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Reaction-based Hg^{2+} signaling by excimer–monomer switching of a bis-pyrene dithioacetal

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ABSTRACT

A novel reaction-based probe for fluorescence signaling of Hg^{2+} ions was developed. Selective Hg^{2+}-induced cleavage of a dithioacetal resulting in switching from pyrene excimer to monomer emission was used for the signaling. Changes in excimer and monomer emissions of pyrene were readily employed for ratiometric signaling of Hg^{2+} ions in aqueous acetonitrile. Selective signaling of Hg^{2+} ions over other common metal ions was observed with a detection limit of 9.8×10^{-7} M.

Pyrene is one of the most widely used fluorophores for the construction of a variety of smart chemosensors.[1] In particular, signaling using the characteristic monomer–excimer switching of pyrene emission has attracted much research attention.[2] An excimer is a unique pyrene fluorophore emission that occurs as molecular conformation changes allow two pyrene units to become close in proximity. Intricate probes using pyrene monomer–excimer switching have been successfully developed for the signaling of a number of important metal ions, anions, and neutral molecules such as Cu^{2+},[3] Zn^{2+},[4] Hg^{2+},[5] Ag^{+},[6] fluoride,[7] ATP and ADP,[8] DNA,[9] and carbohydrates.[10] Sensor activation is based on various supramolecular interactions that induce the conformation of the pyrene groups to attain close proximity, such as guest-induced ring flips or molecular rotation,[5,11] complexation-induced dimerization,[12] and interaction with cyclodextrin.[13]

Hg^{2+} ions are toxic heavy metal ions widely used in various industrial activities and have a serious environmental impact.[14] A number of well-designed chemosensors for the selective and sensitive signaling of this important species have been reported.[15] Among the many approaches, reaction-based chemosignaling systems for Hg^{2+} ions have attracted considerable research interest. In particular, sulfur derivatives that utilize the thiophilic nature of Hg^{2+} ions are widely employed for this purpose. Representative examples of thio-functionalized reaction-based probes for Hg^{2+} ions are a squaraine–sulfide conjugate,[16] anthracene thioamide,[17] thiocoumarins,[18] rhodamine thiosemicarbazides,[19] rhodamine thioureas,[20] and rhodamine thiocarbonyl-benzothiazole derivative.[21] In addition, sulfide-based probes for Hg^{2+} ions have utilized the hydrolysis of a dithiolane protected coumarin to the corresponding aldehyde,[22] elimination followed by intermolecular cyclization of dithiaspiroacenaphthene quinine with *o*-phenylenediamine,[23] and conversion from a non-fluorescent dithioacetal bearing a triphenylamine moiety to the fluorescent aldehyde.[24] However, the example of reaction-based excimer–monomer switching of pyrenes is rare and has only recently been used for signaling of fluoride ions by fluoride-induced Si–O bond cleavage of pyrene dimers.[25]

In this Letter, we devised a novel reaction-based probe for the signaling of Hg^{2+} ions based on the Hg^{2+}-assisted cleavage of a dithioacetal moiety. The deprotection of dithio-acetal and ketals by the selective cleavage with Hg^{2+} ions proceeds under mild conditions and used for the protection of aldehydes and ketones in organic synthesis (Scheme 1).[26] Using this deprotection process, a compound with two pyrene moieties linked by a dithioacetal subunit was designed as a Hg^{2+} probe. The probe structure could allow a conformation in which two pyrene moieties would be situated in close proximity for excimer emission. Upon dithioacetal hydrolysis, the pyrene subunits are no longer linked, and excimer emission would not be possible. Using this approach, we obtained an efficient pyrene excimer to monomer switching by Hg^{2+} ions, that is a novel strategy for the signaling of this important but toxic species.

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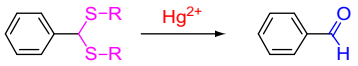
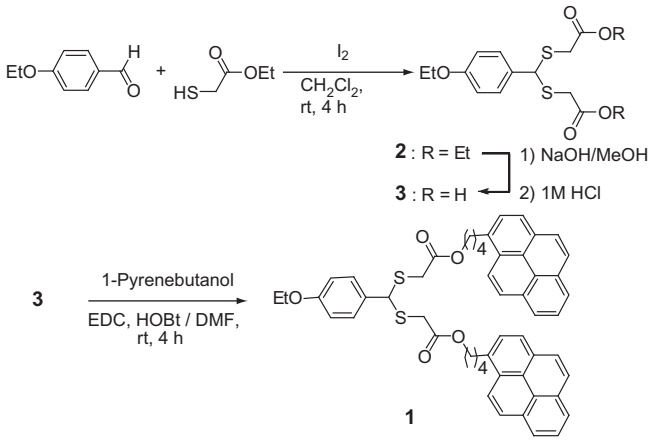


Scheme 1. Deprotection of dithioacetal with Hg^{2+} ions.

Dithioacetal probe **1** was prepared by the three-step reaction sequence shown in Scheme 2. Reaction of 4-ethoxybenzaldehyde with ethyl thioglycolate afforded diester **2** (I_2, CH_2Cl_2, 94%), which was hydrolyzed to dicarboxylic acid **3** (NaOH, aqueous MeOH, 77%). Esterification of **3** with 1-pyrenebutanol (EDC, HOBt, DMF) yielded dithioacetal **1** in moderate yield (60%) (Scheme 2).[27]

Signaling behavior of **1** by excimer–monomer switching was optimized in a series of mixed aqueous solutions of varying water content. A strong pyrene excimer was observed in mixtures up to 50% aqueous acetonitrile, while higher proportion of water led to unstable fluorescence due to limited solubility of **1**. However, the signaling profile of **1**, including the concentration dependent emission behavior and relative intensities of monomer and excimer, was most favorable in 10% aqueous acetonitrile. Therefore, all subsequent signaling measurements of probe **1** were carried out in 10% aqueous acetonitrile.

The fluorescence spectrum of **1** in 10% aqueous acetonitrile was characterized by a strong excimer emission at 480 nm along with weak monomer emissions at 375–395 nm. Upon treatment with Hg^{2+} ions, a prominent emission at 375–415 nm appeared, while the pyrene excimer emission disappeared (Fig. 1). This excimer to monomer switching is due to cleavage of the dithioacetal moiety



Scheme 2. Preparation of dithioacetal probe **1**.

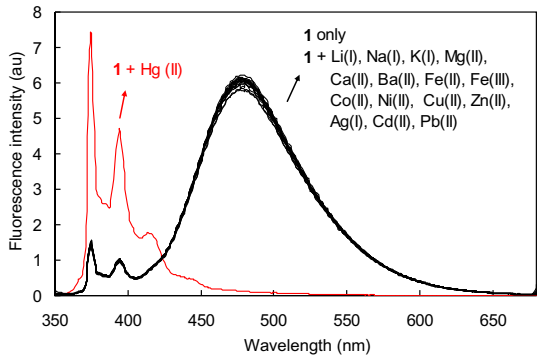


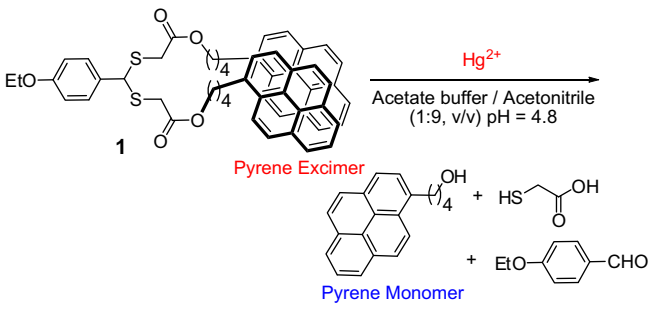
Figure 1. Fluorescence spectra of probe **1** in the presence of various metal ions. [**1**] = 5.0×10^{-6} M, [Hg^{2+}] = [Pb^{2+}] = [Fe^{3+}] = 5.0×10^{-5} M, [M^{n+}] = 1.0×10^{-4} M for other metal ions. In a mixture of acetate buffer (pH 4.8) and acetonitrile (1:9 v/v). [Acetate buffer] = 10 mM. λ_{ex} = 340 nm.

of probe **1** (vide infra). Other metal ions resulted in virtually no changes in the fluorescence profile. Meanwhile, the UV–vis spectrum of **1** was characterized by strong pyrene absorptions at 326–342 nm (Fig. S1, Supplementary data). However, changes induced by Hg^{2+} ions were not observed because the electronic properties of the pyrene moiety were not significantly affected by dithioacetal cleavage.

The Hg^{2+}-selective signaling behavior of **1** was more clearly visualized by ratiometric analysis of changes in fluorescence spectra induced by various metal ions (Fig. 1). Changes in the fluorescence intensity ratio of excimer and monomer at 480 and 395 nm (I_{480}/I_{395}) clearly showed the Hg^{2+} selectivity of **1**. Upon treatment with Hg^{2+} ions, the intensity ratio significantly decreased from 6.1 to 0.03 (Fig. S2, Supplementary data). Other metal ions gave a nearly constant ratio (I_{480}/I_{395} = 6.0 for Cu^{2+} and 6.3 for Fe^{3+}).

Signaling from excimer–monomer switching is due to Hg^{2+}-induced cleavage of the dithioacetal moiety of **1** to the corresponding precursor compounds.[26] Cleavage of the dithioacetal group of **1** by Hg^{2+} ions removes the distance restriction between pyrene groups, which drastically reduced the tendency for excimer formation (Scheme 3). From this transformation, as shown in Figure 1, the signaling strategy using excimer–monomer conversion of dithioacetal **1** by Hg^{2+} ions performed well. The signaling process could be followed by ^1H NMR and mass spectral measurements. The ^1H NMR spectrum obtained for the purified reaction product of probe **1** in the presence of 5 equiv of Hg^{2+} ions revealed 1-pyrenebutanol (Fig. 2). In addition, when the ^1H NMR spectrum was obtained directed from the reaction mixture, resonances for 4-ethoxybenzaldehyde, thioglycolic acid, as well as 1-pyrenebutanol were observed (Fig. S3, Supplementary data). The resonance for an aldehyde proton of 4-ethoxybenzaldehyde at 9.83 ppm appeared while resonance for the same methine proton at 5.15 ppm of the dithioacetal moiety disappeared. Under the measuring conditions, thioglycolic acid forms a stable complex with Hg^{2+} ions to form $Hg(SCH_2CO_2H)_2$ ($\log K_{assoc}$ = 43.82).[28] The mass spectral measurement of the **1**-Hg^{2+} system also revealed a peak for 1-pyrenebutanol at m/z = 274.12. These observations suggest that the Hg^{2+}-induced dithioacetal cleavage product was further hydrolyzed to produce 1-pyrenebutanol and Hg^{2+}-complexed thioglycolic acid under the signaling conditions. The signaling of Hg^{2+} ions by **1** was fast, allowing analysis within 10 min after sample preparation (Fig. S4, Supplementary data).

To assess the potential for practical applications of the probe, competitive signaling of Hg^{2+} ions by **1** was measured. In the presence of 10 equiv of a variety of common metal ions as background, Hg^{2+}-selective signaling was not significantly affected (Fig. 3). Only Fe^{3+} ions gave significant interference. The interaction of triply charged Fe^{3+} with the ester carbonyls of probe **1** appears to hinder the approach of Hg^{2+} ions and the subsequent cleavage reaction.



Scheme 3. Hg^{2+} signaling by pyrene excimer to monomer conversion via cleavage of dithioacetal **1**.

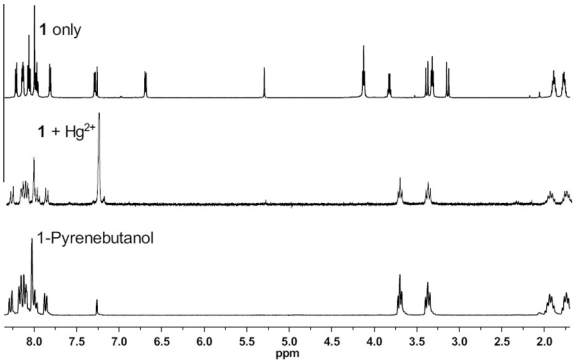


Figure 2. Partial ^{1}H NMR spectra of **1**, the purified reaction product of **1** with Hg^{2+} ions, and 1-pyrenebutanol in $CDCl_3$. [**1**] = [1-pyrenebutanol] = 2.7×10^{-2} M.

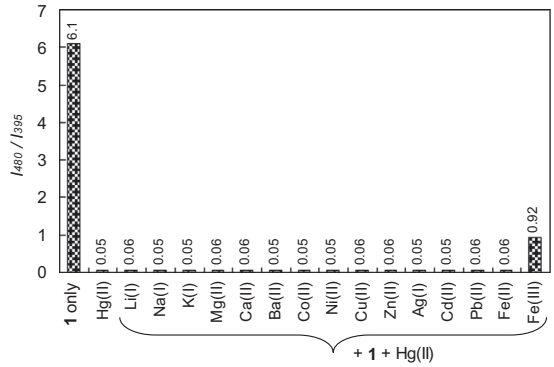


Figure 3. Competitive signaling as expressed by fluorescence intensity ratio (I_{480}/I_{395}) of Hg^{2+} by **1** in the presence of various metal ions as background. [**1**] = 5.0×10^{-6} M, [Hg^{2+}] = 5.0×10^{-5} M, [M^{n+}] = 5.0×10^{-5} M. In a mixture of acetate buffer (pH 4.8) and acetonitrile (1:9 v/v). [Acetate buffer] = 10 mM. λ_{ex} = 340 nm.

Attempts to suppress the interference by Fe^{3+} with ascorbate, citrate, ammonium fluoride, and hydroxylamine masking agents failed. For instance, while interference from Fe^{3+} was effectively suppressed with ascorbate, the desired Hg^{2+} signaling of **1** was also significantly affected.

Finally, quantitation of the Hg^{2+} signaling behavior of **1** was determined by measuring concentration-dependent fluorescence changes. As the concentration of Hg^{2+} ions increased, the excimer intensity of **1** at 480 nm steadily decreased, while strong monomer emissions at 374, 395, and 415 nm increased (Fig. 4). The excimer–monomer switching of **1** was readily analyzed by ratiometry using

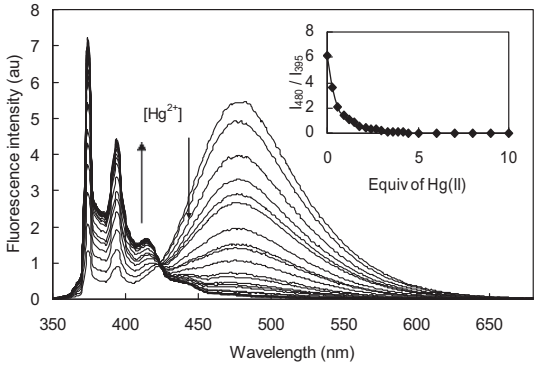


Figure 4. Changes in the fluorescence spectrum of **1** as a function of Hg^{2+} concentration. [**1**] = 5.0×10^{-6} M, [Hg^{2+}] = 0–5.0×10^{-5} M. In a mixture of acetate buffer (pH 4.8) and acetonitrile (1:9 v/v). [Acetate buffer] = 10 mM. λ_{ex} = 340 nm. Inset: Changes in fluorescence ratio I_{480}/I_{395} as a function of Hg^{2+} concentration.

the fluorescence intensities of two characteristic emissions at 395 and 480 nm. In particular, the ratio changed significantly with up to 1.0×10^{-5} M of Hg^{2+} ions and could be used as a calibration plot for Hg^{2+} quantification. The detection limit of **1** for the determination of Hg^{2+} ions was 9.8×10^{-7} M.[29]

In summary, a new reaction-based probe for the signaling of Hg^{2+} ions using excimer to monomer switching of pyrene emission was investigated. Cleavage of the dithioacetal linkage of bis-pyrene compound by Hg^{2+} ions resulted in pronounced fluorescence signaling. The signaling was readily analyzed by a ratiometric approach using the changes in excimer and monomer pyrene emissions. The designed reaction-based strategy using excimer to monomer switching of suitably designed bis-pyrene compounds could be useful for the development of other smart molecular devices.

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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.2013.07.109. These data include MOL files and InChiKeys of the most important compounds described in this article.

References and notes

1. Manandhar, E.; Wallace, K. J. *Inorg. Chim. Acta* **2012**, *381*, 15–43.
2. Karuppannan, S.; Chambron, J. C. *Chem. Asian J.* **2011**, *6*, 964–984.
3. Yang, J.-S.; Lin, C.-S.; Hwang, C.-Y. *Org. Lett.* **2001**, *3*, 889–892.
4. Yuasa, H.; Miyagawa, N.; Izumi, T.; Nakatani, M.; Izumi, M.; Hashimoto, H. *Org. Lett.* **2004**, *6*, 1489–1492.
5. Moon, S.-Y.; Youn, N. J.; Park, S. M.; Chang, S.-K. *J. Org. Chem.* **2005**, *70*, 2394–2397.
6. Wang, F.; Nandhakumar, R.; Moon, J. H.; Kim, K. M.; Lee, J. Y.; Yoon, J. *Inorg. Chem.* **2011**, *50*, 2240–2245.
7. Kim, S. K.; Bok, J. H.; Bartsch, R. A.; Lee, J. Y.; Kim, J. S. *Org. Lett.* **2005**, *7*, 4839–4842.
8. Xu, Z.; Spring, D. R.; Yoon, J. *Chem. Asian J.* **2011**, *6*, 2114–2122.
9. Yamana, K.; Ohshita, Y.; Fukunaga, Y.; Nakamura, M.; Maruyama, A. *Bioorg. Med. Chem.* **2008**, *16*, 78–83.
10. Phillips, M. D.; Fyles, T. M.; Barwell, N. P.; James, T. D. *Chem. Commun.* **2009**, 6557–6559.
11. (a) Wegner, S. V.; Okesli, A.; Chen, P.; He, C. *J. Am. Chem. Soc.* **2007**, *129*, 3474–3475; (b) Xie, J.; Ménand, M.; Maisonneuve, S.; Métivier, R. *J. Org. Chem.* **2007**, *72*, 5980–5985.
12. Kim, H. J.; Hong, J.; Hong, A.; Ham, S.; Lee, J. H.; Kim, J. S. *Org. Lett.* **2008**, *10*, 1963–1966.
13. Kobayashi, N.; Saito, R.; Hino, Y.; Ueno, A.; Osa, T. *J. Chem. Soc., Chem. Commun.* **1982**, 706–707.
14. (a) Nendza, M.; Herbst, T.; Kussatz, C.; Gies, A. *Chemosphere* **1997**, *35*, 1875–1885; (b) Boening, D. W. *Chemosphere* **2000**, *40*, 1335–1351.
15. (a) Nolan, E. M.; Lippard, S. J. *Chem. Rev.* **2008**, *108*, 3443–3480; (b) Du, J.; Hu, M.; Fan, J.; Peng, X. *Chem. Soc. Rev.* **2012**, *41*, 4511–4535.
16. Ros-Lis, J. V.; Marcos, M. D.; Martinez-Manez, R.; Rurack, K.; Soto, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 4405–4407.
17. Chae, M. Y.; Czarnik, A. W. *J. Am. Chem. Soc.* **1992**, *114*, 9704–9705.
18. Choi, M. G.; Kim, Y. H.; Namgoong, J. E.; Chang, S.-K. *Chem. Commun.* **2009**, 3560–3562.
19. Yang, Y.-K.; Ko, S.-K.; Shin, I.; Tae, J. *Org. Biomol. Chem.* **2009**, *7*, 4590–4593.
20. Yang, Y.-K.; Yook, K.-J.; Tae, J. *J. Am. Chem. Soc.* **2005**, *127*, 16760–16761.
21. Wang, F.; Nam, S.-W.; Guo, Z.; Park, S.; Yoon, J. *Sens. Actuat. B-Chem.* **2012**, *161*, 948–953.
22. Kim, J. H.; Kim, H. J.; Kim, S. H.; Lee, J. H.; Do, J. H.; Kim, H. J.; Lee, J. H.; Kim, J. S. *Tetrahedron Lett.* **2009**, *50*, 5958–5961.
23. Ren, W. X.; Bhuniya, S.; Zhang, J. F.; Lee, Y. H.; Lee, S. J.; Kim, J. S. *Tetrahedron Lett.* **2010**, *51*, 5784–5786.
24. Cheng, X.; Li, S.; Zhong, A.; Qin, J.; Li, Z. *Sens. Actuat. B-Chem.* **2011**, *157*, 57–63.
25. Gai, L.; Chen, H.; Zou, B.; Lu, H.; Lai, G.; Li, Z.; Shen, Z. *Chem. Commun.* **2012**, 10721–10723.
26. Greene, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*, 4th ed.; John Wiley & Sons: New York, 2007. pp. 477–481.
27. *Preparation of **1**:* 1-pyrenebutanol (0.19 g, 0.70 mmol) was added to a solution of **3** (0.10 g, 0.32 mmol), EDC-HCl (0.18 g, 0.96 mmol), HOBt (0.043 g,

0.32 mmol), and diisopropylethylamine (0.27 mL, 1.6 mmol) in DMF (5.0 mL). The mixture was stirred for 4 h at room temperature. The resulting mixture was partitioned between water and CH_2Cl_2, and the organic layer was separated and washed with 0.1 N HCl, 0.1 N K_2CO_3 solution, and water. The organic solution was dried over anhydrous $MgSO_4$ and filtered and evaporated. The crude product was purified by silica gel chromatography using CH_2Cl_2/MeOH (19:1 v/v) and hexane/ethyl acetate (5:1 v/v) as eluent to give compound **1** as a brown syrup (0.16 g). Yield, 60%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.21 (d, J = 9.2 Hz, 2H), 8.19–7.93 (m, 14H), 7.81 (d, J = 7.7 Hz, 2H), 7.29 (d, J = 8.6 Hz, 2H), 6.69 (d, J = 8.6 Hz, 2H), 5.29 (s, 1H), 4.13 (t, J = 6.8 Hz, 4H), 3.82 (q, J = 7.0 Hz, 2H), 3.38 (d, J = 15.0 Hz, 2H), 3.32 (t, J = 7.8 Hz, 4H), 3.14 (d, J = 15.0 Hz, 2H), 1.88 (dd, J = 15.1, 7.9 Hz, 4H), 1.77 (dd, J = 14.9, 6.7 Hz, 4H), 1.32 (t, J = 7.0 Hz, 3H): ^{13}C NMR (151 MHz, $CDCl_3$) δ 170.0, 158.9, 136.2, 131.4, 130.9, 130.0, 129.8, 129.1, 128.6, 127.5, 127.3, 127.2, 126.6, 125.8, 125.1, 125.0, 124.9, 124.8, 124.7, 123.2, 114.5, 65.2, 63.3, 53.1, 33.9, 32.9, 28.5, 28.0, 14.7; MS (ESI+); m/z calcd for $C_{53}H_{48}NaO_5S_2$ $[M+Na]^+$: 851.3, found 851.3.

28. Stricks, W.; Kolthoff, I. M.; Heyndrickx, A. *J. Am. Chem. Soc.* **1954**, *76*, 1515–1519.
29. Shortreed, M.; Kopelman, R.; Kuhn, M.; Hoyland, B. *Anal. Chem.* **1996**, *68*, 1414–1418.