Tetrahedron Letters 52 (2011) 4903–4905

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A rapid Hg^{2+} sensor based on aza-15-crown-5 ether functionalized 1,8-naphthalimide

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ARTICLE INFO

Article history:
Received 5 May 2011
Revised 7 July 2011
Accepted 12 July 2011
Available online 21 July 2011

Keywords:
Fluorescent sensor
Hg^{2+}
1,8-Naphthalimide
ICT

ABSTRACT

A new 1,8-naphthalimide derivative bearing an aza-15-crown-5 macrocycle (**1**) has been synthesized as a chemosensor for Hg^{2+} by a two-step reaction. The sensor shows selectivity to Hg^{2+} over 11 other metal cations in aqueous media. Upon addition of Hg^{2+}, the fluorescence emission of the sensor at 537 nm is significantly quenched along with 22 nm blue-shift that makes this compound a useful sensor for Hg^{2+} measurement.

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As a detrimental metal ion, Hg^{2+} has continually received concern for its deleterious effects on nature, environment, and human health.[1] There have been many reports on the toxicity of Hg^{2+} to human's central nervous system and immune system, consequently resulting in brain damage, vision loss and death.[2] In particular, the poisoning effect of Hg^{2+} is reflected on its efficient bioaccumulation by methylating inorganic mercury to methylmercury.[3] In contrast to Hg^{2+}, methylmercury is able to cross the cell membrane and is accumulated in the cell, causing irreversible damage to nucleic acids and proteins.[4] Despite the high toxicity, Hg^{2+} is still being used in many industrial processes that contribute a significant portion of Hg^{2+} contamination.[5] Therefore, developing effective methods for Hg^{2+} detection keeps attracting great interest in the sensing community.[6]

Compared to traditional approaches for Hg^{2+} analysis relied on complicated sample preparation or sophisticated instrumentation, fluorogenic probes provide a rapid, facile, and sensitive tool for Hg^{2+} detection.[7] In the past years, many efforts have been devoted to develop fluorescent sensors based on various sensing strategies.[8] However, for most of the reported fluorescent sensors, the selectivity and signal intensity are still major challenges.[9] There continues to be a strong demand for fluorescent sensors of Hg^{2+} with high signal/noise ratio and affinity.[10]

Among diverse fluorophores providing signal for fluorescent sensors, the *N*-aryl-1,8-naphthalimides attract particular interest due to their brightness, photo stability, and internal charge transfer (ICT) structure.[11] Recently, numerous 1,8-naphthalimide-based fluorescent sensors have been reported for the detection of various molecules.[12] Compared to other fluorophores, the fluorescence emission spectra of 1,8-naphthalimides are significantly affected by substituents on the naphthalene ring that provide an excellent sensing switch for sensor design.[13] Aza-15-crown-5 is a widely used ligand with high coordinating ability with metal cations.[14] Herein, we report a 1,8-naphthalimide-aza-15-crown-5 conjugate (e.g. **1**) that functioned as a Hg^{2+} sensor at pH 7.4. Sensor **1** displays high binding ability to Hg^{2+} and selectivity against other competitive metal cations in aqueous media. Upon binding Hg^{2+}, **1** exhibits strong fluorescence depletion and a blue-shift that indicates the achievability of an ICT sensor for Hg^{2+} analysis.

The synthesis of **1** is shown in Scheme 1. Condensation between 4-bromo-1,8-naphthalic anhydride and 4-methoxyaniline gives **2** in pyridine (130 °C for 3 h).[15] Then, 1-aza-15-crown-5 is refluxed with purified **2** to afford a yellow solid **1** in 79% yield. The structure of **1** is confirmed by ^{1}H NMR, ^{13}C NMR and elemental analysis (see Supplementary data).[16]

Spectroscopic measurements are collected in aqueous buffer (i.e., 10 mM HEPES containing 20% MeOH at pH 7.4) at ambient temperature. Sensor **1** displays the maximum absorption at 432 nm and the fluorescence emission at 537 nm, respectively. The optical responses of sensor **1** to various metal cations are investigated by the UV–vis and fluorescence spectroscopy. In the presence of Hg^{2+} (40 mol equiv), the emission spectrum of **1** (1.0×10^{-6} M) exhibits substantial quenching at 537 nm (λ_{ex} = 432 nm) together with a 22 nm blue-shift that is attributed to the formation of **1**–Hg^{2+} complex (Fig. 1). The coordination between Hg^{2+} and aza-15-crown-5 macrocycle may reduce the electron-donating ability of the amino group on the naphthalene ring that results in fluorescence

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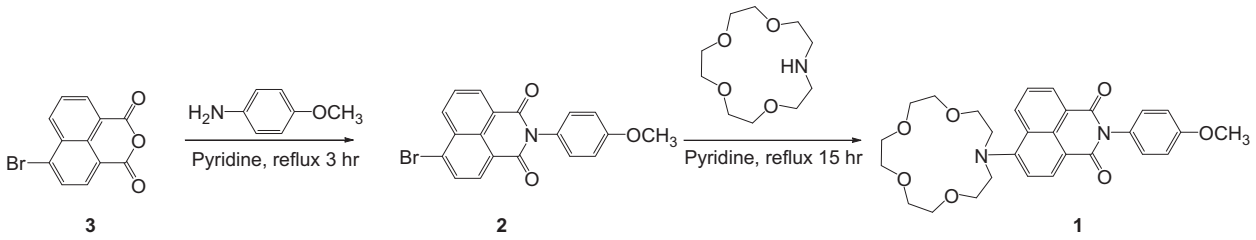
0040-4039/$ - see front matter Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2011.07.056



Scheme 1. Synthetic route of fluorescent chemosensor **1**.

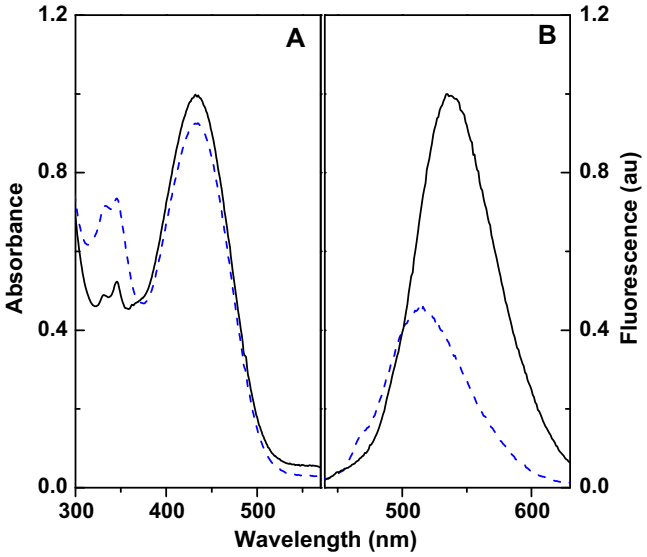


Figure 1. Absorption (A) and fluorescence emission (λ_{ex} = 432 nm) (B) spectra of **1** (1.0×10^{-6} M) in aqueous buffer (i.e., 10 mM HEPES containing 20% MeOH at pH 7.4), prior to (—) and following addition of 20 mol equiv of Hg^{2+} (- - -).

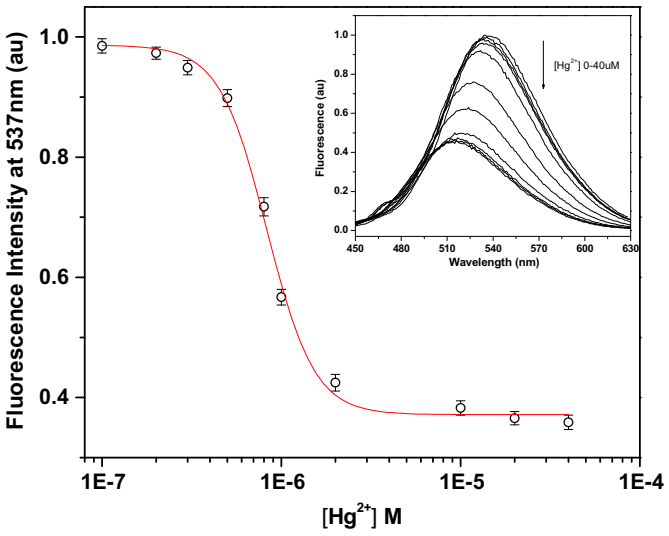


Figure 2. Fluorescence titration of **1** (1.0×10^{-6} M) in response to increasing amounts of Hg^{2+} (λ_{ex} = 432 nm) in aqueous buffer (i.e., 10 mM HEPES containing 20% MeOH at pH 7.4).

quenching and blue-shift.[17] Upon addition of Hg^{2+}, the absorption spectrum of **1** also displays significant change, the peak at 432 nm decreases and the peak at 346 nm increases (Fig. 1). The changes of both of absorption and emission spectra indicate that the formation of **1**–Hg^{2+} complex interrupts ICT between the nitrogen atom on the aza-15-crown-5 macrocycle and the naphthalimide moiety, and also make **1** have the necessary spectral properties to serve as a sensitive chemosensor for Hg^{2+} detection. Further titration experiments are conducted to investigate the binding ability between **1** and Hg^{2+} (Hg^{2+}: 0–4.0×10^{-5} M). As shown in Figure 2, with the gradual addition of Hg^{2+}, the fluorescence emission of **1** at 537 nm keeps decreasing. The maximal spectral change is observed upon addition of near 20 mol equiv of Hg^{2+} relative to **1** (1.0×10^{-6} M) with 64% fluorescence depletion and a 22 nm blue-shift. Based on titration data, the binding constant of **1** with Hg^{2+} is found to be 2.24×10^5 M^{-1}.

The selectivity of **1** toward Hg^{2+} over other competitive species is investigated in the presence of various biologically and environmentally relevant metal ions. All of measurements are conducted by using the perchlorate of metal ion (4.0×10^{-5} M) and **1** (1.0×10^{-6} M) in aqueous buffer (i.e., 10 mM HEPES containing 20% MeOH at pH 7.4). As shown in Figure 3, the introduction of Hg^{2+} to **1** elicits significant fluorescence depletion at 537 nm because of ICT interruption caused by **1**–Hg^{2+} complex. By contrast, K^+, Na^+, Ag^+, Ba^{2+}, Ca^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}, Fe^{2+}, Pb^{2+}, and Mg^{2+} are examined under the same condition, but no marked emission quenching is observed. Fe^{2+} results in 19% quenching on a much smaller scale than Hg^{2+}. K^+, Na^+, and Mg^{2+} lead to slight fluorescence enhancement that may be the result of interaction with the O atom on naphthalimide moiety. [10] Moreover, the **1**–Hg^{2+} complex also displays a 22 nm blue-shift that makes **1** more selective to Hg^{2+} over other metal cations (Fig. S1). The further investigation for **1**'s binding affinity to Hg^{2+} is carried out by competition experiments. Possible competition between Hg^{2+} and other metals against **1** are measured by using mixed solutions containing 4.0×10^{-5} M Hg^{2+} and 4.0×10^{-5} M each of K^+, Na^+, Ag^+, Ba^{2+},

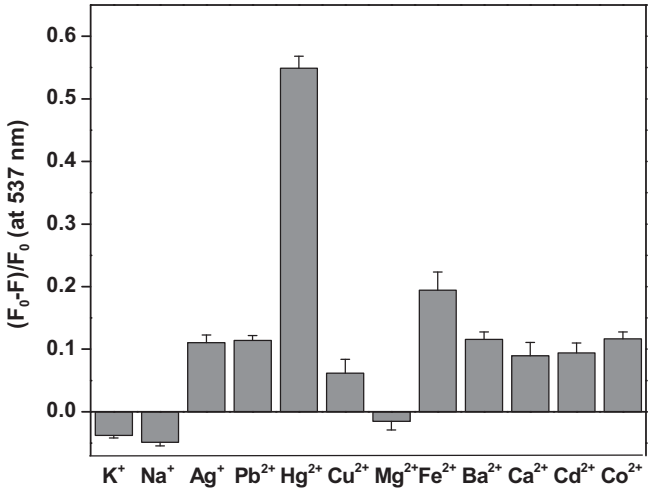


Figure 3. The gray bars represent the fluorescence change of **1** (1.0×10^{-6} M) at 537 nm in presence of K^+, Na^+, Ag^+, Pb^{2+}, Hg^{2+}, Cu^{2+}, Mg^{2+}, Fe^{2+}, Ba^{2+}, Ca^{2+}, Cd^{2+}, and Co^{2+} (40 equiv) in 10 mM HEPES buffer (containing 20% MeOH at pH 7.4) (λ_{ex} = 432 nm).

Ca^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}, Fe^{2+}, Pb^{2+}, and Mg^{2+}. With the addition of mixture solution, **1** shows significant quenching in all of the samples that suggests the strong interaction between **1** and Hg^{2+} (Fig. S2 in Supplementary data). Moreover, several anions, including Cl^-, NO_3^-, ClO_4^-, AcO^-, SO_4^{2-}, CO_3^{2-} and PO_4^{3-} (obtained by using their sodium salt; 4.0×10^{-5} M), also are used to examine possible interference in the binding interaction between **1** and Hg^{2+}. No fluorescence quenching triggered by these anions is observed (Fig. S3 in Supplementary data), indicating that **1** represents a robust sensor for high-throughput measurements against Hg^{2+}.

In conclusion, we have successfully devised a naphthalimide-aza-15-crown-5 conjugate that behaved as a selective fluorescent Hg^{2+} sensor by a simple two-step synthesis. Sensor **1** displays significant turn-off and blue-shift responses of fluorescence following Hg^{2+} recognition. Although **1** requires MeOH as co-solvent to increase solubility in aqueous media, this sensor still offers a facile analysis method for Hg^{2+} detection and also may contribute to the development of more efficient chemosensors based on the 1,8-naphthalimide platform.

Acknowledgments

This research is supported by Mini-Grant, URF, and URCA in the University of Nebraska at Kearney.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.056.

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15. A mixture of 4-bromo-1,8-naphthalic anhydride (0.277 g, 1.0 mmol) and 4-methoxyaniline (0.123 g, 1.0 mmol) in 10 mL pyridine was refluxed for 3 h under argon atmosphere. The reaction mixture was poured into 40 mL 1.0 M cold HCl solution to collect precipitate. The crude product was purified by column chromatography (silica, 220–400 mesh, dichloromethane/EtOAc = 3:1 v/v). The product was isolated as a brown powder **2** (0.35 g, 91%). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.82 (s, 3H), 7.06 (d, J = 8.9 Hz, 2H), 7.29 (d, J = 9.8 Hz, 2H), 8.05(t, J = 7.4 Hz, 1H), 8.26 (d, J = 7.5 Hz, 1H), 8.35 (d, J = 8.9 Hz, 1H), 8.60 (d, J = 6.1 Hz, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 55.8, 114.6, 123.2, 124.0, 128.7, 129.4, 129.7, 130.6, 131.4, 131.9, 132.1, 133.1, 159.4, 163.8. MS: m/z $(MH)^+$ 381.23. Anal. Calcd for $C_{19}H_{12}BrNO_3$: C, 59.71; H, 3.16; N, 3.66. Found: C, 59.34; H, 3.28; N, 3.49.
16. Compound **2** (0.191 g, 0.5 mmol) and 1-aza-15-crown-5 (0.153 g, 0.7 mmol) in 5 mL pyridine were refluxed for 15 h under argon atmosphere. Then pyridine was removed by rotary evaporation to afford crude product **1** that was purified by column chromatography (silica, 220–400 mesh, MeOH/EtOAc = 1:4 v/v). Product was collected as a bright yellow powder **1** (0.14 g, 53%). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 3.75 (m, 20H), 3.90 (s, 3H), 7.07 (m, 2H), 7.25(m, 2H), 7.52 (d, J = 8.9 Hz, 1H), 7.71 (t, J = 7.4 Hz, 1H), 8.55 (d, J = 9.0 Hz, 1H), 8.62 (d, J = 7.6 Hz, 1H), 8.75 (d, J = 9.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO-d_6) δ: 54.2, 55.5, 69.4, 70.8, 71.2, 114.6, 116.1, 117.2, 123.3, 125.3, 127.1, 128.3, 129.4, 131.4, 131.5, 132.3, 155.7, 159.4, 164.3. MS: m/z $(MH)^+$ 520.65. Anal. Calcd for $C_{29}H_{32}N_2O_7$: C, 66.91; H, 6.20; N, 5.38. Found: C, 67.03; H, 6.01; N, 5.32.
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