



A simple and dual responsive ultrasensitive thioether-functionalized pyrenesulfonamide for the cascade detection of mercury ion and dithiouracil, a mimetic system for molecular logic gates



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ABSTRACT

A thioether-functionalized probe with a dipodal pyrene-sulfonamide fluorophore (probe **1**) was synthesized for the selective and sensitive detection of Hg²⁺ in aqueous solutions. In addition, a probe with a monopod pyrene-sulfonamide unit was prepared (probe **2**). Among various metal ions, these two probes appeared to selectively bind to Hg²⁺ at a 1:1 ratio, with a stronger association of probe **1** than probe **2**, as evidenced by titration experiments. The green emission displayed by probe **1** was completely quenched by the coordination of Hg²⁺ to sulfur (*ON-OFF*), presumably *via* energy transfer from the pyrene fluorophore to the [sulfur-Hg²⁺] unit. The limit of detection (LOD) was 1 nM (0.22 ppb), one of the lowest values obtained so far. Furthermore, the *in situ*-prepared [**1**+Hg²⁺] complex continued to be utilized to selectively detect dithiouracil (DTU) *via* an “*OFF-ON*” mechanism among diverse biomolecules, along with an LOD of 20 nM. Thus, probe **1** alone or together with Hg²⁺ allowed the cascade detection of Hg²⁺ and DTU with high selectivity and ultra-sensitivity. The current study indicates that probe **1** not only serves as an ‘INHIBIT and AND’ logic gate, but also works as an “*ON-OFF-ON*” molecular switch triggered by the sequential addition of Hg²⁺ and DTU.

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1. Introduction

The biological functions of many enzymes are controlled by metal ions. Metal ions can modify the electron distribution and flow of polar groups present in a substrate or the active site of an enzyme, thus effectively carrying out enzyme-catalyzed reactions [1–5]. In metalloenzymes, a biochemical reaction catalyzed by an appropriate metal ion may not proceed or proceeds very slowly in the absence of the metal ion. Some metal ions such as mercury, lead, and arsenic are very toxic to organisms including humans [6–8]. Due to the strong affinity to thiol group commonly present in biological macromolecules, mercury ions and their derivatives often cause dysfunctions of cells, often leading to serious health problems. In humans, methyl mercurial species are readily absorbed by the gastrointestinal (GI) tract and can target the central nervous system through the blood-brain barrier [9–15]. Moreover, mercury ions are implicated in a variety of human health problems such as immune system dysfunction, prenatal brain dam-

age, and cognitive disorders even at relatively low concentrations, while it can also be accumulated in plants, leading to a reduction in the rates of photosynthesis and transpiration. The use of methyl mercury-tainted seed grains for bread led to a noteworthy epidemic in Iraq. In drinking water, the upper limit for Hg²⁺ mandated by the United States Environmental Protection Agency (EPA) is 2 ppb (10 nM) [16]. Due to strong health concerns over exposure to mercury ions, many scientists are motivated to explore a selective and efficient method for Hg²⁺ detection in environmental and biological samples [17–19]. A number of architectures such as thioether-containing thioureas [20–23], podands [24–27], crown ethers/acetals [28–30], amides/amines [31–36], spiro-lactones [37,38], and heterocycle-based moieties [39–42] appended with different kinds of fluorescent units have been developed for Hg²⁺ sensing. However, most of these sensors lack reversibility in Hg²⁺ sensing (*i.e.*, chemodosimeters). Several sensors that can reversibly detect Hg²⁺ (*i.e.*, chemosensors) often have limitations due to the interference of other metal ions such as Ag⁺ and Cu²⁺ [43–47]. As a continuation of our research efforts to invent highly effective sensors [48,49], we focused on development of a fluorescent-based Hg²⁺ sensor in aqueous media in this study.

Uracil, a naturally occurring pyrimidine analog, is an important constituent of RNA. Uracil derivatives/analogues have been utilized in

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various applications such as pharmaceuticals [50], coenzymes [51], pesticides [52], drug delivery, and enzyme synthesis. Fluorouracil is currently used to combat versatile diseases including porokeratosis [53], psoriasis, sun-damaged skin, and genital warts [54] as well as various cancers including cervical, bladder, breast, colorectal, ovarian, pancreatic, and stomach cancers [55–61]. Thiouracils inhibit kidney stone formation; effectively act as neoplastigenic, tumorigenic, carcinogenic, and teratogenic agents; and possess antidote properties for mercury poisoning. These agents serve as ligands in biochemical processes [62,63] and are used for the treatment of hyperthyroidism [64,65]. These features of uracil derivatives escalated our interest in detecting dithiouracil (DTU) in an environmental or biological sample.

Pyrene has been extensively used as an excellent fluorophore in chemical sensor research. Upon target binding, this fluorophore shows different emission characteristics depending on its association state (monomer (blue) or excimer (green)) [49,66–69]. From previous studies of optical molecular probes, π - π and/or hydrogen bond interactions have been found to play significant roles in excimer formation [67–69]. Based on this observation, we built a dipodal fluorophore based on pyrene-1-sulfonamide (*i.e.*, probe **1**) for the stepwise detection of Hg^{2+} and dithiouracil (DTU) in a phosphate-buffered saline (PBS)-EtOH solution. For a comparative purpose, a monopod analog with only one pyrene unit (probe **2**) was also prepared. Both probes (probes **1** and **2**) contain a thioether-functionalized central alkyl chain served for metal ion binding and were readily synthesized in a single step by the reaction of pyrene-1-sulfonyl chloride with 2,2'-thiobis(ethylamine) in good yields. The current study showed that the excimer fluorescence of probe **1** was quenched selectively in the presence of Hg^{2+} among various metal ions by forming a strong probe- Hg^{2+} complex. This complex was further used to detect DTU of versatile biomolecules with high selectivity and sensitivity. The selectivity and sensitivity were less obvious for the monopod variant (probe **2**), indicating the importance of the dipodal architecture in an effective Hg^{2+} detection.

2. Experimental

2.1. General chemicals and materials

All reagents and solvents used in the experiments were purchased from Aldrich (analytical grade) and used without further purifications. Pyrene-1-sulfonyl chloride was synthesized according to a procedure reported previously [69]. ^1H and ^{13}C NMR spectra were recorded using a Bruker AM-400 spectrometer with tetramethylsilane (Me_4Si) used as the internal standard. The FAB mass spectra were recorded using a Jeol JMS 700 high-resolution mass spectrometer at the KBSI (Korea Basic Science Institute) Daegu Center. The UV-visible absorption spectra were recorded using a Shimadzu UV-2600PC spectrophotometer. The fluorescence spectra were obtained by employing a fluorescence spectrometer (Horiba Jobin Yvon FL3-11, USA) equipped with a Xe discharge lamp using 1-cm quartz cells with a 3-nm slit width. All of the measurements were carried out at 298 K.

2.2. Theoretical calculations

The optimized geometries of the two probes (probes **1** and **2**) were obtained *via* the gradient-correlated density functional theory (DFT) using Becke's three-parameter exchange functional [70] and the Lee-Yang-Parr (B3LYP) exchange correlation functional [71] with 6-31G* basis sets for C, H, N, and O. B3LYP/6-31G* calculations were employed for the excited-state optimization of probes **1** and **2**. For simplicity, all calculations were carried out under vacuum (*i.e.*, solvent effects were not included in the calculations). All stationary

points were verified as the minima *via* calculations from Hessian and harmonic frequency analyses [72,73].

2.3. Synthesis of probes 1 and 2

2.3.1. 2,2'-Thiobis(ethyl-pyrene-1-sulfonamide) (probe 1)

2,2'-Thiobis(ethylamine) (48 mg, 0.4 mmol) was added to a solution of pyrenesulfonyl chloride (300 mg, 1.0 mmol) and *N,N*-diisopropylethylamine (260 mg, 2.0 mmol) dissolved in CH_2Cl_2 (25 mL). The resulting solution was vigorously stirred at room temperature for 30 min and then at 50 °C under argon atmosphere. After completion of the reaction, as determined by TLC, the organic layer was washed with 1 N HCl (2 × 50 mL) and 5% aqueous NaCl (100 mL). Then, the organic layer was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated under reduced pressure, and the resulting residue was purified by column chromatography using CH_2Cl_2 : CH_3OH (9:1) as the eluent (R_f =0.3) to yield probe **1** as a white solid (230 mg, 70% yield). m.p.=260 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 2.27 (t, J =7.2 Hz, 4H, 2 × CH_2), 2.81 (t, J =6.4 Hz, 4H, 2 × CH_2), 8.17–8.21 (m, 4H, 4 × ArH), 8.24 (bs, 2H, 2 × SO_2NH), 8.32 (t, J =8.4 Hz, 4H, 4 × ArH), 8.41–8.46 (m, 6H, 6 × ArH), 8.50 (d, J =8.4 Hz, 2H, 2 × ArH), 8.91 (d, J =9.2 Hz, 2H, 2 × ArH). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 30.61, 42.35, 123.15, 123.41, 124.13, 124.27, 126.54, 126.83, 127.01, 127.08, 127.14, 129.48, 129.68, 129.93, 130.51, 132.46, 133.92. HR-FAB MS, m/z calc'd for $\text{C}_{36}\text{H}_{29}\text{N}_2\text{O}_4\text{S}_3$ ($\text{M}+\text{H}$) $^+$ = 649.1284 vs. the observed value of 649.1292.

2.3.2. *N*-(2-((2-aminoethyl)thio)ethyl)pyrene-1-sulfonamide (probe 2)

A solution of pyrenesulfonyl chloride (300 mg, 1.0 mmol) in CH_2Cl_2 (40 mL) was added dropwise to a stirred solution of 2,2'-thiobis(ethylamine) (240 mg, 2.0 mmol) and *N,N*-diisopropylethylamine (130 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) at 0 °C under argon atmosphere. Following complete addition, the reaction mixture was further stirred at room temperature for 3 h. The CH_2Cl_2 layer was washed with 1 N HCl (2 × 100 mL) and 5% aqueous NaCl (100 mL), dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by column chromatography with CH_2Cl_2 : CH_3OH (9:1) as the eluent (R_f =0.10) to yield probe **2** as a light yellow solid (315 mg, 82% yield). m. p. = 142 °C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$): δ 2.32 (t, J =6.8 Hz, 2H, CH_2), 2.41 (t, J =7.2 Hz, 2H, CH_2), 2.47 (t, J =6.8 Hz, 2H, CH_2), 3.00 (t, J =7.2 Hz, 2H, CH_2), 3.45–3.47 (bs, 3H, $\text{NH}_2 + \text{H}^+$), 8.21 (t, J =7.6 Hz, 1H, ArH), 8.29 (d, J =8.8 Hz, 1H, ArH), 8.38–8.49 (m, 5H, 5 × ArH), 8.61 (d, J =8.0 Hz, 1H, ArH), 8.98 (d, J =9.2 Hz, 1H, ArH). ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$): δ 30.72, 34.79, 41.30, 42.83, 123.18, 123.46, 124.22, 124.31, 126.63, 126.85, 127.03, 127.14, 127.17, 129.51, 129.71, 129.97, 130.55, 132.57, 133.98. HR-FAB MS, calc'd m/z value of $\text{C}_{20}\text{H}_{21}\text{N}_2\text{O}_2\text{S}_2$ ($\text{M}+\text{H}$) $^+$ = 385.1039 vs. the observed value of 385.1045.

3. Results and discussion

3.1. Synthesis and characterization of probes 1 and 2

Probes **1** and **2** were efficiently synthesized in a single step using pyrenesulfonyl chloride and 2,2'-thiobis(ethylamine) (Scheme 1). The chemical structures of these probes were characterized by ^1H and ^{13}C NMR spectroscopy. Because of the molecular symmetry, the S- CH_2 and N- CH_2 signals of probe **1** appeared as a triplet at 2.27 and 2.81 ppm, respectively, along with the SO_2NH signal at 8.24 ppm. The other signals were in well accordance with the presence of 18 aromatic protons in two pyrene units. The mass data also matched the molecular weight of probe **1** ($(\text{M}+\text{H})^+$, m/z = 649.1292).

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