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A highly selective chemodosimeter for the rapid detection of Hg^{2+} ions in aqueous media

Ambadas B. Rode, Jinkwon Kim, Sang-Ho Kim, Gajendra Gupta, In Seok Hong *

Department of Chemistry, College of Natural Science, Kongju National University, 182 Shinkwan-dong, Gongju, Chungnam 314-701, Republic of Korea

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ABSTRACT

A novel *S,S′*-diallyl carbohydrazonodithioate derivative **3** of rhodamine B hydrazone was developed as a chemodosimeter for selective detection of mercury ions based on Hg^{2+} promoted cyclization. The allyl groups of **3** play a key role in the binding and selection of Hg^{2+} ions. The probe responds selectively to Hg^{2+} over various other competitive cations with marked chromo- and fluorogenic changes. The formation of stable oxadiazole derivative **8** was a strong driving force for this high selectivity. Practically, this probe is more promising because of the remarkable high selectivity, faster response, low detection limit, and aqueous solubility of **3**.

Introduction

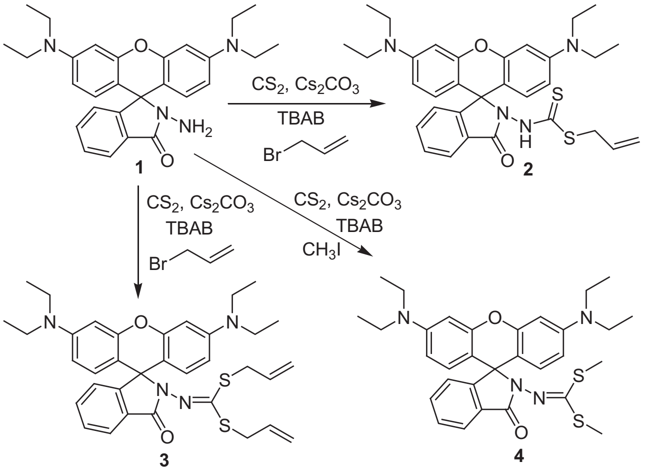
Recently, considerable attention has been focused on fluorescent chemosensors for selective and rapid detection of toxic heavy metal ions. The Hg^{2+} ion is an especially important target due to its high affinity to the thiol group in proteins, causing many health problems.[1] Several fluorescent chemosensors have been reported for selective detection of Hg^{2+} ions.[2–4] Fluorescent chemodosimeters have become a focus of recent research compared to well-developed fluorescent sensors.[5] This alternative approach involves the use of highly selective and specific chemical reaction between the dosimeter molecules and the target.

Several fluorescent chemodosimeters have been employed for the selective detection of Hg^{2+} ions based on the strong thiophilic nature of Hg^{2+} ion.[6] However, several significant challenges still exist, such as elevated temperatures, long reaction time, the need for excess quantities of Hg^{2+}, and cross sensitivities toward other less thiophilic metal ions, such as Ag^{+} and Pb^{2+}. Accordingly, there is a need for new optimal chemodosimeters for Hg^{2+} detection, which must have fast response time at ambient temperature and the ability to detect Hg^{2+} selectively at parts per billion levels in aqueous media.

In this Letter, we report a rhodamine B derivative containing an *S,S′*-diallyl carbohydrazonodithioate group as a simple and novel chemodosimeter for Hg^{2+} ion, which can give a highly selective and rapid spectroscopic response to mercury ions.

Result and discussions

Mercury ions have a strong ability to bind to sulfur atoms, and they can also bind to a double bond as a Lewis acid. Initially, based on these binding abilities of Hg^{2+}, we tried to synthesize an allyl dithiocarbazate derivative **2** of rhodamine B as shown in Scheme 1. The reaction was carried out by a one-step three-component coupling reaction with rhodamine B hydrazide **1**, carbon disulfide, and allyl bromide in the presence of cesium carbonate (Cs_2CO_3) and



Scheme 1. Synthetic route of rhodamine B derivatives **3** and **4**.

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* Corresponding author. Tel.: +82 41 850 8498; fax: +82 41 856 8613.
E-mail address: ishong@kongju.ac.kr (I.S. Hong).

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tetrabutylammonium bromide (TBAB). However, the *S*,*S*′-diallyl carbohydrazonodithioate derivative **3** was formed dominantly instead of mono alkylated derivative **2**. Even though the equivalent of allyl bromide was adjusted to 0.5 equiv of rhodamine B hydrazide, mono-alkylated product was still not detected. That might be due to the highly nucleophilic character of sulfur atom.

The presence of two allyl groups in **3** was confirmed by ^{1}H NMR, ^{13}C NMR, and HR-Mass. To clarify the exact structure of **3**, single crystals of compound **3** were grown from acetone/petroleum ether as white needles. The crystal structure of **3** clearly showed two allyl groups bound to the sulfur atoms, the double bond character of the C29–N4 bond and five-membered spiro-lactam ring (Fig. 4a). Additionally, as a control compound, the *S*,*S*′-dimethyl carbohydrazonodithioate derivative **4** was prepared by the same method using a methyl iodide to examine the role of double bond. Both compounds **3** and **4** displayed a colorless solution and emitted no fluorescence. When compound **3** was mixed with mercury ions, the color of solution was immediately changed to pink, and the solution emitted the strong fluorescence. Interestingly, the solution of **4** incubated with Hg^{2+} did not change color and did not emit any fluorescence.

Figure 1 shows the spectral variation of **3** upon gradual addition of mercury ions. As expected, **3** itself displays a colorless solution and emits no fluorescence, indicating that it predominantly exists in spirocyclic form. With increasing concentrations of the Hg^{2+} ions, a new emissive peak centered at 576.5 nm appeared with increasing fluorescence intensity (Fig. 1a).

Figure 1b shows the absorbance titrations, which were carried out using 20 μM of **3** with varied concentration of Hg^{2+}. There was also a new absorption band centered at 570 nm which appeared with increasing absorbance intensity and, was consistent with the fluorescence spectra results. The increase in absorption and fluorescence intensity after addition of more than one equivalent of Hg^{2+} suggests that there is no 1:1 stoichiometry between **3** and Hg^{2+} ions. Moreover, *S*,*S*′-dimethyl carbohydrazonodithioate derivative **4**, in which the allyl groups were replaced with the two methyl groups, did not show any absorbance and fluorescence response toward Hg^{2+} ions.

To assess the specificity of this chemodosimeter, various ions, including heavy metal ions, were examined in parallel under the same condition. As shown in Figure 2a and b, the reaction of **3** with Hg^{2+} produces both strong fluorescence and absorbance responses; whereas other metal ions do not show this behavior.[7] Therefore, it can be concluded that **3** displays an extremely high selectivity for Hg^{2+} ion only against the other metal ions examined. Tae et al. also reported a similar rhodamine-based probe,[2e] which can selectively detect mercury ions. However, in addition to Hg^{2+}, Tae's probe showed some sensitivity toward other less thiophilic cations, for example, Ag^+ and Zn^{2+}. Our probe doesnot show any sensitivities toward other 16 metal cations showed in Figure 2 except Hg^{2+}. This unique property enables Hg^{2+} to be directly detected by the naked eye. However, dimethyl derivative **4** did not show any color change in the presence of mercury ions (Fig. 2c).

Furthermore, the time dependence response of **3** to Hg^{2+} ions revealed that the reaction of **3** with one equivalent Hg^{2+} started immediately, as there was a sudden change in fluorescence intensity, and completed within ⩽1 min. The fluorescence intensity was saturated after 10 min.[8]

Next, ^{1}H NMR titration of **3** with Hg^{2+} was conducted to elucidate the binding mode. As shown in Figure 3, new sets of peaks appeared after the addition of Hg^{2+}. The olefinic protons and allylic protons of two allyl groups displayed new peaks in the downfield, which suggested that Hg^{2+} initially bound to the allyl group of **3**.

Moreover, ^{1}H NMR titration of **4** with mercury ions showed no change of any chemical shifts (Fig. 3d), which is consistent with the results of no fluorescence response toward Hg^{2+} and other various

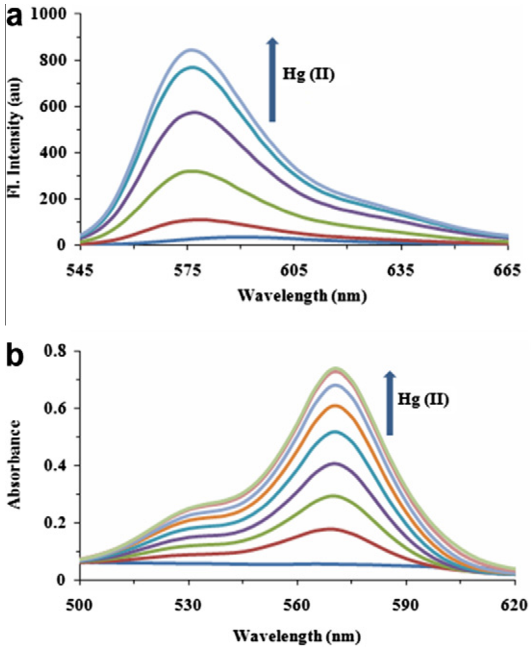


Figure 1. (a) Fluorescence (λ_{ex} = 530 nm) titration spectra of **3** (1 μM) with [Hg^{2+}] from 0, 0.4, 1.0, 1.4, 2.0, and 2.4 μM (water/ethanol:80/20(v/v)). (b) UV–vis absorption titration spectra of **3** (20 μM with Hg^{2+} from 0, 20, 39.2, 57.7, 75.5, 92.6, 109.1, 125, and 140.4 μM.

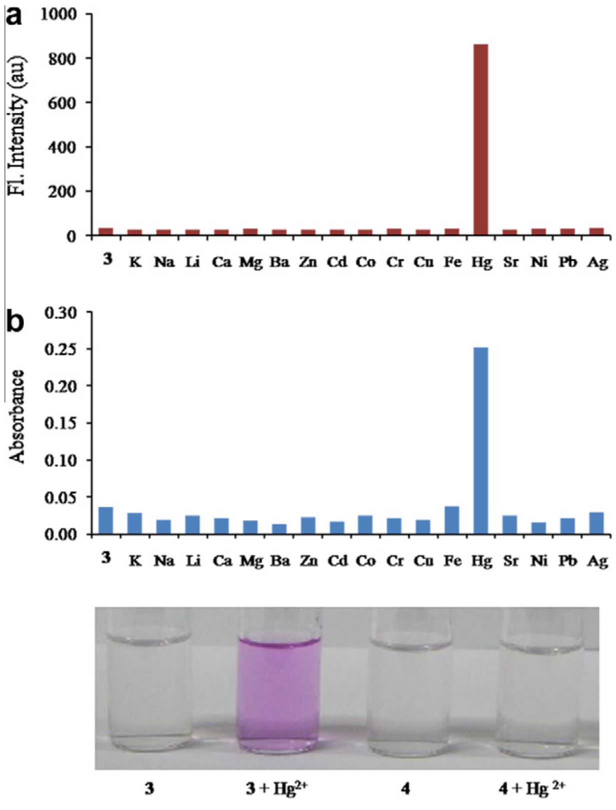


Figure 2. (a) Fluorescence response of **3** (5 μM) with 5 μM of all metal ions (λ_{em} = 576.5 nm, λ_{ex} = 530 nm). (b) Absorbance (570 nm) of **3** (20 μM) with various metal ions species (20 μM). Metal ions examined; K^+, Na^+, Li^+, Ca^{2+}, Mg^{2+}, Ba^{2+}, Zn^{2+}, Cd^{2+}, Co^{2+}, Cr^{3+}, Cu^{2+}, Fe^{2+}, Hg^{2+}, Sr^{2+}, Ni^{2+}, Pb^{2+}, and Ag^+. (c) Color changes after addition of Hg^{2+} to probe **3** and **4** ([probe] = [Hg^{2+}] = 20 μM).

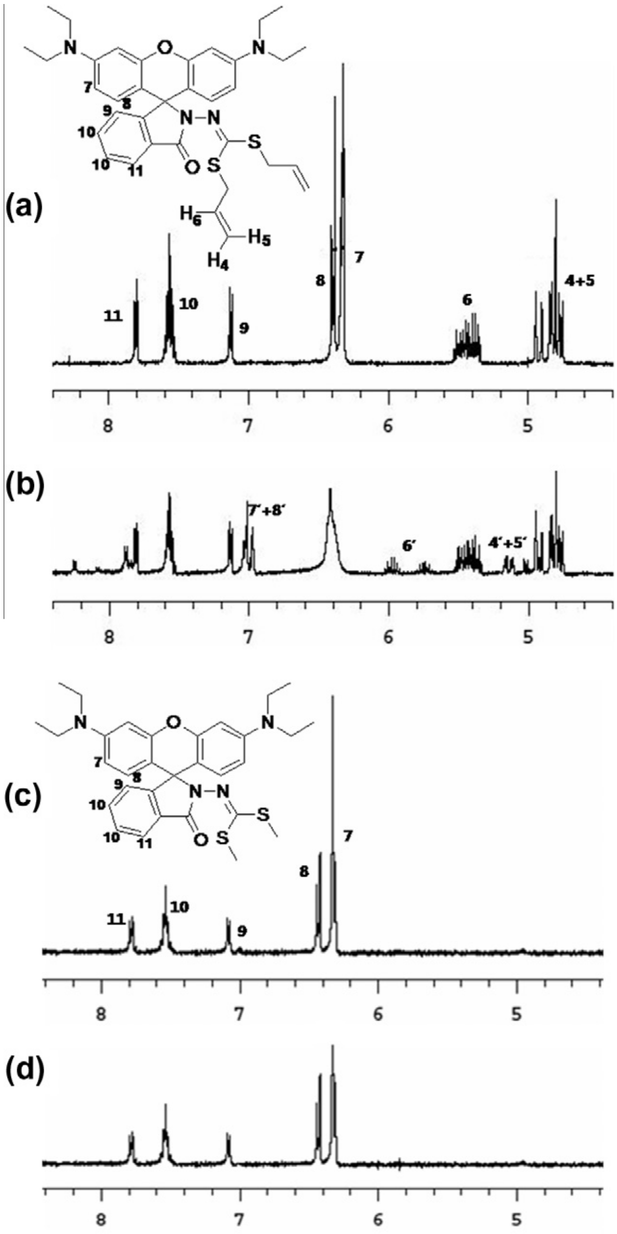


Figure 3. ^{1}H NMR titration of **3** and **4** with Hg^{2+} ions (DMSO-d_6). (a) **3** only (b) **3** with 1 equiv of Hg^{2+} (c) **4** only (d) **4** with 1 equiv of Hg^{2+}. Upper dashes indicate newly appeared peaks after addition of mercury ions.

metal ions. These results suggest that the allyl groups in **3** play a key role in the initial Hg^{2+} binding. An early study by Shin et al. showed Hg^{2+} initially binds to oxygen and sulfur and promotes cyclization of thiosemicarbazide to 1,3,4-oxadiazole.[9] However, in our case, the fact that allyl groups in **3** play a key role in the initial binding is further confirmed by ^{1}H NMR titration of **4** with mercury ions, which showed no change of any chemical shifts. Unlike compound **4**, there were significant changes in the NMR signals of compound **3**, in both the xanthene hydrogens and *N*,*N*-diethyl groups. Downfield shifts of both the methylene and methyl signals in *N*,*N*-diethyl group of **3** clearly suggest that Hg^{2+} induced the formation of delocalized xanthene moiety of the rhodamine B. Most noticeably, there was broadening and downfield shifts of xanthene protons around 6.4 ppm. We conclude that this broadening is due to slow exchange between the complexed spirolactam ring opened form and free **3**.

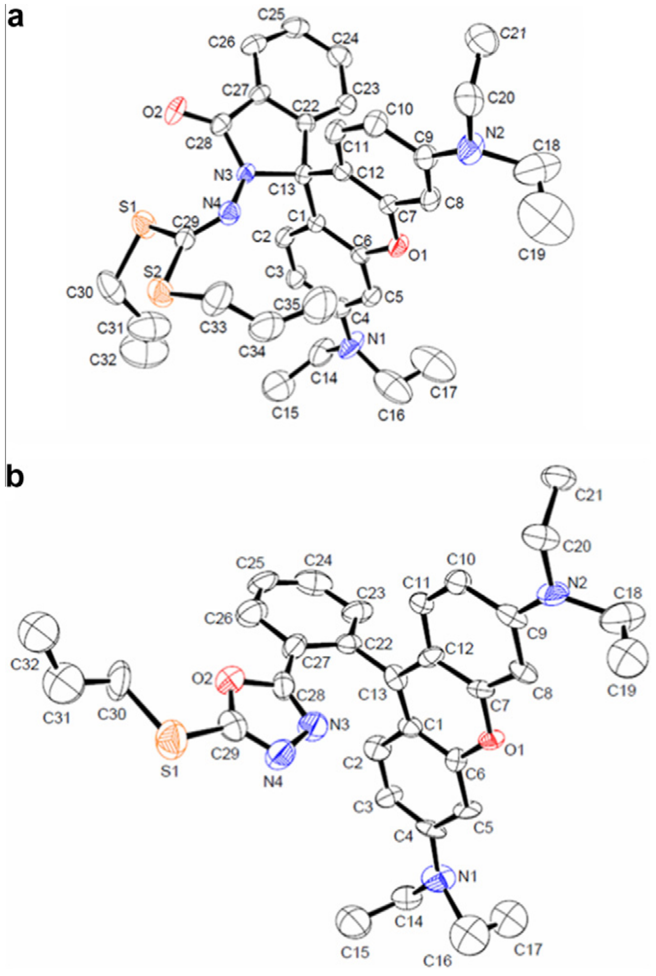
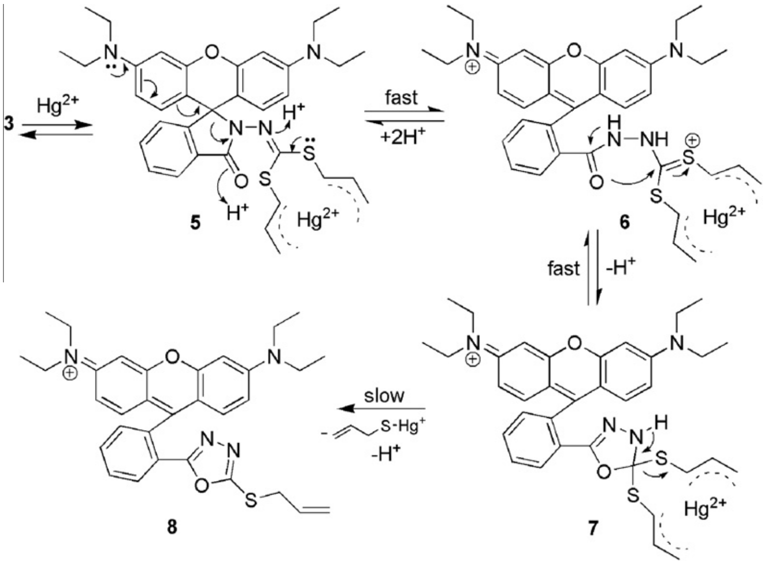


Figure 4. (a) Crystal structure of **3** (b) Crystal structure of **8** with displacement atomic ellipsoids drawn at the 30% probability level. All hydrogen atoms are omitted for clarity.

Figure 3b shows the peaks of free **3** as well as those of Hg^{2+}-bound **5**/**6**/**7**. This means that there are equilibriums between **3** and mercury ions. As shown in Scheme 2, the mercury-bound derivative **5** was quickly converted to the spiro-lactam ring opened **6**, which emitted the strong fluorescence. Then, intramolecular cyclization of **6** generated intermediate **7**, which was slowly transformed to the stable oxadiazole derivative **8**. The lack of further increase of fluorescence after initial emission and gradual increase of fluorescence in increasing concentration of Hg^{2+} ions strongly indicate there were fast equilibriums between **5**, **6** and **7**. The equilibriums between **3**, **5**, **6** and **7** were further confirmed by treatment of KI,[3e] which caused immediate disappearance of the color and the fluorescence. The color and fluorescence of the solution were restored after treatment of the excess amounts of Hg^{2+} ions (data were not shown.)

Finally, a stable cyclic 2-allylthio-1,3,4-oxadiazole derivative **8** was formed through removal of *S*-allyl-Hg^+ group. The structure of the stable 2-allylthio-1,3,4-oxadiazole **8** was also confirmed by X-ray crystallography analysis.[10] Figure 4b clearly showed the formation of an oxdiazole ring with opened spirolactam ring and no additional bound mercury ions. To the best of our knowledge, this is the first case reporting the crystal structure of 1,3,4-oxadiazole based rhodamine B derivative.

For practical applicability, the proper pH condition of this new chemodosimeter was also evaluated. The ring opening of free rhodamine B derivative **3** took place spontaneously under acid



Scheme 2. Proposed mechanisms for the production of 2-allythiol-1,3,4-oxadiazole derivative of rhodamine B.

conditions (pH <5) because of the strong protonation. When the pH of the solution was over 5, no significant ring opening of **3** was observed. However, in the presence of the Hg^{2+} ions, there was an obvious fluorescence OFF–ON change between pH 5 and 9.[8] Thus, chemodosimeter **3** can detect Hg^{2+} ions over a wide pH range from 5 to 9. This property of chemodosimeter **3** suggests that no buffer solutions are required for the detection of Hg^{2+} ion, which is convenient for practical application.

Moreover, to assess the possibility of detecting Hg^{2+} at a low concentration, fluorescence titrations were conducted with 15 μM of **3**. The fluorescence intensity was found to increase with the Hg^{2+} concentration in the range from 4 to 61 ppb.[8] From this titration experiment, the detection limit of this chemodosimeter system was estimated to be about 4 ppb, which is comparable to those of some previously reported highly sensitive sensors.

Conclusion

In summary, we devised a ratiometric fluorescent probe **3** for mercury species based on Hg^{2+} promoted cyclization. We showed that the allyl groups of **3** play a key role in the binding and selection of mercury ions. The good features of this system, such as remarkably high selectivity toward Hg^{2+} ions over miscellaneous competitive cations, quick response ($\leqslant$1 min), aqueous solubility, the limit of quantification (about 4 ppb), and a wide pH range from 5 to 9, make it promising to determine Hg^{2+} ions in aqueous solution for practical analysis.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.03.040.

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7. As a reviewer suggested, the reactivity of **3** toward Pd^{2+} and Pt^{2+} was examined to check the formation of allyl-metal complex. Pt^{2+} ions showed no activity to bind to **3**. However, the solution of **3** and Pd^{2+} showed color change and emitted strong fluorescence similar to Hg^{2+} ions. This supports further formation of allyl–metal complex.
8. See Supplementary data.
9. Ko, S. K.; Yang, Y. K.; Tae, J.; Shin, I. *J. Am. Chem. Soc.* **2006**, *128*, 14150.
10. Crystallographic data (excluding structure factors) for structures **3** and **8** in this Letter have been deposited with the Cambridge crystallographic data centre as supplementary publications Nos. CCDC-860194 and 860195, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, [fax: +44 (0)1223 336033 or email: deposit@ccdc.cam.ac.uk].