



Hg²⁺-selective fluorogenic chemodosimeter based on naphthoflavone

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ABSTRACT

A new Hg²⁺-selective chemodosimeter based on α -naphthoflavone was investigated. The chemodosimetric behavior is based on the Hg²⁺-triggered desulfurization of flavothione into its oxygen analogue flavone. The signaling was effective in aqueous environment and the selective signaling was not affected in the presence of common physiologically and environmentally important metal ions.

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The development of selective signaling systems for Hg²⁺ ions has attracted interest in the chemosensing field because of the toxic nature of Hg²⁺ and the substantial impact of mercurials on the environment.¹ The human body is continually exposed to an increasing number of mercury sources, and the toxic impact of mercurials has been well documented. A number of sophisticated signaling systems have been developed to accommodate varying sample concentrations and origins of Hg²⁺-containing compounds.² A chemodosimetric approach frequently yields successful results in the selective and sensitive signaling of Hg²⁺ ions. Several Hg²⁺-selective systems based on versatile fluorophores such as rhodamine, fluorescein, anthracene, 1,8-naphthalimide, squaraine dye, and organopalladiums have been devised,³ beginning with the classical anthracene-based dosimeter⁴ developed by Czarnik et al. Other sophisticated chemodosimeter systems are based on sulfur-containing derivatives⁵ and employ desulfurization or subsequent transformation reactions of thioamide,⁶ thiourea,⁷ and thione.⁸ We have recently reported that the simple transformation of thio-coumarin to its desulfurized derivative can be used for efficient Hg²⁺-selective chemodosimeter system.⁹

Conversion of thiocarbonyl compounds into their carbonyl analogues has attracted the interest of synthetic organic chemists.¹⁰ These conversions include oxidative procedures that involve inorganic and organic reagents, as well as hydrolytic reactions.¹¹ For the hydrolysis of thiocarbonyl compounds, processes catalyzed by metal ions result in clean reactions because the metal ion acts as an electrophile for thiocarbonyl group sulfur, thus weakening the C=S bond.¹⁰ Among the frequently employed metal ions, Ag⁺, Au³⁺, Fe³⁺, Cu⁺, and Hg²⁺ are especially effective. For example, the desulfurization of thioesters proceeds rapidly using solutions of Hg²⁺ carboxylates in chloroform or pyridine.¹²

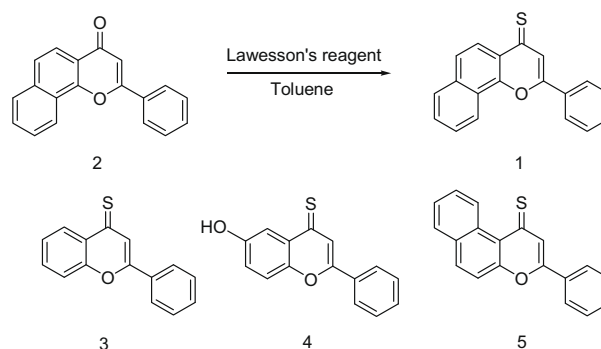
In this Letter we report a simple chemodosimeter system for selective Hg²⁺ signaling that is based on the Hg²⁺-induced transformation of flavothione into flavone. The photophysical properties of

flavones have been widely investigated and crowned flavone has been utilized as a fluorescent chemosensor for HSO₄⁻ or H₂PO₄⁻ ions.¹³ Naphthoflavothione showed a sensitive, Hg²⁺-selective signaling behavior in an aqueous environment.

Naphthoflavothione **1** was prepared from α -naphthoflavone **2** by reaction with Lawesson's reagent in good yield (Scheme 1).¹⁴ Thiocarbonyl derivatives **3–5** of other representative flavones, including β -naphthoflavone, were similarly prepared from their flavone precursors.

The UV–vis spectroscopic behavior of **1** toward representative metal ions was investigated by treating it with physiologically important alkali, alkaline earth, and transition metal perchlorates in aqueous 50% methanol solution. Flavothione **1** exhibited strong absorption bands at 370 and 400 nm. Upon interaction with various metal ions, significant changes in absorption spectra were observed particularly with Hg²⁺ and Cu²⁺ (Fig. S1). A concomitant chromogenic change from yellow to colorless was observed. Other metal ions caused relatively minor changes in the absorption spectra of **1**.

Fluorescence signaling of **1** was investigated in the presence of 100 equiv of representative metal perchlorates in the same solvent system. Generally, flavothiones are known to exhibit very weak



Scheme 1. Preparation of flavothione chemodosimeters.

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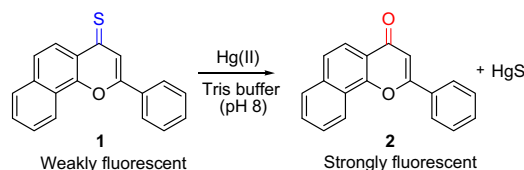
emission compared to their flavone analogues,¹⁵ and in fact, flavothione **1** exhibited a weak fluorescence centered around 440 nm, and a pronounced 'off-on' type signaling toward Hg²⁺ ions (Fig. 1). Upon interaction with various metal ions, the fluorescence intensity at 438 nm was markedly enhanced (45-fold) with Hg²⁺ ions, while other metal ions did not cause any noticeable responses (I/I_0 varied between 0.57 for Na⁺ and 1.79 for Cd²⁺) (Fig. S2).

The signaling mechanism is based on Hg²⁺-induced desulfurization of the thio derivative (Scheme 2). The thioether group of **1** is readily transformed to its ketone function by reaction with Hg²⁺ ions¹⁶ and the liberated sulfur atom forms a stable species of HgS with Hg²⁺ ions.¹⁷ As a result of this transformation, the weakly fluorescent flavothione **1** ($\Phi = 0.003$ in 50% aqueous methanol) is transformed into a strongly emitting naphthoflavone **2** ($\Phi = 0.107$).¹⁸

The proposed transformation was confirmed by ¹H NMR measurements. Upon treatment with 2 equiv of Hg²⁺ ions, the ¹H NMR spectrum of **1** was converted to that of **2** (Fig. 2). Among the changes, particularly, the significant shift for the resonance of 3-H proton from 8.06 to 7.21 ppm was noticeable. Fluorescence measurements also supported the conversion from flavothione to flavone (Fig. S3). The chemodosimetric nature of the signaling was further verified by testing reversibility of the **1**-Hg²⁺ system with EDTA treatment. The enhanced fluorescence of the **1**-Hg²⁺ system was not affected by treatment with EDTA, but in the presence of EDTA, the fluorescence of **1** was not enhanced upon addition of Hg²⁺ ions (Fig. S4). These observations demonstrated that the **1**-Hg²⁺ signaling system operates based on an irreversible chemodosimetric process.

Based on these results, the potential for general Hg²⁺ signaling by representative flavones was assessed. Neither the fluorescence of flavone nor that of 6-hydroxyflavone was sufficiently strong for an effective 'off-on'-type Hg²⁺-signaling system, using the same experimental conditions as used for **1**. In addition, β -naphthoflavone, which has a slightly different structure than the α -isomer and exhibited similar Hg²⁺-selective signaling behavior, also failed to exhibit sufficiently strong fluorescence compared to the α -isomer. Under the testing conditions, only α -naphthoflavone out of several typical flavones surveyed exhibited fluorescence strong enough for the construction of an efficient 'off-on' signaling of Hg²⁺ ions through transformation from the flavothione into the desulfurized flavone analogue (Fig. S5).

The effects of other common metal ions on the Hg²⁺ signaling of **1** were assessed under competitive conditions. The fluorescence increase was not significantly affected by the presence of other metal ions at 100 equiv, except for Cu²⁺ (Fig. 3). In the presence of Cu²⁺



Scheme 2. Off-on type Hg²⁺ signaling by desulfurization of **1**.

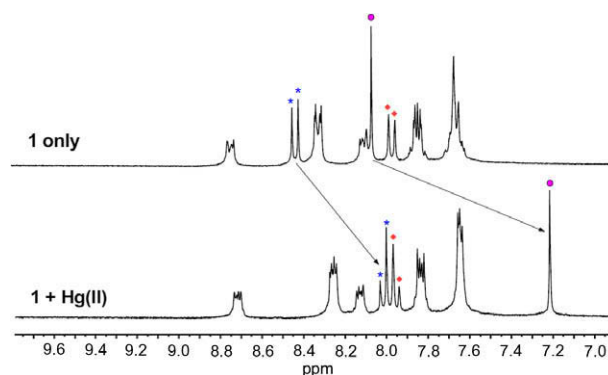


Figure 2. Partial ¹H NMR spectra of **1** in the absence and presence of Hg²⁺ ions in DMSO-*d*₆. [**1**] = 5.0 × 10⁻³ M, [Hg²⁺] = 1.0 × 10⁻² M.

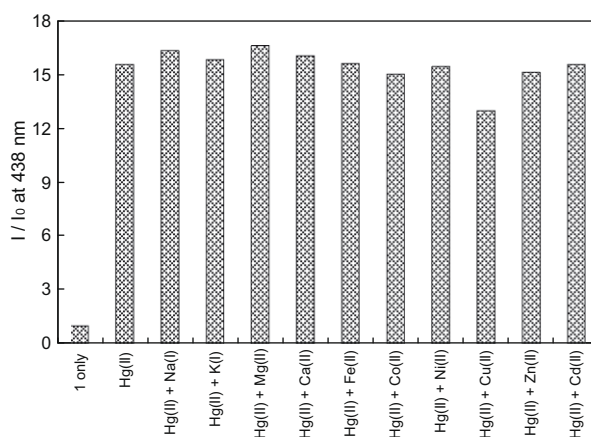


Figure 3. Fluorescence intensity ratio (I/I_0) at 438 nm of **1**-Hg²⁺ system in the presence of various metal ions. [**1**] = 5.0 × 10⁻⁶ M, [Hg²⁺] = 5.0 × 10⁻⁵ M. [Mⁿ⁺] = 5.0 × 10⁻⁴ M. λ_{ex} = 350 nm.

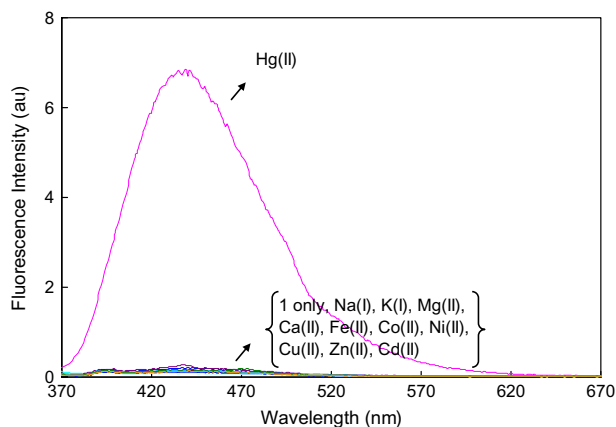


Figure 1. Changes in fluorescence spectra of **1** in the presence of various metal ions. In H₂O/CH₃OH (1:1) at pH 8.09 (10 mM tris buffer). [**1**] = 5.0 × 10⁻⁶ M, [Mⁿ⁺] = 5.0 × 10⁻⁴ M. λ_{ex} = 350 nm.

ions, the fluorescence increase was somewhat less effective, reaching 83% of the **1**-Hg²⁺ system. The decreased fluorescence might be due to the quenching nature of paramagnetic Cu²⁺ ions (Fig. S6). The observation indicated that Hg²⁺-selective signaling is retained in the presence of common physiologically and environmentally important metal ions, except for Cu²⁺ ions.

Fluorescence titration was carried out to gain quantitative insight into the signaling behavior of **1** toward Hg²⁺ ions. As the concentration of Hg²⁺ ions increased, the fluorescence intensity increased steadily without any shifts in emission maximum (Fig. 4). From the Hg²⁺ concentration dependency of the signaling behavior, the detection limit of **1** for the analysis of Hg²⁺ ions was estimated to be 1.6 × 10⁻⁶ M.

The Hg²⁺ signaling of **1** was relatively slow compared with that of other chemodosimeters based on sulfur derivatives. A time trace revealed that signaling was complete within about 30 min at 20 °C (Fig. 5). Although the signaling could be moderately hastened within 20 min at elevated temperature of 37 °C, these observations

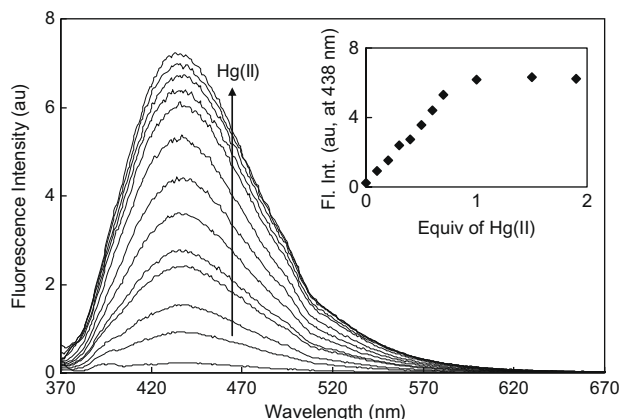


Figure 4. Fluorescence titration of **1** with Hg^{2+} ions. [**1**] = 1.0×10^{-5} M, $\text{H}_2\text{O}/\text{CH}_3\text{OH}$ (1:1) at pH 8.09 (10 mM tris buffer). $\lambda_{\text{ex}} = 350$ nm.

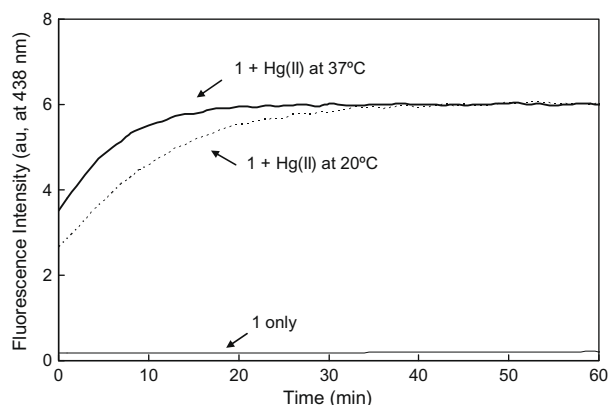


Figure 5. Time trace of the Hg^{2+} -signaling of **1**. [**1**] = 5.0×10^{-6} M, [Hg^{2+}] = 5.0×10^{-4} M. $\text{H}_2\text{O}/\text{CH}_3\text{OH}$ (1:1) at pH 8.09 (10 mM tris buffer). $\lambda_{\text{ex}} = 350$ nm.

are somewhat undesirable for a practical applicability of naphthoflavothione as a Hg^{2+} -selective chemodosimeter. On the other hand, flavothiones such as 3-hydroxyflavothione, which has a closely related structure to **1**, are known to be easily photodegraded.¹⁹ In the present case, the flavothione **1** was also found to be slowly decomposed; however, spontaneous decomposition of **1** itself under the same experimental conditions was rather slow and proceeded about 0.3% after 30 min and less than 2% even after 3 h from preparation. These observations suggest that the selective determination of Hg^{2+} ions by fluorescence enhancement could be practically feasible with flavothione **1**.

In summary, a simple Hg^{2+} -selective chemodosimetric system based on naphthoflavothione was investigated. The signaling is due to the Hg^{2+} -induced desulfurization of flavothione. The transformation induced Hg^{2+} -selective chromogenic and fluorogenic Hg^{2+} signaling behaviors of **1**. The Hg^{2+} -induced transformation from thioketone to ketone might be used for the construction of novel switching or signaling systems for Hg^{2+} ions.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.10.111.

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