₂₄H₃₄N₄O₂: C 70.21, H 8.35, N 13.65; found: C 69.14, H 8.22, N 13.38.

RESULTS AND DISCUSSION

The sensing behaviours of MMN and EEN to cations in aqueous solution were first studied. The results show that they are sensitive to H⁺. Inspired by some research work on 1,8-naphthalimide-based fluorescent sensors for metal ions in DMF^{7,25,34}, we studied the sensing behaviours of MMN and EEN in DMF. Without the cations, the DMF solutions of MMN and EEN (10 μM) are dark yellow in colour and show almost no fluorescence. Upon addition of Na⁺, K⁺, Ca²⁺, Mg²⁺, Cu²⁺, Zn²⁺, Cr³⁺, Pb²⁺, Ni²⁺, Fe²⁺, Mn²⁺, Co²⁺, Cd²⁺, Hg²⁺ (100 μM) to the sensor solutions, no significant fluorescence intensity changes were observed. However, the same amount of Fe³⁺ led to an exceptional enhancement in fluorescence intensity and the fluorescence enhancement (FE) is 20-fold and 22-fold for MMN and EEN, respectively (Fig. 1), which indicates that MMN and EEN have high selectivity and sensitivity to Fe³⁺ in DMF. Upon addition of Fe³⁺, the appearance of a clear shining yellow-green fluorescence could be observed by the naked-eye. The fluorescence enhancement occurs immediately and the response time is less than 1 s. The results show that MMN and EEN behave as highly selective and sensitive Fe³⁺ fluorescent sensors in DMF.

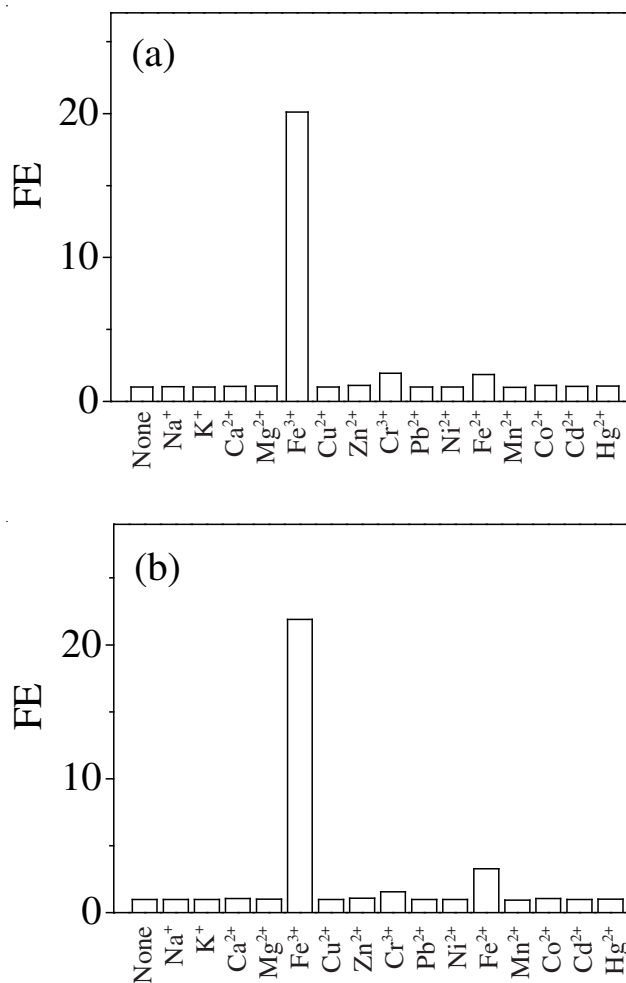


Fig. 1. Fluorescence enhancement (FE) of sensors (10 μM) caused by different ions (100 μM) in DMF. (a) MMN, λ_{ex}: 441 nm, λ_f: 527 nm; (b) EEN, λ_{ex}: 442 nm, λ_f: 523 nm

The fluorescence titration experiments of MMN and EEN (10 μM) with Fe³⁺ show that the fluorescence intensity is strengthened gradually with the increase of the Fe³⁺ concentration (Fig. 2).

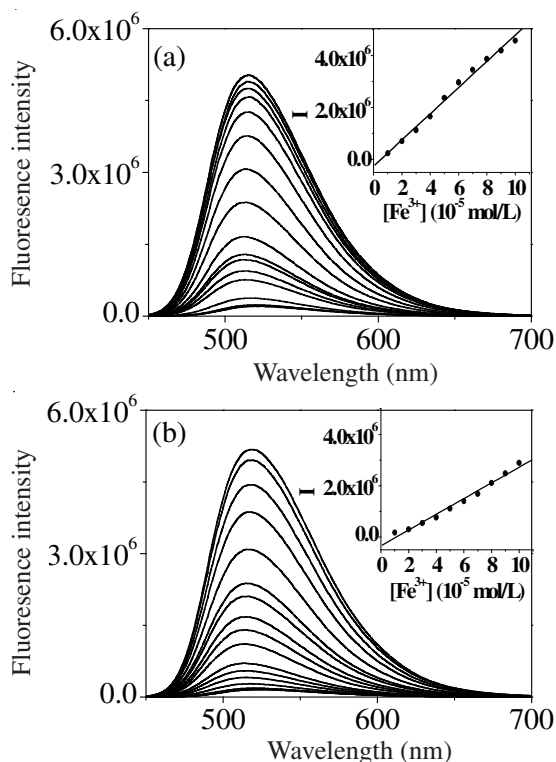


Fig. 2. Fluorescence spectra of sensors (10 μM) in DMF with various concentrations of Fe³⁺ (0-160 μM). (a) MMN, λ_{ex}: 441 nm, λ_f: 527 nm; (b) EEN, λ_{ex}: 442 nm, λ_f: 523 nm. From bottom to top, the equiv. of Fe³⁺: 0, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10, 12, 14, 15 and 16. The insets showed the linear relationship between the maximal fluorescence intensity (I) and the concentration of Fe³⁺

Furthermore, it was found that the maximal fluorescence intensity (I) of the sensors increased linearly with the concentration of Fe³⁺ ([Fe³⁺]) when the [Fe³⁺] was varied from 10-100 μM (Fig. 2). The linear fit equations could be described by $I = -308739.4958 + 510537.8151 \times [Fe^{3+}]$ and $I = -330649.2510 + 304567.0442 \times [Fe^{3+}]$ for MMN and EEN with linearly dependent coefficients as 0.9966 and 0.9929, respectively.

Job's plot method³⁵ employed to estimate the binding stoichiometry of Fe³⁺ and MMN (or EEN) showed that a 2:1 metal-ligand complex was formed between Fe³⁺ and MMN (or EEN). The sensors may bind Fe³⁺ via a bidentate chelation to nitrogen atoms both from the imide side and the C-4 position of aromatic amine, which is similar to that described in the literature²⁵.

The detection limit (3σ/m) was calculated based on the fluorescence titration³⁶, where σ is the standard deviation of blank measurement, m is the slope of the fit lines in Fig. 2. To determine σ, the emission intensity of MMN and EEN without any metal ions was measured by 6 times. The detection limits for MMN and EEN were found to be 180 and 310 nM, respectively.

The effects of coexisting biologically relevant ions on the detection of Fe³⁺ are exhibited in Fig. 3. In the DMF solution

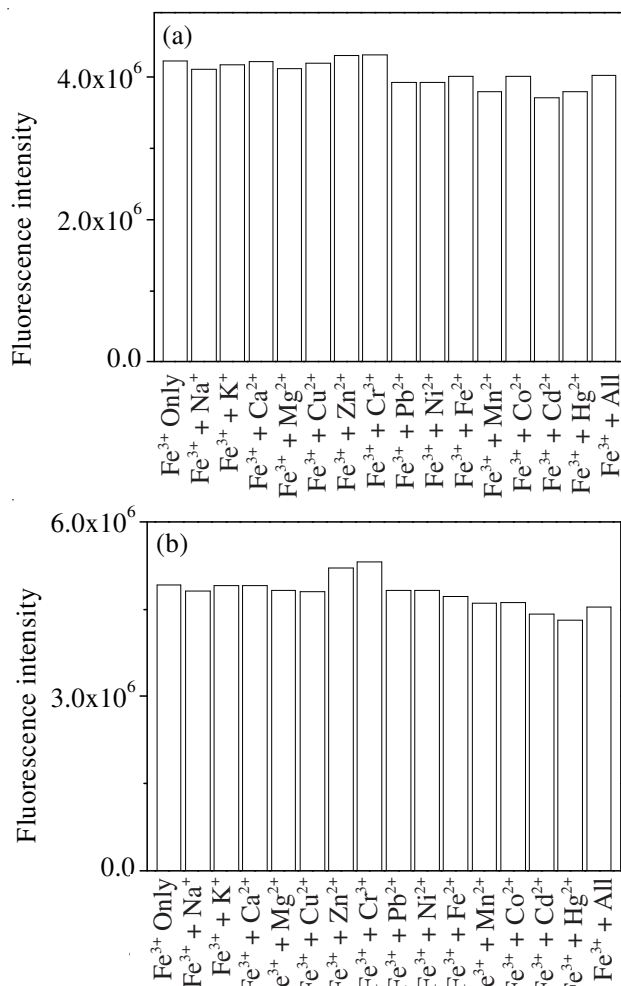


Fig. 3. Effects of coexisting ions on the fluorescence maxima of sensors (10 μM) and Fe³⁺ (100 μM). (a) MMN, λ_{ex}: 441 nm, λ_f: 527 nm; (b) EEN, λ_{ex}: 442 nm, λ_f: 523 nm. Solvent: DMF. Concentration of the coexist ions: 1 mM for Na⁺, K⁺, Ca²⁺, Mg²⁺; 100 μM for Cu²⁺, Zn²⁺, Cr³⁺, Pb²⁺, Ni²⁺, Fe²⁺, Mn²⁺, Co²⁺, Cd²⁺, Hg²⁺

of MMN and EEN (10 μM), adding 10 equiv. of Fe³⁺ caused a drastic increase in fluorescence intensity. Na⁺, K⁺, Ca²⁺, Mg²⁺ had a very small effect on the fluorescence spectrum of the sensors and Fe³⁺, even at a concentration as high as 1 mM. Other cations such as Cu²⁺, Zn²⁺, Cr³⁺, Pb²⁺, Ni²⁺, Fe²⁺, Mn²⁺, Co²⁺, Cd²⁺, Hg²⁺ at the same concentration as Fe³⁺ (100 μM) also had very little influence on the fluorescence spectrum of the sensors and Fe³⁺, which indicates that MMN and EEN in DMF are reliable and highly selective "turn-on" Fe³⁺ sensors.

Conclusion

In the present study, two 1,8-naphthalimide-based fluorescent sensors, 2-(2-(dimethylamino)ethyl)-6-((2-(dimethylamino)ethyl)amino)-1H-benzo[de]isoquinoline-1,3(2H)-dione (MMN) and 2-(2-(diethylamino)ethyl)-6-((2-(diethylamino)ethyl)amino)-1H-benzo[de]isoquinoline-1,3(2H)-dione (EEN), have been synthesized under mild conditions. Their selectivity to cations is greatly affected by solvent. In DMF, they can distinguish Fe³⁺ from Na⁺, K⁺, Ca²⁺, Mg²⁺, Cu²⁺, Zn²⁺, Cr³⁺, Pb²⁺, Ni²⁺, Fe²⁺, Mn²⁺, Co²⁺, Cd²⁺, Hg²⁺ and are highly selective and sensitive Fe³⁺ sensors.

ACKNOWLEDGEMENTS

This work is funded by the National Natural Science Foundation of China (21074085), the Open Research Foundation of the National Engineering Laboratory for Modern Silk, Soochow University (SS115801) and the Priority Academic Program Development of Jiangsu Higher Education Institutions.

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