JOC Note

A Rhodamine-Based Hg^{2+} Sensor with High Selectivity and Sensitivity in Aqueous Solution: A NS_2-Containing Receptor

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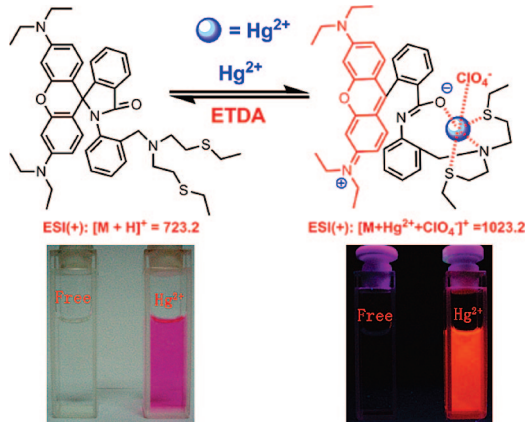
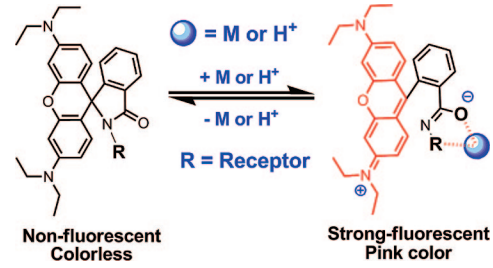


A rhodamine-based sensor **1** was designed and synthesized by incorporation the rhodamine fluorophore and ionophore NS_2 with high affinity to Hg^{2+}. Sensor **1** exhibits a high selectivity and an excellent sensitivity and is a dual-responsive colorimetric and fluorescent Hg^{2+}-specific sensor in aqueous buffer solution. In addition, the 1:1 binding mode was proposed based on the ^1H NMR and ES(+)MS studies.

Rhodamine B and its derivatives (**RhBs**) are well-known for their desirable properties, including good photostability, high extinction coefficient (>75000 cm^{-1} M^{-1}), and high fluorescence quantum yield, particularly in its nucleotide and nucleic acid conjugates.[1] Recently, rhodamine-based sensors for cations and other analytes have received ever-increasing interest in areas such as for sensors for Pb^{2+}, Cu^{2+}, Hg^{2+}, Fe^{3+}, Cr^{3+}, NO, and OCl^-.[2−8] The mechanism is based on the switch off/on of the spirocyclic moiety mediated by guests as shown in Scheme 1.[2−9] When guests are bound to the sensors, the spirocyclic form of **RhBs**, which is colorless and nonfluorescent, is converted to the opened-cyclic form which is pink and strongly fluorescent.[2−9] However, this conversion is strongly dependent on the organic solvent content or pH value in detecting solution system.[2−9] For the known reversible sensors based on the rhodamine moiety, most of them work well in a pure organic solvent media (such as MeCN[2,3c,5d,e,6c,e] or MeCN/methanol[6a]) or an aqueous solution containing at least 50% organic cosolvent (such as DMF,[5f] ethanol,[5b,6b,7a,b] methanol,[4c] or MeCN[3b,d]). Also, some of them work well in strong acidic solution at pH 3−4[5g,h,10] or strong basic solution at pH 12.[8b] Moreover, this conversion will reverse when some competitive solvents, such as water, are added into the sensing system. These limitations, including organic cosolvent dependence and pH dependence, to some extent, lower the sensitivity and restrict the application of rhodamine-based sensors in biological systems and environmental determinations.[11] In fact, only a few of them, particularly in irreversible rhodamine-based ion sensors,[4a,b,d] work well in

SCHEME 1. Representative Mechanism of the Chemosensor Based on the RhB



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(10) Proton could induce the opened-cycle of spirolactam below pH5.0; therefore, the acid media was not suitable to determine targeted-analytes.

(11) In general, the sensor for biological application works in near neutral conditions.

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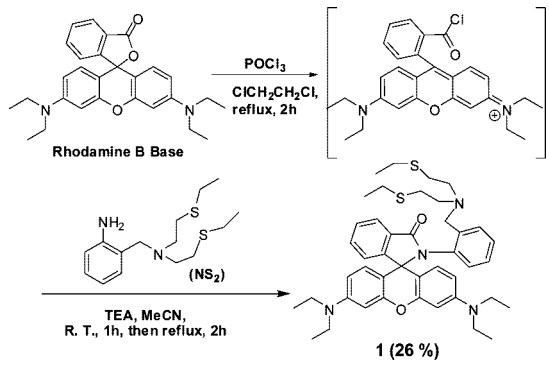
SCHEME 2. Synthesis of 1



aqueous buffer solution containing less than 20% organic cosolvent[8a] or in neutral pure water.[5a,f] To solve this problem, the simplest method is to introduce an appropriate receptor **R** (Scheme 1) which has several features, including (1) reversible binding to guest molecules, (2) high affinity to guest molecules, and (3) conformational preorganization to facilitate capture of guest molecules.[12] Obviously, the receptor introduced should improve the ability to competitively bind the guest molecules in aqueous buffer solution and reduce the amount of organic cosolvent in the detecting solution.

Herein, we designed a new rhodamine B-based chemosensor **1** for Hg^{2+}.[13] In **1**, the receptor contained the NS_2 fragment, which is a well-known specific and reversible binding receptor of Hg^{2+} due to the thiophilic nature of mercury and has been used in a fluorescein-based PET sensor.[13a] Therefore, we speculated that the introduction of the NS_2 receptor to a rhodamine-based probe would (1) increase the affinity to Hg^{2+} in competitive aqueous media, (2) quickly induce the fluorescent and color responses, that is, realize the real-time detection, (3) improve the selectivity, and (4) recognize Hg^{2+} reversibly. Compound **1** was synthesized and characterized by NMR in addition to mass data. The preliminary experiments showed that **1** displayed a high selectivity and sensitivity for Hg^{2+} in buffer solution. The bind mode was proposed by the ^1H NMR titration study and ES(+)-MS analysis.

NS_2 was synthesized according to the published procedure.[13a] Compound **1** was synthesized by treating rhodamine B with $POCl_3$, which was followed by NS_2. After column chromatography using DCM/MeOH (100/3, v/v) as eluent, sensor **1** was obtained in a 26% yield (Scheme 2).

The pH response of **1** in MeCN/water solution (2/8, v/v) was first evaluated as shown in Figure S3, Supporting Information.

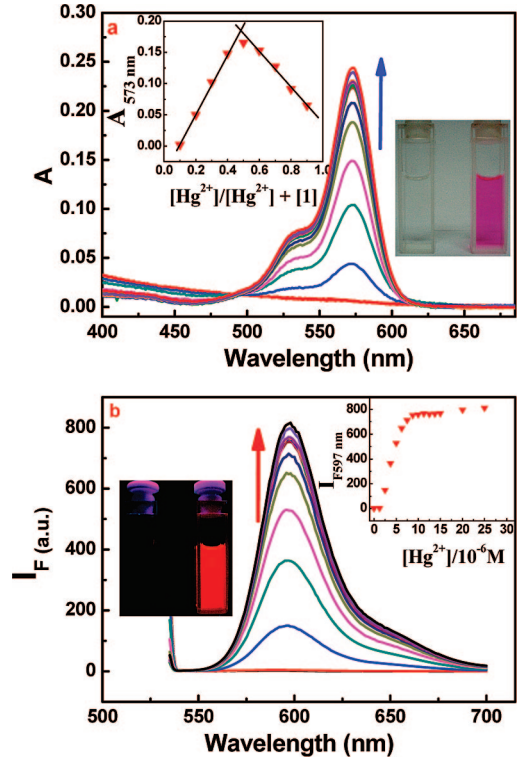


FIGURE 1. (a) Absorption spectra of **1** (5 μM) in buffer solution upon addition of different amounts of Hg^{2+} ions. Inset: the Job's plot; the total concentration of ($[Hg^{2+}] + [\mathbf{1}]$) was 10 μM. The photograph shows the color change of **1** (5 μM) in solution. (b) Fluorescence spectra of **1** (5 μM) under the same conditions upon addition of different amounts of Hg^{2+} ion. Excitation was performed at 530 nm. Inset: fluorescence enhancement at 597 nm as a function of Hg^{2+} concentration. The photograph shows the fluorescent color of **1** (5 μM) upon addition 2.0 equiv Hg^{2+} in solution with 365 nm excitation.

The acid−base titration experiments revealed that **1** did not emit any obvious and characteristic (excitation at 530 nm) fluorescence in the pH range from 6.0 to 12.0, suggesting that it was insensitive to pH near 7.0 and could work in approximate physiological conditions with a very low background fluorescence.[13a] Therefore, further UV/vis and fluorescent studies were carried out in MeCN/HEPES mixed buffer solution (MeCN/water = 15/85, v/v, pH 6.98, 20 mM HEPES, 50 mM KCl).

Like most of the spirocycle **RhB** derivatives, the free **1** remained colorless and did not exhibit apparent absorption above 500 nm in the above buffer system (as shown in Figure 1). This indicated that the spirolactam form (Scheme 1) was the predominant species.[2−8] Upon addition of Hg^{2+} ion, a new strong absorption band centered at 573 nm was formed and led to the color change from colorless to purple. This indicated that the opened-ring form (Scheme 1) of **1** became the main species in the examined solution.[2−8] The emission spectra were also recorded under the same conditions. Free **1** displayed a very weak fluorescence. When Hg^{2+} ion was added to the buffer solution of **1**, a significant increase (almost 400-fold enhancement of I_F/I_0, herein I_0, indicated the fluorescence intensity of free **1**; I_F indicated the fluorescence intensity upon adding 2.0 equiv Hg^{2+}) of fluorescence at 597 nm was observed, that is, Hg^{2+} ion induced the formation of open-cycle **RhBs** with strong fluorescence (Scheme 1).[2−8] The 1:1 stoichiometry between **1** and Hg^{2+} was confirmed by the Job's plot shown in the inset of Figure 1a. The binding constant K_a was $(1.18 \pm 0.13) \times 10^6$

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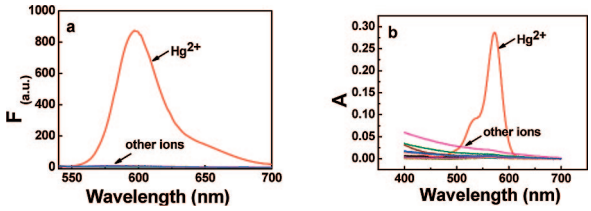

FIGURE 2. Fluorescent and absorption spectra of **1** (5 μM) in the presence of different metal ions: (a) fluorescent spectra, Hg^{2+} (2.0 equiv) and other ions (10.0 equiv), excitation was performed at 530 nm; (b) UV/vis spectra, Hg^{2+} (2.0 equiv) and other ions (10.0 equiv).

M^{-1}, inferred from the Hg^{2+} titration curves (Figure S4, Supporting Information).[14] In addition, the EDTA-adding experiments were conducted to examine the reversibility of this reaction as shown in Figure S5 (Supporting Information). When EDTA was added to the solution of equimolar **1**/Hg^{2+}, the color changed from pink to colorless and the fluorescence was turned off. These results indicated that **1** was a reversible chemosensor for Hg^{2+}; a similar result was reported in a sensor with the same receptor.[13a]

To validate the selectivity of **1** in practice, some other cations were added to a solution of **1** under the same conditions. The various alkali, alkaline earth metal ions, and transition metal ions (Pb^{2+}, Cu^{2+}, Cd^{2+}, Fe^{3+}, Fe^{2+}, Zn^{2+}, Cr^{3+}, Co^{2+}, and Ni^{2+}) did not induce any apparent fluorescent enhancement and color change even upon addition of 10 equiv of the respective metal ions (as shown in Figure 2 and Figure S6, Supporting Information). The ratio of I_F/I_0 at 597 nm (here, I_0 indicates the fluorescence intensity of free **1** and I_F indicates the fluorescence intensity upon addition of different metal ions) of **1** in the presence of various other metal ions is shown in Figure S6a (Supporting Information). For Hg^{2+}, the I_F/I_0 value was almost 400-fold, while the values for the other metal ions were less than 10-fold. Therefore, **1** was a highly selective chemosensor for Hg^{2+}. The competitive experiments were conducted in the presence of 2.0 equiv of Hg^{2+} mixed with 10.0 equiv of various cations, respectively. No significant variation in fluorescence intensity was found by comparison with that without other metal ions besides Hg^{2+} (Figure S6b, Supporting Information). These results indicated that **1** was a Hg^{2+}-specific fluorescent sensor.

As a sensor, real-time determination was necessary. We next investigated the time evolution of the responses of **1** (5 μM) in the presence of 2.0 equiv of Hg^{2+} in same buffer solution. As shown in Figure 3, the recognition interaction was completed immediately after addition of the Hg^{2+} without any detectable time-delay. Compared to its analogues (which need a equilibrium time before detection[3a,5a,d]), therefore, sensor **1** was a sensitive sensor and could be used in real-time determination of Hg^{2+} in environmental analysis.

As mentioned above, the 1:1 coordination mode was confirmed by the Job's plot, which was also supported by ES(+)-MS.[15] Without Hg^{2+} ion, the peak *m/z* 723.2 corresponds to **[1 + H]**$^+$. When 1.0 equiv of Hg^{2+} is introduced to a **1** solution, a peak appears at *m/z* 1023.3 (Figure S7, Supporting Information) and is assigned to single-charged complex **[1 + Hg**$^{2+}$ **+ ClO**$_4^-$**]**$^+$ (the calculated value is 1023.3). To further elucidate the binding mode, the ^{1}H NMR-titration experiments were conducted. As shown in Figure 4 and Figure S8 (Supporting Information), a set of new peaks appeared with the increase of Hg^{2+} ion in the range of 0.0−1.0 equiv, while there was no further change after addition of more than 1.0 equiv of Hg^{2+}, which further confirmed the 1:1 stoichiometry. That H_5 and H_6 beside the "S" group displayed an apparent downfield shift (from peak centered at 3.33 ppm to 3.63 ppm, the $\Delta\delta$ = 0.30 ppm, upon addition of 1.0 equiv of Hg^{2+} ion) originated from the coordination "S" to "Hg^{2+}". H_4 displayed a similar downfield shift (from peak centered 2.40 ppm to 2.68 ppm, the $\Delta\delta$ = 0.28 ppm), and it suggested that Hg^{2+} bound to the "N" and induced the decrease of the electronic density in H_4. H_7 (the signal of H_7 was overlapped with H_2) also showed an apparent downshift. In addition, the downshift of H_1 and H_2 clearly suggested that the Hg^{2+} induced the formation of delocalized xanthene moiety of the rhodamine, which increased the deshielding effect and caused the H_1 and H_2 downshift of 0.28 and 0.17 ppm, respectively. The downshift of peaks near δ6.0 ppm, which were assigned to the proton signal of xanthene, also proved the delocalization of xanthene; that is, Hg^{2+} ion induced the opening of spirocycle. Taken together, the above results indicate a plausible interaction mode of **1**/Hg^{2+} as proposed in Figure 5, in which Hg^{2+} was coordinated with two "S", "N", and carbonyl "O".

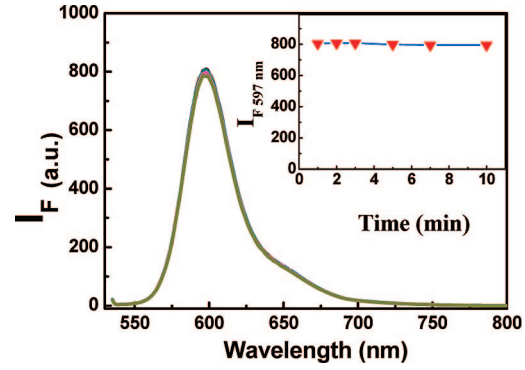

FIGURE 3. Time evolution of sensor **1** (5 μM) in MeCN/water (15/85, v/v) buffer (pH6.98, 20 mM HEPES, 50 mM KCl) in the presence of 2.0 equiv of Hg^{2+} ion. Inset: changes of fluorescence intensity at 597 nm as a function of time (0.0 to 10.0 min). Excitation was performed at 530 nm.

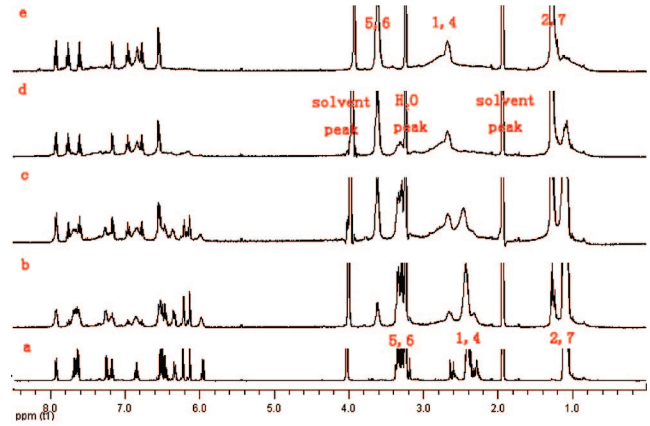

FIGURE 4. (a) Hg^{2+} ^{1}H NMR titration of **1** (10.0 mM) in CD_3CN and CD_3OD (1:1): (a) **1** only; (b) **1** + 0.25 equiv of Hg^{2+}; (c) **1** + 0.50 equiv of Hg^{2+}; (d) **1** + 0.75 equiv.of Hg^{2+}; (e) **1** + 1.00 equiv of Hg^{2+}.

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(15) (a) The ESI experiment was carried out in MeCN−water (1/9, v/v) solution considering the interference of HEPES salts: **1** (2 μM); Hg^{2+} (2 μM). (b) ESI(+) was extensively used to determine the complexe ration between ligand and metal ion: Pratesi, A.; Zanello, P.; Giorgi, G.; Messori, L.; Laschi, F.; Casini, A.; Corsini, M.; Gabbiani, C.; Orfei, M.; Rosani, C.; Ginanneschi, M. *Inorg. Chem.* **2007**, *46*, 10038–10040.

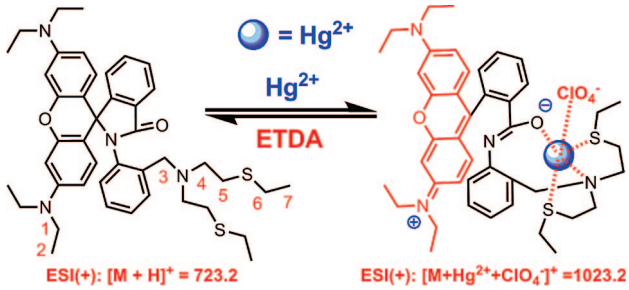

FIGURE 5. Proposed binding mode between **1**/Hg^{2+}.

In conclusion, we report a rhodamine derivative **1** used as a selective and sensitive chemosensor, which could specifically recognize Hg^{2+} ion in aqueous buffer solution by the "naked eye", UV/vis, and fluorescent responses. Compared with the reported rhodamine-based chemosenor, **1** reduced the amount of organic cosolvent in detecting media and improved sensitivity and selectivity through a rational incorporation of NS_2 receptor (NS_2 has high affinity toward Hg^{2+} due to the thiophilic nature of mercury) to the rhodamine structure. These results also indicated that the introduction of receptor with high affinity to targeted analytes in the rhodamine-based sensor would improve the selectivity and sensitivity. In addition, the spectral response toward Hg^{2+} was established to be reversible by the EDTA-titration experiments. Furthermore, the 1:1 coordination mode was proposed on the basis of the ^{1}H NMR titration experiments and ES(+)-MS analysis.

Experimental Section

Compound NS_2. Synthesis according to reported method:[13a] ^{1}H NMR ($CDCl_3$) δ 1.20 (t, 6H, J = 7.6 Hz), 2.45 (q, 4H, J = 7.6 Hz), 2.62−2.66 (m, 4H), 2.69−2.73 (m, 4H), 3.65 (s, 2H), 4.75 (br, 2H), 6.62−6.67 (m, 2H), 6.98 (d, 1H, J = 7.6 Hz), 7.08 (td, 1H, J_1 = 7.6 Hz, J_2 = 1.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.8, 25.9, 29.1, 53.3, 58.4, 115.6, 117.6, 122.4, 128.6, 130.4, 147.1.

Compound 1. A solution of rhodamine B base (0.45 g, 1.0 mmol) in 1,2-dichloromethane (15 mL) was stirred, and phosphorus oxychloride (0.4 mL) was added dropwise over 2 min. The solution was refluxed for 2 h. The reaction mixture was cooled and evaporated in vacuo to give rhodamine B acid chloride, which was not purified and used in the next step directly. The crude acid chloride was dissolved in acetonitrile (80 mL) and added dropwise over 1 h to a solution of **2** (0.30 g, 1.0 mmol) and TEA (0.5 mL) in acetonitrile (20 mL) at room temperature. The reaction mixture was then refluxed for 1 h. After the solvent was evaporated under reduced pressure, the crude product was purified by column chromatography (DCM/MeOH, 100:3, v/v) to give 188 mg of **1** (yield 26%): mp 77−79 °C; ^{1}H NMR (CD_3CN) δ 1.08−1.68 (m, 18H), 2.32−2.46 (m, 12H), 2.67 (d, 1H, J = 16.0 Hz), 3.25 (d, 1H, J = 16.0 Hz), 3.28−3.40 (m, 8H), 6.00 (d, 1H, J = 4.0 Hz), 6.15 (d, 1H, J = 2.4 Hz), 6.25 (d, 1H, J = 2.4 Hz), 6.36 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.8 Hz), 6.49 (dd, 1H, J_1 = 8.8 Hz, J_2 = 2.4 Hz), 6.57 (t, 2H, J = 8.4 Hz), 6.87 (t, 1H, J = 7.6 Hz), 7.19−7.25 (m, 2H), 7.63−7.07 (m, 3H), 7.92 (d, 1H, J = 6.8 Hz); ^{13}C NMR (CD_3CN) δ 11.7, 14.3, 11.9, 25.4, 29.1, 44.0, 44.1, 53.5, 53.9, 67.8, 96.8, 97.5, 106.4, 107.3, 107.6, 108.5, 116.8, 117.3, 122.8, 124.3, 126.1, 127.9, 128.3, 128.8, 128.9, 130.2, 132.5, 132.8, 134.4, 140.5, 149.2, 151.5, 153.9, 154.5, 165.6; HRMS (ESI+) found 723.3755 $(M + H)^+$, calcd for $C_{43}H_{55}N_4O_2S_2$ 723.3766.

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Supporting Information Available: Synthesis and characterization of **1**; HRMS, ^{1}H NMR, and ^{13}C NMR spectra and the spectroscopic data; pH-titration of free **1**; the curve fitting; ESI(+)-MS experiment and spectrum in the presence of the equimolar Hg^{2+}/**1** (2 μM); EDTA-titration of absorption and emission; selective and competitive experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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