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Fluorescent coumarinyldithiane as a selective chemodosimeter for mercury(II) ion in aqueous solution

Ja Hyung Kim [a], Hyun Jung Kim [a], Sang Hoon Kim [a], Jae Hong Lee [a], Jung Ho Do [b], Hae-Jo Kim [b,*], Joung Hae Lee [c], Jong Seung Kim [a,*]

[a] Department of Chemistry, Korea University, Seoul 136-701, Republic of Korea
[b] Department of Chemistry, Kyonggi University, Suwon 443-760, Republic of Korea
[c] Korea Research Institute of Standards and Science, Taejon 305-600, Republic of Korea

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ABSTRACT

A coumarin-based dithiane (**1**) was synthesized for the selective detection of Hg^{2+} with respect to dual chromo- and fluorogenic changing events in an aqueous solution by the mercury-promoted transformation of a dithiane group into an aldehyde functional unit. The Hg^{2+}-selective response of the chemodosimeter was clearly observed in aqueous buffer as well as in human blood plasma medium.

Chemical sensors for heavy metals such as mercury, cadmium, and lead are of growing interest due to their bioaccumulation, biomagnification, and persistence in the environment.[1] In particular, mercury ion detection by optical probes is a rapidly growing area owing to its strong toxicity within the human body.[2a] Mercuric salts exist in many industrial materials such as electrical equipment, catalysts, paints, and mining byproducts that produce high concentrations of mercury pollutants. When ingested by humans, methylmercury triggers several serious disorders stemming from sensory, motor, and neurological damages.[2b] For example, when ingested by a pregnant woman, methylmercury readily crosses the placenta and targets the developing fetal brain and central nervous system, potentially causing developmental delays in the child.[2c,d] Accordingly, it is exigent to provide analytical methods for the sensitive and selective detection of the mercury ion.

Recently, a number of chemical sensors were developed as potent luminescent probes. A particularly attractive alternative is the use of chemodosimeter as a chemical sensor through a specific chemical reaction between a dosimeter molecule and target species, leading to the formation of a fluorescent or colored product.[3] One of the equally attractive approaches in this field involves the use of highly selective reactions (usually irreversible) induced by target analytes, in which an accumulative effect is directly related to analyte concentration. As an approach of the chemodosimeters toward the Hg^{2+} ion, desulfurization of a thioacetal can be taken into account. To date, a variety of desulfurization methods have been devised by using heavy or transition metal salts with additives, such as Ag^+/NBS or NCS,[4] $AgNO_3/I_2$,[4d] $CuCl_2/CuO$,[5,6] HgO/$Et_2O{\cdot}BF_3$,[7] and $Hg(ClO_4)_2/CaCO_3$.[8] Notably, desulfurization of the thioacetal can also occur with $HgCl_2/HgO/LiBF_4$ under reflux in aqueous MeCN.[6] Although these efforts have improved chemodosimetric functionality toward the Hg^{2+} ion, their application toward biological samples have been hampered by poor chemodosimeter solubility in water and modest sensitivity, as well as their short wavelength absorption and low quantum yield.

To further application in the environmental and biological fields, we have focused on the synthesis of a new thioacetal derivative of thioacetalized coumarin (**1**) and investigated its chemodosimetric properties to provide sensitive detection of the Hg^{2+} ion in viewpoint of color and fluorescence changes in an aqueous environment. In addition, to the best of our knowledge, the desulfurization of a thioacetal was rarely successful under mild and environment-friendly conditions (aqueous media and room temperature), both prerequisites for a chemodosimetric sensing system. Thus, herein the chemodosimetric behavior of **1** toward the Hg^{2+} ion with respect to fluorescence and color changes, in addition to the mechanistic study of the transformation of coumarinyl thioacetal (**1**) to coumarinaldehyde (**2**) under mild conditions and without any catalyst is reported.

Compound **2** was synthesized from 4-(diethylamino)salicylaldehyde in two steps according to a literature procedure.[9]

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* Corresponding authors. Tel.: +82 2 3290 3143; fax: +82 2 3290 3121.
E-mail addresses: haejkim@kgu.ac.kr (H.-J. Kim), jongskim@korea.ac.kr (J.S. Kim).

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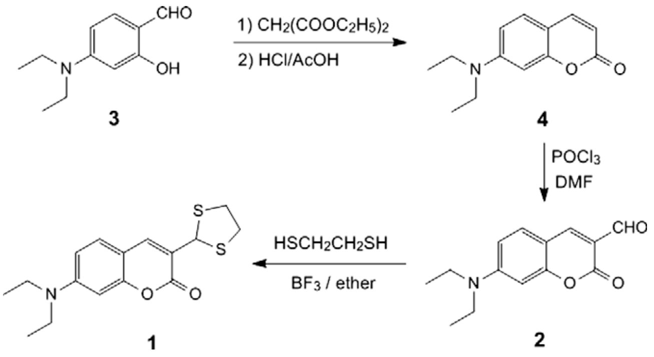
Subsequently, **1** could be prepared from the reaction of **2** with 1,2-ethanedithiol in the presence of $Et_2O{\cdot}BF_3$ in diethyl ether (Scheme 1). The molecular structure of **1** was clearly characterized by its ^{1}H- and ^{13}C NMR, mass spectra, infrared spectra, and X-ray single crystal structure analysis (Fig. 1). All details concerning the crystal structure are in Supplementary data.

Figure 2 shows that the absorption band of **1** in the UV–vis spectrum originally appears at 393 nm ($\varepsilon = 3.6 \times 10^4\ M^{-1}cm^{-1}$) in a solution of 30:70 MeOH/H_2O. As soon as the Hg^{2+} ion was added at room temperature, the absorption maximum of **1** at 393 nm decreases gradually whereas a new absorption maximum at 443 nm ($\varepsilon = 5.1 \times 10^4\ M^{-1}cm^{-1}$) increases with an isosbestic point at 410 nm. The shift in the absorption band reached a maximum within 10 min, indicative of a rapid desulfurization of **1** (Fig. S1).

Excess metal ion salts (50 equiv, chlorides as counteranions) of Li^+, Na^+, K^+, Ag^+, Cs^+, Mg^{2+}, Ca^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Sr^{2+}, Cd^{2+}, Ba^{2+}, Hg^{2+}, and Pb^{2+} (total of 17) were tested to investigate selectivity. Only the Hg^{2+} ion promoted a bathochromic shift in the UV–vis absorbance from 393 to 443 nm, while other metal ions did not cause any significant changes under identical conditions (Fig. 3a). Figure 3b shows the absorption spectra of **1**, **2**, and **1** + Hg^{2+}, respectively. The absorption spectra of **2** and **1**+Hg^{2+} are nearly identical, indicating that desulfurization of **1** by Hg^{2+} ions affords **2** with a short reaction time.

The selectivity of probe **1** for the Hg^{2+} ion was also observed by fluorescence measurements. The fluorescence intensity of **1** at λ_{em} 481 nm (λ_{ex} 393 nm) decreased significantly upon the addition of 10 equiv of Hg^{2+} ion to **1** (2.0 μM) in aqueous methanol (30:70 methanol/water (v/v), 50 mM HEPES at pH 7.4), as shown in Figure S2.

The results of cation competitive experiments are also depicted in Figure S3. The selectivity and sensitivity of **1** toward Hg^{2+} were not influenced by biologically active metal ions such as highly concentrated Na^+, K^+, Ca^{2+}, and Mg^{2+} (100 equiv). Compound **1** retained a high Hg^{2+}-selective chemodosimetric response, even under polluted conditions containing heavy and transition metal cations such as Mn^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+} (Fig. S3). The selectivity factor, defined as F_0/F, for the Hg^{2+} ion was also calculated to give 4.5, while the factors for other metals were less than 1.1 (Fig. 4). Moreover, **1** can give a response to Hg^{2+} in the



Scheme 1. Synthetic scheme of **1**.

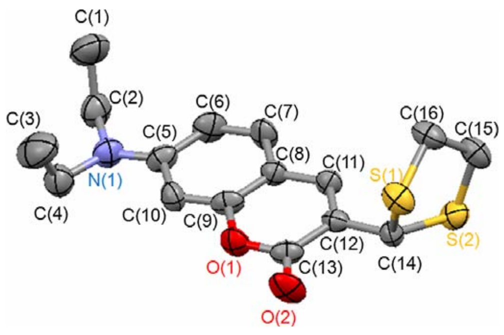


Figure 1. Crystallographic representation of probe **1**.

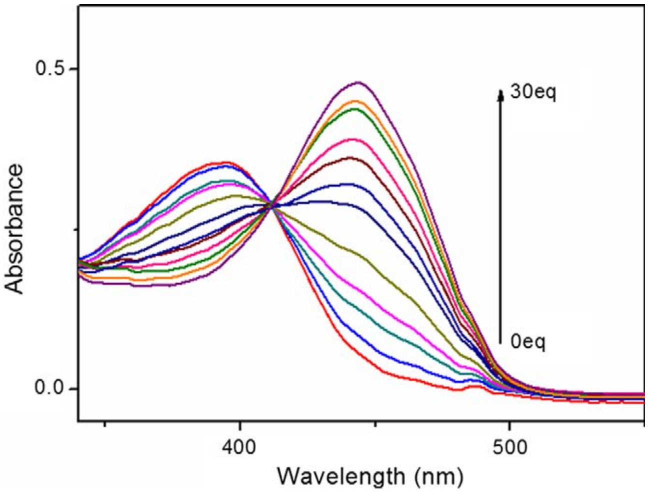


Figure 2. Absorption spectra of **1** (10.0 μM) at different concentrations of Hg^{2+} in 30:70 MeOH/H_2O.

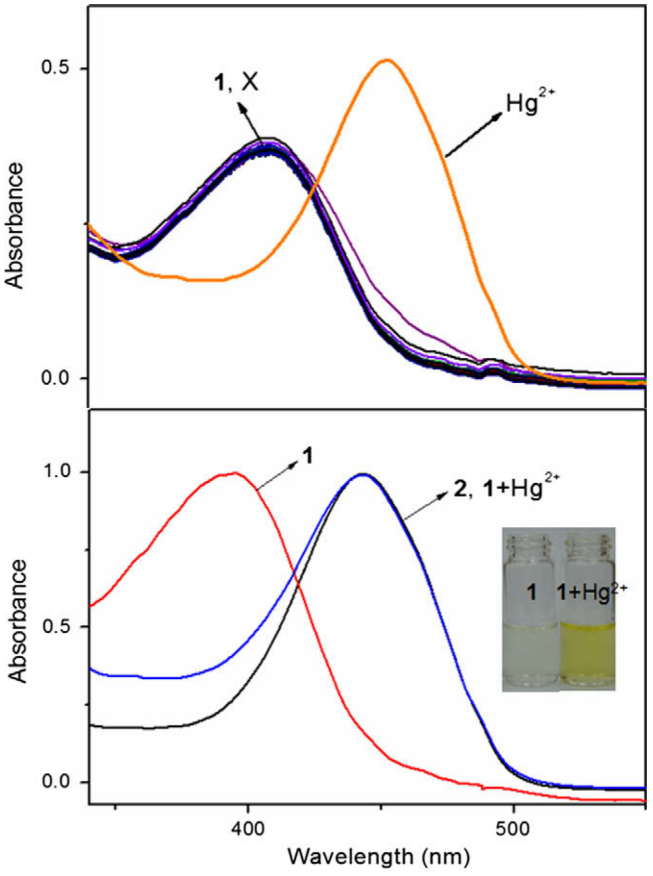


Figure 3. (a) Absorption spectra of **1** (10.0 μM) upon the addition of Li^+, Na^+, K^+, Ag^+, Cs^+, Mg^{2+}, Ca^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Sr^{2+}, Cd^{2+}, Ba^{2+}, Hg^{2+}, and Pb^{2+} (50 equiv, respectively) in 30:70 MeOH/H_2O. (b) Normalized absorption spectra of **1** (red), **2** (black), and **1**+30 equiv of Hg^{2+} (blue).

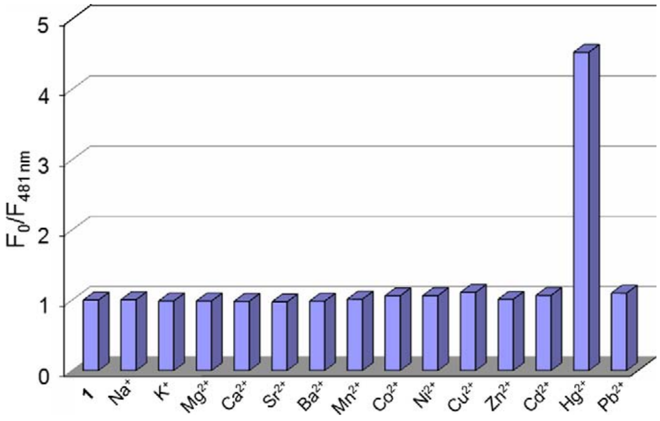


Figure 4. Selectivity of **1** (2.0 μM) with different metals (100 equiv, except 10 equiv Hg^{2+}) in 30:70 MeOH/H_2O (50 mM HEPES at pH 7.4), where F_0 is an initial fluorescence intensity of **1** at λ_{em} 481 nm (λ_{ex} 393 nm) and F is the intensity after the addition of each metal.

'naked-eye' manner (inset of Fig. 3b). For the Hg^{2+}-induced chemodosimetric mechanism, the reactivity of **1** toward other thiophilic metal cations (Cu^{2+} and Ag^+) was also investigated by measuring fluorescence intensities centered at 481 nm; no fluorescence changes occurred in **1**.

The fluorescence responses of **1** to metal ions were also detectable by using a fluorescence microscope (λ_{ex} band 330–385 nm, λ_{em} 400 nm). The obvious fluorescence decrease was prominently observed exclusively for the Hg^{2+} ion. Most other metal ions did not induce the significant fluorescence change in **1** (Fig. 5).

To examine the sensitivity of **1** for Hg^{2+} ion sensing, its fluorescence intensity versus [Hg^{2+}] was plotted (Fig. 6). Upon variation of the Hg^{2+} ion concentration from 4.0 to 200 μM, it was found that the addition of, at most, 10 μM Hg^{2+} ions, completely quenched the fluorescence of **1** (2.0 μM) in buffered aqueous methanol (30:70 methanol/water, 50 mM HEPES at pH 7.4) (Fig. 6). The sensitivity curve is indicative of less than 2.0 ppm of Hg^{2+} ion detectable. This indicates that probe **1** can be utilized in the analysis of micromolar concentrations of Hg^{2+} ions present in water and enables its application in fish assays and drinking water for safe human consumption.[10]

To gain a deeper insight into the possible utility of **1** as a Hg^{2+} chemodosimeter, Hg^{2+} was added to samples of deproteinized human blood plasma containing **1**. Almost immediately, the UV–vis absorbance of **1** bathochromically shifted and the fluorescence intensity decreased, which is in good accordance with those tested in the absence of blood plasma (Fig. S5).

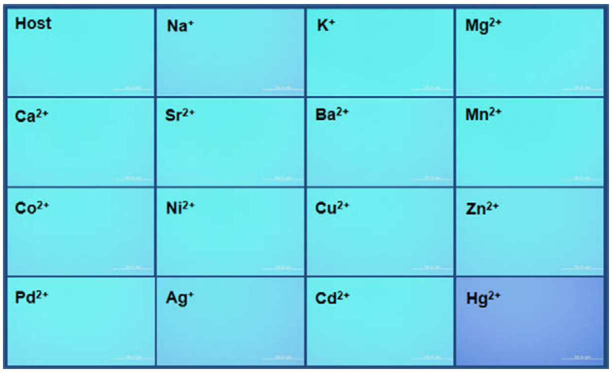


Figure 5. Fluorescence microscopic images of **1** (30 μM, 50 mM HEPES at pH 7.4) in the presence of various metals (each in 100 equiv). λ_{ex} band 330–385 nm, λ_{em} 400 nm, scale bar 50 μm.

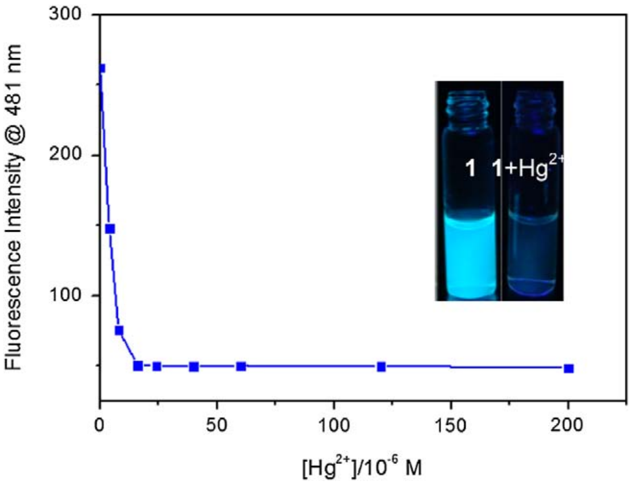


Figure 6. Mercuric ion sensitivity of **1** (2.0 μM) in 30:70 MeOH/H_2O (50 mM HEPES at pH 7.4). λ_{ex} 393 nm and λ_{em} 481 nm.

Changes in ^1H NMR spectroscopic and mass spectrometric analyses also enabled confirmation of the transformation of **1** into **2** in the presence of Hg^{2+} at room temperature. Upon the addition of Hg^{2+} (3.0 equiv) into **1** in a 50:50 CD_3CN:D_2O, the 1,3-dithiane methine proton at δ 5.92 ppm disappeared with a concomitant appearance of a new peak at δ 10.13 ppm, assignable to the corresponding aldehyde proton of **2**. The ^1H NMR spectrum of **1**+Hg^{2+} was identical to that of the standard, **2** (Fig. S6). In addition, the mass spectrum of the isolated product from the reaction was the same as that of **2**, demonstrating that **1** was, indeed, transformed into **2** by Hg^{2+} ions.

To address the possibility of interference from other chelating chemicals for the Hg^{2+} ion-mediated desulfurization of **1**, EDTA was added to the **1**–Hg^{2+} solution. The resulting red-shifted absorption bands of **1** caused by Hg^{2+} showed no absorption changes upon the addition of highly concentrated EDTA (10 mM), demonstrating that unlike other chemosensors, chemodosimeter **1** proceeds by an irreversible chemical reaction upon the addition of Hg^{2+} (Fig. S4).

From the results observed, the authors propose a Hg^{2+}-promoted desulfurization mechanism. The coordination of $HgCl_2$ with the sulfur atom, due to the thiophilicity of the mercuric ion, activates the carbon atom of the thioacetal that is then hydrolyzed by water to afford the corresponding aldehyde unit (Scheme S1).

In summary, a water-soluble coumarin derivative (**1**) capable of chemodosimetric Hg^{2+} ion detection was synthesized. Not only color changes and UV–vis changes, but also fluorescence changes of **1** were eminently shown upon the addition of Hg^{2+}, from which chemodosimeter **1** exclusively detected the Hg^{2+} ion with a 2 ppm detection limit within less than a reaction time of 1 min. Compound **1** exhibited a high selectivity toward Hg^{2+} that was unimpeded by the presence of other metal ions. Chemodosimeter **1** and its selective and sensitive Hg^{2+} detection in aqueous systems give a potential guideline in biological and environmental application-oriented chemodosimeter research.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.08.045.

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10. U.S. EPA, Regulatory Impact Analysis of the Clean Air Mercury Rule: *EPA-452/R-05-003*, 2005.*Preparation of (**1**)*: To a solution of 500 mg (3.0 mmol) of **2** in 5.0 mL of ethyl ether were added dropwise 505 µL (6.0 mmol) of ethanedithiol and 184 µL (1.5 mmol) of boron trifluoride etherate for 24 h at room temperature and then evaporated in vacuo. The resulting solid was dissolved in CH_2Cl_2, and the organic layer was washed three times with water, dried over anhydrous $MgSO_4$, filtered, evaporated, and recrystallized from *n*-hexane to give 250 mg (yellow solid, 38%) of **1**. Mp: 116–118 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.91 (s, 1H, Ar*H*), 7.28 (s, 1H, Ar*H*), 6.59–6.55 (dd, 1H, Ar*H*, $J = 2.53$ Hz, 8.78 Hz), 6.49–6.48 (d, 1H, Ar*H*, $J = 2.49$ Hz), 5.73 (s, 1H, C*H*), 3.44–3.37 (q, 4H, CH_2CH_3, $J = 7.09$ Hz), 3.32 (s, 4H, SCH_2CH_2S), 1.22–1.17 (t, 6H, CH_2CH_3, $J = 7.05$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): 155.4, 139.3, 129.2, 121.7, 109.0, 97.2, 50.5, 45.0, 39.1, 12.6 ppm. FAB MS *m/z* (M^+): calcd, 321.09; found, 321.38 (**1**), 322.39 (**1**+H^+). IR $\nu = 2969$, 2926, 2356, 1706, 1606, 1528, 1421, 1363, 1271, 1235, 1185, 1135, 792 cm^{-1}.