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A ‘turn-on’ fluorescent probe that selectively responds to inorganic mercury species

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ABSTRACT

A fluorescent probe selectively senses inorganic mercury in the turn-on mode through a mercury ion-promoted hydrolysis reaction that leads to a coumarin, among various other metal species except Au(III).

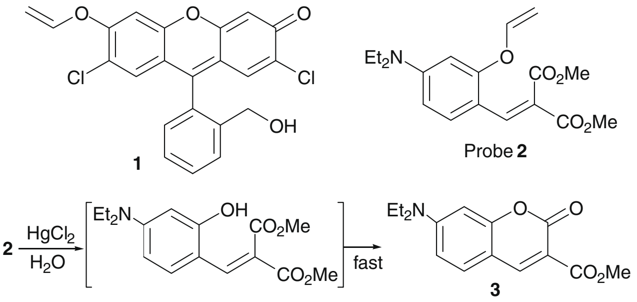
Mercury is a highly poisonous element and exists as elemental, inorganic, and organic mercury forms. Contaminated living species, soil, and water typically contain inorganic and organic mercury forms.[1]

Many fluorescent molecular probes for mercury ions have been developed recently.[2] Fluorescent probes provide easy and affordable detection methods, in addition to the typical instrumental methods such as atomic absorption or emission spectroscopy and ion-coupled plasma emission-mass spectrometry.[3] Fluorescent probes can be categorized to two types based on the sensing mechanism: one based on metal coordination and the other based on a chemical reaction.[2a] The reaction-based fluorescent sensing approach for inorganic mercury species has attracted sudden research interest recently, plausibly owing to the high selectivity obtainable.[2b,2h–m,2q–v,2y] Recently, we devised a novel reaction-based fluorescent probe that selectively detects methylmercury in addition to inorganic mercury among various metal species.[4] The sensing mechanism of the probe (vinyl ether **1** Scheme 1) is the mercury ion-promoted hydrolysis of the vinyl ether group, which is discriminated from those of most known probes that are based on the coordination of hetero-atom-based ligands (particularly sulfur) to mercury ions.[5]

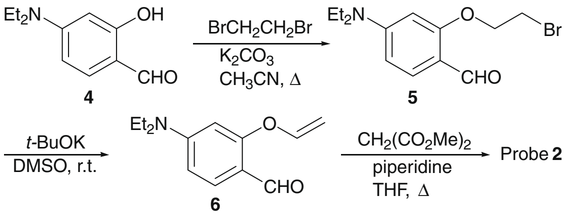
We have investigated other vinyl ether systems that may give a different selectivity pattern, such as the discrimination of methylmercury from inorganic mercury species or vice versa. Herein, we wish to report vinyl ether **2** that fluorescently senses only inorganic mercury, not methylmercury along with other metal species, in the turn-on mode.

Our rationale in the design of probe **2** is depicted in Scheme 1. The mercury ion-promoted hydrolysis of the vinyl ether group in **2** would generate the hydroxy intermediate, which will readily form coumarin **3**. Because vinyl ether **2** is almost nonfluorescent but coumarin **3** is highly fluorescent, we can realize a turn-on-type sensing. An additional feature of the sensing system is that the fluorescent compound **3** is a two-photon absorbing material. A similar sensing scheme, the deprotection–cyclization strategy, was used to detect fluoride ions by Swager and co-workers.[6]

Vinyl ether **2** was readily synthesized in three steps (overall 14% yield), starting from commercially available 4-(diethylamino)salicylaldehyde **4** (Scheme 2). We have found that introduction of the vinyl group, conversion of compounds **4** to **6**, can be significantly improved by using a conventional bromoethylation–elimination process (44% yield), compared with the previous copper-mediated coupling with toxic tetravinyltin (16% yield).[4]



Scheme 1. The reaction of probe **2** with HgCl$_2$.



Scheme 2. Synthesis of probe **2**.

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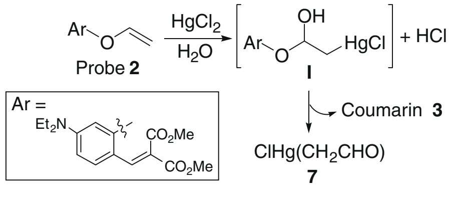
A solution of vinyl ether **2** in a PBS buffer (pH 7.4) containing 5% DMSO exhibited little fluorescence; however, upon treatment with $HgCl_2$ it became highly fluorescent as shown in Figure 1a. After the reaction, we were able to isolate and characterize the product **3**, which is responsible for the high fluorescence. Also, the hydrolysis process was confirmed by ^1H NNR titration. A time-dependent fluorescence measurement for a 1:1 mixture of vinyl ether **2** and $HgCl_2$ in the buffer solution at 25 °C showed that the fluorescence intensity reaches ~80% of the saturation after 50 min (Fig. 1a inset). Thus, the mercury ion-promoted hydrolysis of vinyl ether **2** is slower compared to the case of probe **1**. However, it is not necessary to wait the fluorescence saturation for the quantification purpose, as we can obtain a linear relationship between the concentration of mercury ions and the fluorescence intensity at an arbitrary time span.

Particularly, vinyl ether **2** does not respond to methylmercury under the reaction conditions (Fig. 1b), whereas vinyl ether **1** senses both methylmercury and inorganic mercury species.[4] This selectivity difference may be originated from the reactivity difference between **1** and **2**. The reactivity data suggest that, in the present case, the 'second' oxymercuration–hydrolysis reaction by the hydrolyzed alkylmercury species $HgCl(CH_2CHO)$ **7**, which occurs readily in the case of probe **1** (Scheme 3), seems to proceed slowly.

Fluorescence titrations of probe **2** with varying amounts of $HgCl_2$ (from 0 to 1.0 equiv) shows saturation in the emission intensity at the equivalent point (Fig. 1c), which also supports the above reasoning.

Probe **2** is specific toward mercury ions and shows essentially no response toward other metal ions (as the chloride salts) such



Scheme 3. Hydrolysis of probe **2** by $HgCl_2$.

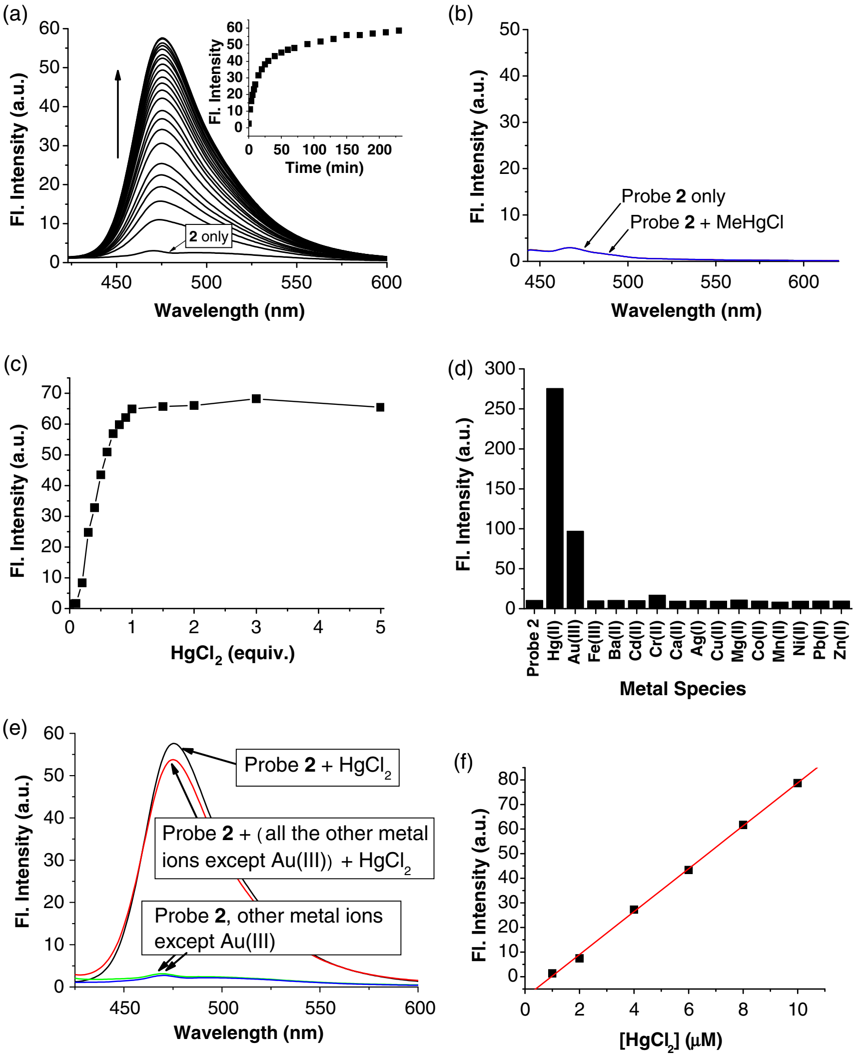


Figure 1. (a) Time-dependent fluorescence change acquired for a 1:1 mixture of probe **2** and $HgCl_2$. Inset: a plot of the fluorescence intensity change as a function of the reaction time. (b) Fluorescence change for probe **2** only and for a 1:1 mixture of probe **2** and MeHgCl, acquired after 1 h. (c) Fluorescence intensity change of probe **2** as a function of equiv of $HgCl_2$, taken after 1 h for each addition. (d) Fluorescence change for a 1:1 mixture of probe **2** and each of the various metal ions (Cr^{2+}, Ca^{2+}, Mg^{2+}, Co^{2+}, Mn^{2+}, Ni^{2+}, Pb^{2+}, Zn^{2+}, Ba^{2+}, Cd^{2+}, Au^{3+}, Fe^{3+}, Cu^{2+}, Ag^{+}, and Hg^{2+}; as the chloride salts), acquired after 1 h. (e) Fluorescence changes for probe **2** in the presence of $HgCl_2$, all the metal species and an equimolar amount of each metal species except Au^{3+}, acquired after 1 h. (f) A plot of fluorescence intensity versus [$HgCl_2$] (1–10 μM) obtained for a 1:1 mixture of probe **2** and $HgCl_2$ after 1 h of each mixing. All the measurements were carried out with 3.0 μM of probe **2** in PBS buffer (pH 7.4) containing 5% DMSO (excitation at 405 nm; the intensity was estimated by the peak height at $\lambda = 475$ nm).

as Cr^{2+}, Ca^{2+}, Mg^{2+}, Co^{2+}, Mn^{2+}, Ni^{2+}, Pb^{2+}, Zn^{2+}, Ba^{2+}, Cd^{2+}, Fe^{3+}, Cu^{2+}, and Ag^{+}, except Au(III) that is highly alkynophilic (Fig. 1d). This specificity should result from the negligible hydrolysis of vinyl ether **2** by the other metal species. Indeed, probe **2** fully responds to the mercury ions even in the presence of all other metal ions except Au(III) (Fig. 1e).

Other mercury ions such as $Hg(OAc)_2$ hydrolyzes probe **2**, similarly as $HgCl_2$ does.

Probe **2** responds to $HgCl_2$ linearly in the micromolar level concentration range (Fig. 1f), and, from which, the detection limit of the probe is estimated to be 0.2 ppm [Hg(II)].

Fluorescence titrations of probe **2** with $HgCl_2$ at different pH conditions (pH 4.0–9.0) were carried out. At pH 6 or pH 9, the fluorescence increased slowly and also the intensity was lower than the case of pH 7 up to 1.5 h. At pH 4, the fluorescence increased steadily as time went; the increase crossed over that of pH 7 after 50 min. In the absence of $HgCl_2$, however, there was little change in the fluorescence at pH 4, which indicates that the first step, oxymercuration, is crucial for the vinyl ether hydrolysis up to this pH. As we pointed out previously,[4] hydrolysis of the oxymercurated intermediate **I** is promoted by acid and thus becomes faster at lower pH. In the absence of $HgCl_2$, probe **2** itself underwent hydrolysis at a lower pH such as pH 2, but this acid-promoted hydrolysis became very slow at pH 3 and only a slight increase in the fluorescence resulted.

In summary, we have developed a novel reaction-based fluorescent sensing system that shows specific response to inorganic mercury species among methylmercury and various other metal species, except Au(III). The probe shows a turn-on fluorescence change as the vinyl ether undergoes mercury ion-promoted hydrolysis followed by cyclization to give a fluorescent coumarin. Studies are undergoing to detect mercury species by two-photon fluorescence microscopy as well as to develop a new coumarin precursor for improved optical properties.

Acknowledgment

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Supplementary data

Supplementary data (experimental procedures for the synthesis of compound **2** and the other fluorescent analysis data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.081.

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