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Highly Selective Ratiometric Fluorescent Sensing for Hg^{2+} and Au^{3+}, Respectively, in Aqueous Media

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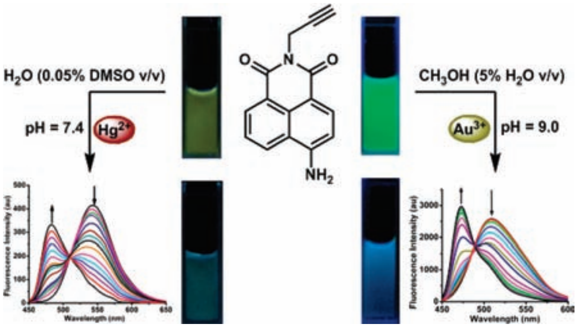
ABSTRACT



A nonsulfur probe based on a 1,8-naphthalimide and alkyne conjugate for the ratiometric fluorescent sensing for Hg^{2+} and Au^{3+} through the tuning of pH in different aqueous solutions is described. This work provides a novel reaction-based approach for selective recognition of these two ions with significant change of fluorescence color and constitutes the first ratiometric case for Au^{3+}.

As one of the most toxic heavy metal elements, mercury can lead to the dysfunction of the brain, kidney, stomach, and central nervous system because of the thiophilic nature in proteins and enzymes.[1] Thus, mercury pollution has sparked interest in the design of new tactics to monitor Hg^{2+} in biological and environmental samples. Especially, various fluorescent chemosensors for Hg^{2+} have been described recently[2] owing to their high sensitivity, selectivity, versatility, and relatively simple handling. Also, since Czarnik pioneeringly described the first synthetic chemodosimeter for the selective determination of Hg^{2+},[3] this new approach based on an irreversible chemical reaction has emerged as an active research area of significant importance.[4]

However, most chemodosimeters contain an "S" group just like traditional reversible chemosensors based on coordination of Hg^{2+} to the S atom.[5] The corresponding mechanisms stem from irreversible organic reactions triggered by extremely strong Hg−S affinity, including: (1) ring opening of spirocyclic systems (rhodamine and fluorescein, etc.),[6] (2) intramolecular cyclic guanylation of thiourea derivatives,[7]

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(1) (a) Von, B. R. *J. Appl. Toxicol.* **1995**, *15*, 483–493. (b) Harris, H. H.; Pickering, I. J.; George, G. N. *Science* **2003**, *301*, 1203. (c) Onyido, I.; Norris, A. R.; Buncel, E. *Chem. Rev.* **2004**, *104*, 5911–5929.

(2) For a recent review, see: Nolan, E. M.; Lippard, S. J. *Chem. Rev.* **2008**, *108*, 3443–3480.

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(4) For a very recent review, see: Quang, D. T.; Kim, J. S. *Chem. Rev.* **2010**, *110*, 6280–6301.

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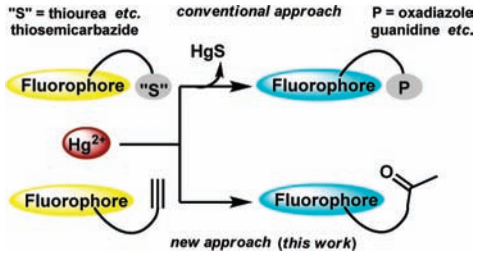
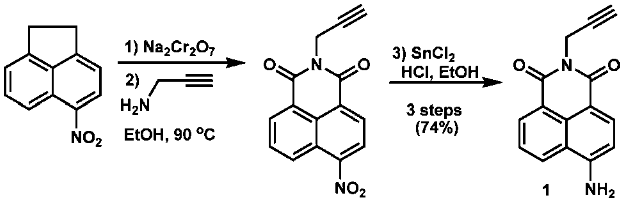
and (3) conversion of thiocarbonyl compounds into their carbonyl analogues[8] (Scheme 1) and a sequential desulfurization–lactonization reaction.[9] This thiophilic approach cannot avoid potential interference in sulfur-rich environments where mercury is abundant,[10] and undesired oxidation of the probes containing a sulfur atom by air or oxidizing reagents always takes place. Other drawbacks may be utilization of elevated temperature or excess quantities of Hg^{2+} to drive these desulfurization reactions to completion. Thus, investigation of a *nonsulfur* strategy[11] except a direct mercuration reaction[12] is highly desirable. Although hydration of alkynes catalyzed by Hg^{2+} (Kucherov reaction)[13] has been known for a century, curiously, the great potential of this classic reaction has not been recognized until recently, and only *two* examples that are limited in the coumarin and fluorescein fluorophores, both of which are not ratiometric, can be found to date.[14] Extension of this methodology to other fluorophores for the development of more effective (especially ratiometric) sensors is still in high demand.

Scheme 1. Reaction-Based Tactics for the Sensing of Hg^{2+}



In connection with our continuing research of sensors for biologically and environmentally important metal ions,[15] herein we report a highly selective ratiometric fluorescent probe for Hg^{2+} in water at neutral pH based on the 1,8-naphthalimide fluorophore tethered via an alkyne moiety. Switch of selectivity to Au^{3+} was also observed after the tuning of pH, which constituted the first ratiometric case. As shown in Scheme 2, the probe **1** was easily prepared from 5-nitroacenaphthene by modifying the reported procedure[16] (see Supporting Information).

Scheme 2. Synthesis of Probe **1**



Next, Hg^{2+}, Ag^{+}, Au^{3+}, Au^{+}, Al^{3+}, Ba^{2+}, Ca^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}, Fe^{2+}, Fe^{3+}, K^{+}, Li^{+}, Mg^{2+}, Mn^{2+}, Na^{+}, Ni^{2+}, Pb^{2+}, Sr^{2+}, and Zn^{2+} ions were used to measure the selectivity of probe **1** (5 μM) in HEPES buffer (0.01 M, pH = 7.4) (0.05% DMSO, v/v), and fluorescence spectra were recorded after 5 min upon the addition of 2.0 equiv of each of these metal ions. Compared to other metal ions examined, only Hg^{2+} caused the change of the maximum fluorescence emission band of probe **1** from 543 to 486 nm (Figure 1a). To validate the selectivity of **1** in practice, the competition experiments were also measured by addition of 0.12 equiv of Hg^{2+} to the aqueous solutions in the presence of 1.0 equiv of other metal ions as shown in Figure 1b. All competitive metal ions had no obvious interference with the detection of the Hg^{2+} ion, which indicated that the system of **1**–Hg^{2+} was hardly affected by these coexistent ions. These results suggested that probe **1** displayed an excellent selectivity toward Hg^{2+} in water at neutral pH.

The fluorescence titration of Hg^{2+} was conducted using a 5 μM solution of **1** in HEPES buffer (0.01 M, pH = 7.4) (0.05% DMSO, v/v). Upon the addition of Hg^{2+} to the solution, a significant decrease of the fluorescence intensity at 543 nm and an increase of fluorescence emission band centered at 486 nm were observed with an isoemission point at 509 nm, which indicated a clear ratiometric fluorescence change (Figure 1c).[17] The ratio of fluorescence intensity at

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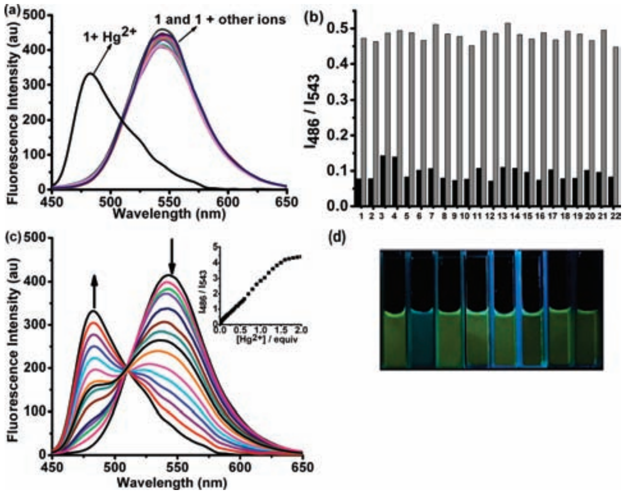

Figure 1. (a) Fluorescence responses of **1** (5 μM) with various metal ions (10 μM) in HEPES buffer (0.01 M, pH =7.4) (0.05% DMSO, v/v) ($\lambda_{ex} = 420$ nm). (b) Metal-ion selectivity of **1** (5 μM). The black bars represent the emission intensity of **1** in the presence of other cations (5 μM). The gray bars represent the emission intensity that occurs upon the subsequent addition of 0.6 μM Hg^{2+} to the above solution. From 1 to 21: none, Ag^{+}, Au^{3+}, Au^{+}, Al^{3+}, Ba^{2+}, Ca^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}, Fe^{2+}, Fe^{3+}, K^{+}, Li^{+}, Mg^{2+}, Mn^{2+}, Na^{+}, Ni^{2+}, Pb^{2+}, Sr^{2+}, Zn^{2+}, and Pd^{2+}. (c) Fluorescent spectra of **1** (5 μM) upon addition of Hg^{2+} ($\lambda_{ex} = 420$ nm). Inset: Ratiometric fluorescence intensity [I_{486}/I_{543}] as a function of [Hg^{2+}]. (d) Fluorescence change of **1**. Left to right: **1** only, Hg^{2+}, Zn^{2+}, Cd^{2+}, Cu^{2+}, Ag^{+}, Au^{3+}, Pb^{2+}.

486−543 nm increased linearly with the concentration of Hg^{2+} (0.01−10 μM). The corresponding detection limit[18] was determined to be 0.05 μM (10 ppb) (Figure S1, Supporting Information). In addition, only the aqueous solution containing Hg^{2+} showed a change of fluorescence color from yellowish green to teal (Figure 1d). These results indicated that **1** can function as a fluorescent ratiometric probe for the Hg^{2+} ion in aqueous solution.

The pH dependence of the fluorescence intensity of **1** and the **1**−Hg^{2+} system is shown in Figures 2 and S2 and S3 (Supporting Information).[19] Free **1** was insensitive against H^{+} and OH^{-}. However, as pH value of the solution decreased, the fluorescence intensity at 486 nm was enhanced more significantly. These results promoted us to explore the function of **1** at an acidic pH value similar to gastric juice. As shown in Figures S4 and S5 (Supporting Information), **1** functions well at very low pH (1.0) and could serve as a potential probe for recognition of the Hg^{2+} under gastric juice condition, although it could not provide a ratiometric response.

Despite considerable recent interest and advances in gold-catalyzed organic transformations,[20] fluorescent sensors for gold ions are underdeveloped.[21] We surmised that the switch of selectivity is feasible owing to strong alkynophilicity of gold ions just like that of mercury.[22,23] To our delight, ratiometric sensing of Au^{3+} is observed through careful adjustment of test conditions.[24]

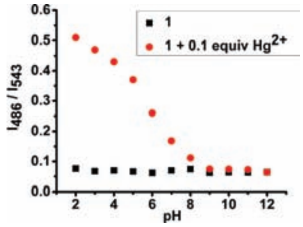

Figure 2. Effect of pH on the ratio of fluorescence intensity at 486 and 543 nm of **1** (5 μM) in HEPES (0.01 M) in the absence and presence of 0.5 μM Hg^{2+}.

Upon the addition of various metal ions to the MeOH−H$_2$O (95:5 v/v, pH = 9.0) solution of probe **1**, only Au^{3+} caused the change of the maximum fluorescence emission band of **1** from 509 to 473 nm (Figure 3a). All competitive metal ions had no obvious interference (Figure 3b). The ratio of fluorescence intensity between 509 and 473 nm increased linearly with increasing Au^{3+} concentration (100−150 μM) (Figure 3c), and a change from green to blue in fluorescence color was also observed (Figure 3d). These results indicated that **1** could be a fluorescent ratiometric probe for the Au^{3+} ion.

The rational analysis of selective recognition of Hg^{2+} and Au^{3+} is accommodated in the well-established Kucherov reaction mechanism[13b] (Scheme 3). In this case, the initial formation of the short-lived π-complex[25] is attacked by water with Markovnikov regioselectivity and *anti* stereoselectivity. The resulting oxymercuration intermediate **2** will be converted to methyl ketone **3** eventually through tautomerization and hydrode-mercuration. It is noteworthy that vinylmercury **2** (Figures S6−S8, Supporting Information) instead of **3** (Figure S9, Supporting Information) is responsible for ratiometric sensing and the blue shift of fluorescence. As

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[18] For the details, see: Chatterjee, A.; Santra, M.; Won, N.; Kim, S.; Kim, J. K.; Kim, S. B.; Ahn, K. H. *J. Am. Chem. Soc.* **2009**, *131*, 2040–2041.

[19] For a fluorescent probe for Hg^{2+} with a broad pH range, see: Shiraishi, Y.; Sumiya, S.; Hirai, T. *Org. Biomol. Chem.* **2010**, *8*, 1310–1314, and references cited therein.

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[22] This similar behavior has been attributed to the common electronic properties for these two elements in the valence shell, in part due to relativistic effects. See: Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395–403.

[23] Use of gold for the hydration of alkyne: Leyva, A.; Corma, A. *J. Org. Chem.* **2009**, *74*, 2067–2074, and references cited therein.

[24] For an example in which subtle change of condition resulted the dramatic switch of selectivity, see: Kim, K. N.; Choi, M. G.; Noh, J. H.; Ahn, S.; Chang, S.-K. *Bull. Korean Chem. Soc.* **2008**, *29*, 571–574.

[25] For the related coinage metal π-complexes, see: Shapiro, N. D.; Toste, F. D. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 2779–2782.

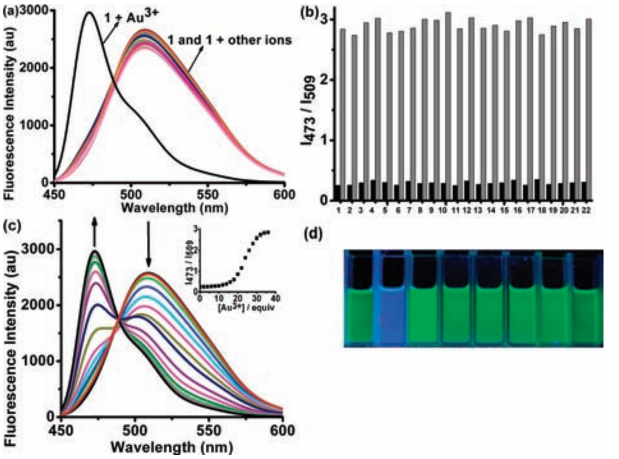
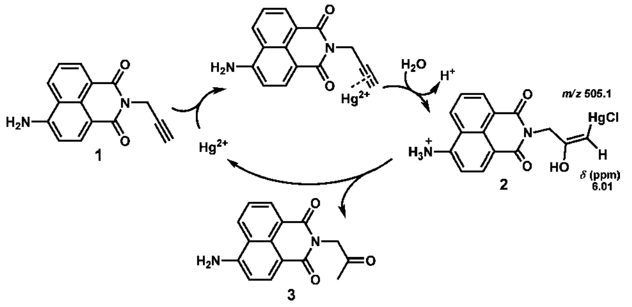


Figure 3. (a) Fluorescence responses of **1** (5 μM) with various metal ions (180 μM) in MeOH−H_2O (95:5 v/v, pH = 9.0) (λ_{ex} = 420 nm). (b) Metal-ion selectivity of **1** (5 μM). The black bars represent the emission intensity of **1** in the presence of other cations (500 μM). The gray bars represent the emission intensity that occurs upon the subsequent addition of 180 μM Au^{3+} to the above solution. From 1 to 21: none, Ag^+, Au^+, Al^{3+}, Ba^{2+}, Ca^{2+}, Cd^{2+}, Co^{2+}, Cu^{2+}, Fe^{2+}, Fe^{3+}, Hg^{2+}, K^+, Li^+, Mg^{2+}, Mn^{2+}, Na^+, Ni^{2+}, Pb^{2+}, Sr^{2+}, Zn^{2+}, and Pd^{2+}. (c) Fluorescent spectra of **1** (5 μM, MeOH−H_2O, 95:5 v/v, pH = 9.0) upon addition of Au^{3+} (0−36.0 equiv) (λ_{ex} = 420 nm). Inset: Ratiometric fluorescence intensity [I_{473}/I_{509}] as a function of [Au^{3+}]. (d) Fluorescence change of **1**. Left to right: **1** only, Au^{3+}, Hg^{2+}, Zn^{2+}, Cd^{2+}, Cu^{2+}, Ag^+, Pb^{2+}.

Scheme 3. Mechanistic Analysis



shown in Figure S10 (Supporting Information), a new peak (δ = 6.01 ppm) assigned as the double bond proton of **2** was observed, and other corresponding signals were all downfield shifted upon the addition of Hg^{2+} to **1**. Mass spectrometry analysis (*m/z* 505.1) also supported the existence of **2** (Figure S11, Supporting Information). In the test conditions, it needed about 5 h for Hg^{2+} and 12 h for Au^{3+} to obtain **3**, respectively. After increasing the concentration of Hg^{2+} or Au^{3+} (∼33 mM), **3** was observed immediately, which was then isolated and characterized by $^1H/^{13}C$ NMR and MS (Figures S19−S21, Supporting Information). The ratiometric sensing of Au^{3+} also followed a similar pathway through the analogus vinylgold intermediate.[26,27]

In summary, we have developed a highly selective ratiometric fluorescent probe for Hg^{2+} or Au^{3+} in aqueous media depending on reaction conditions. This work provides a novel nonsufur approach for selective recognition of these two ions and constitutes the first ratiometric case for Au^{3+}.

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Supporting Information Available: Experimental procedures, spectral data, and copies of $^1H/^{13}C$ NMR and MS. This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) For the selected studies involving characterization of vinylgold species, see: (a) Liu, L.-P.; Xu, B.; Mashuta, M. S.; Hammond, G. B. *J. Am. Chem. Soc.* **2008**, *130*, 17642–17643. (b) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 5232–5241, andreferences cited therein.

(27) The mass spectrum of **1** + $AuCl_3$ displayed two main peaks at *m/z* 534.9 [M + H] and 268.1 [M−$AuCl_2$]. See Figure S12 (SI) for details.