Development of an Indole-Based Boron-Dipyrromethene Fluorescent Probe for Benzenethiols

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Discrimination between chemically related benzenethiols and aliphatic thiols represents a big problem. In this paper, a fluorescent probe, **Bodipy-1**, containing an indole-based Bodipy as a fluorophore and a 2,4-dinitrobenzenesulfonyl group as a recognition unit was constructed to achieve the selectivity between them. The Bodipy group in the prepared probe was selectively released through aromatic nucleophilic substitution by thiolate anions from benzenethiols, resulting in blue−red switching in the emission spectra in buffer solutions; that is, two new peaks of the phenol/phenolate state of **Bodipy-2** at 565 and 629 nm appeared in emission spectra. By varying the pH value from 6.6 to 8.8, the intensity ratio of I_{565}/I_{629} varies from 2.0 to 0.3 after complete conversion to **Bodipy-2**, a ca. 7-fold emission ratio change. This ratiometric emission property by varying the pH value makes **Bodipy-1** a promising probe to discriminate benzenethiols from aliphatic thiols by careful selection of the reaction pH.

Introduction

The development of a highly sensitive and selective recognition of thiols has emerged as a significant interest in areas ranging from the petrochemical industry to food quality control and medicine. For instance, considerable efforts have been devoted to the development of fluorescent sensors or probes for aliphatic thiols in the past decades, mainly designed for glutathione (GSH), cysteine (Cys), and homocysteine (HCys),[1−6] which play a crucial role in maintaining redox homeostasis in biological systems.[7−10] Bezenethiols are useful chemicals in the production of pesticides, polymers, and pharmaceuticals.[11] However, exposure to benzenethiols can induce systemic injuries, including shortness of breath, muscular weakness, nausea, vomiting, coma, and even death, through targeting of the central nervous system, kidney, and liver.[12] Despite having a high toxicity, only a few fluorescent sensors that selectively respond to the widely existent benzenethiols have been reported. Aliphatic thiols and benzenethiols are a class of molecules with close physical and chemical properties. As a result, most fluorescent probes exhibit poor selectivity toward them. Recently, a pioneering work regarding the discrimination of benzenethiols over aliphatic thiols was reported by Wang etc. based on the analyst reactivity and reaction conditions.[13] On the basis of this concept, another two probes with a high sensitivity and selectivity toward benzenethiols were constructed,[14,15] all of which respond to benzenethiols with a change only in flouorescent intensity. Nevertheless, as if the change in fluorescence intensity is the only detection signal, factors, such as environmental conditions and the probe concentration, can interfere with the signal output. In this case, the design of molecules that can induce prominent spectroscopic changes, such as ratiometric fluorescence changes, upon selective binding with benzenethiols is highly desirable for ease of quantifications and signal transductions. We, therefore, want to develop a fluorescent probe that can display a ratiometric response to benzenethiols using an external stimulus.

It is known that, for the design of selective and sensitive sensors for discrimination between chemically closely related analysts, conjugation of a well-established and efficient recognition site with a suitable signaling moiety is the most rewarding approach.[16] As a signaling unit, fluorophores generally have many desirable characteristics in both sensitivity and ease of signal transduction. Among many of the fluorophores, boron-dipyrromethene (Bodipy) fluorescent dyes have been recognized as the promising ones for the construction of molecular sensors because of their excellent characteristics, such as intense fluorescence quantum yields, sharp absorption and fluorescence emission spectra, and high photo- and chemostability.[17] However, no reports have been published concerning Bodipy as a signaling unit for discrimination of thiols, so far. Therefore, in this paper, we attempted to choose Bodipy as a fluorophore and the strongly electron-withdrawing 2,4-dinitrobenzenesulfonyl (DNBS) group as a recognition unit to achieve a sensitive and selective fluorescent probe toward benzenethiols. The DNBS group is now frequently employed as an efficient recognition site for thiols due to its unique and high reactivity toward thiolate anions.[2f,8a,13−15,18] The fluorogenic reaction of these probes occurs through deprotection of the DNBS through aromatic nucleophilic substitution by thiolate anions (Scheme 1), so the degree of thiol dissociation is important for a thiol probe to work.[13−15,18] Thus, careful selection of the reaction pH at 6−8 would allow a judiciously designed probe to discriminate benzenethiols over thiols. This selectivity is possible because the pK_a value of thiophenol is about 6.5, which is lower than that of aliphatic thiols (pK_a of ca. 8.5), and under pH 6−8, the corresponding more nucleophilic thiolate for benzenethiols is the dominant species; in comparison, the aliphatic thiols remain largely in the less reactive neutral form.

Here, we report the synthesis of a novel benzenethiol probe, Bodipy-1, having an indole-based Bodipy as a fluorophore and a DNBS group as a recognition unit, whose function is based

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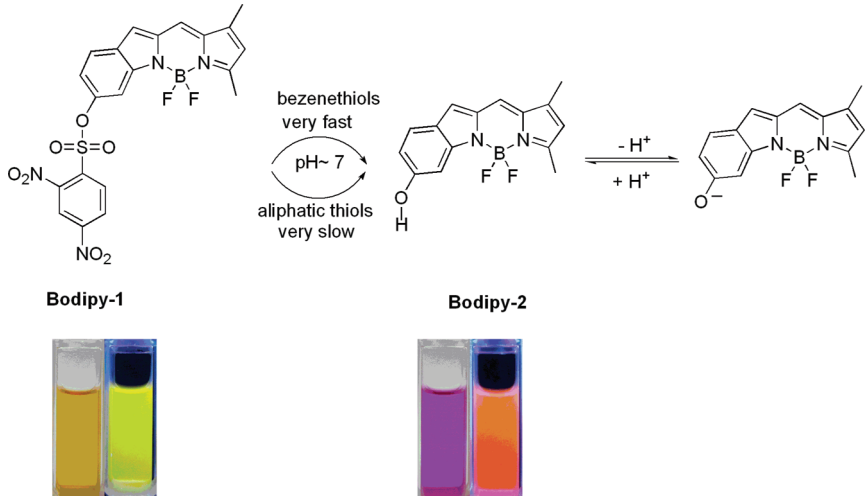
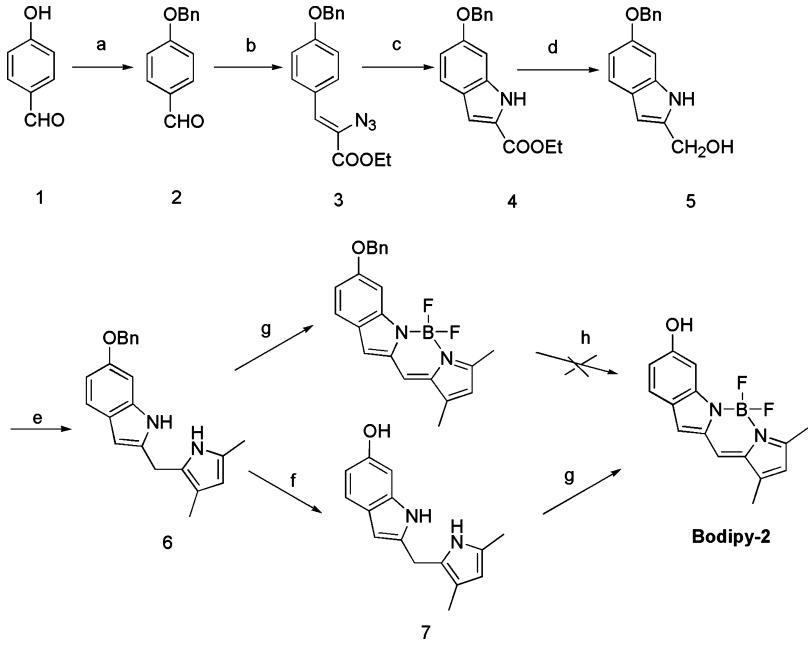
SCHEME 1: Probe Bodipy-1 and the Releasing Bodipy-2 by Benzenethiols at pH 7.4 in Sodium Phosphate Buffer Solutions



SCHEME 2: Synthesis of Bodipy-2[a]



[a] Reagents and conditions: (a) BnCl, K_2CO_3, acetone, reflux 15 h; (b) N_3CH_2COOEt, NaOEt, EtOH, 0 °C to rt, 6 h; (c) toluene, reflux, 2 h; (d) $LiAlH_4$, THF, 1 h; (e) 2,4-dimethylpyrrole, CH_3COOH, heat to 40 °C, 1 h; (f) 10%$Pd(OH)_2$/C, MeOH/EtOAc, rt, 3d; (g) DDQ, CH_2Cl_2, rt, 1 h, NEt_3, BF_3-OEt_2, 30 min; (h) 10%Pd/C, MeOH/EtOAc, rt, 24 h.

upon the well-established effective thiolysis of DNBS. The Bodipy group in the prepared probe can be selectively released through aromatic nucleophilic substitution by thiolate anions from benzenethiols (Scheme 1), resulting in a higher quantum yield and phenol/phenolate-dependent blue−red switching in the absorption and emission spectra in buffer solutions. Compared to the reported examples of the fluorescent sensing of thiols, which function by just the enhancement of fluorescence signals, our probe with ratiometric emission properties by varying the pH conditions can eliminate ambiguities by self-calibration of the two emission bands, as if the change in fluorescence intensity is the only detection signal; factors, such as instrumental efficiency, environmental conditions, and the probe concentration, can interfere with the signal output.

Experimental Methods

Fluorometric Measurements. A stock solution of the probe (2×10^{-3} M) was prepared in THF. The test solution of the probe (4 μM) in 3 mL of neutral aqueous conditions (0.2 M sodium phosphate buffer, pH 7.4) was prepared by mixing 20 μL of the probe stock solution and 10 mL of 0.2 M phosphate buffer (pH = 7.4). The solutions of various testing species were prepared from cysteine, $PhNH_2$, PhOH, glucine, $PhCH_2SH$, or CH_3PhSH.

Materials and General Methods. All reagents and solvents were commercially available and used without further purification. Proton NMR and ^{13}C NMR were measured on a Bruker AV-400 spectrometer with chemical shifts reported in parts per million (in $(CD_3)_2CO$ or $CDCl_3$; TMS as an internal standard). Mass spectra were measured on an HP 1100 LC-MS spectrometer. All pH measurements were made with a Sartorius basic pH meter PB-10. Fluorescence spectra were determined on a VARIAN CARY Eclipse Fluorescence spectrophotometer. Absorption spectra were determined on a VARIAN CARY 100 Bio UV−visible spectrophotometer.

Results and Discussion

Synthesis of a Novel Indole-Based Boron-Dipyrromethene Fluorescent Dye, Bodipy-2. Although Bodipy derivatives are among the most widely studied fluorescent dyes, very few investigations have been carried out on their analogues based on an indole building block. In our search for new fluorophores with excellent photophysical properties, we first prepared **Bodipy-2** and examined its photophysical properties in buffer solutions. Scheme 2 depicts the preparation of the dipyrromethane intermediate **5** and its subsequent production of **Bodipy-2** in dichloromethane. The intermediate **4** was prepared in three steps, commencing from *p*-hydroxybenzenaldehyde according to the literature procedure.[19] Treatment of the ester **4** with an excess of sodium aluminum hydride in tetrahydrofuran afforded the corresponding 2-methanol **5** in 92% isolated yield. This alcohol was found to be sensitive to acidic environments and liable to condense with excess 2,4-dimethylpyrrole in glacial acetic acid to produce the dipyrromethane **6**. Beginning with dipyrromethane **6**, two synthetic routes were adopted to get **Bodipy-2**. In the first approach, the condensation product **6** was first oxidized with DDQ, followed by neutralization with NEt_3, and subsequently treated with BF_3-Et_2O to afford the desired Bodipy compound. However, deprotection of phenol carried out using 10% Pd/C in methanol/EtOAc to give **Bodipy-2** was unsuccessful. The double bond in the meso position was indeed reduced to a single bond. The second route was then investigated. Prior to the oxidation with DDQ, compound **6** was first deprotected to furnish the intermediate dipyrromethane **7**. This intermediate was then subject to oxidation with DDQ, followed by neutralization with NEt_3, and subsequently treated with BF_3-Et_2O to afford the desired **Bodipy-2**.

Effect of pH on the Photophysical Properties of Bodipy-2. The pH dependence of **Bodipy-2** was next investigated in sodium phosphate buffer solutions, as shown in Figure 1. UV−vis of **Bodipy-2** revealed the absorption with a maximum at 520 nm, attributed to the neutral form of **Bodipy-2**. However, as the pH values were increased from 5 to 9, the absorption band at 520 nm was progressively decreased, which was accompanied with a simultaneous increase of the absorption at 600 nm, coming from the phenolate form (Ph−OH → PhO^-). Varying the pH also gave rise to an isosbestic point at 546 nm, indicating the existence of an equilibrium between phenol and the phenolate form in buffer solutions within the physiological pH value. In the same way as the absorption spectra, when **Bodipy-2** was excited at the wavelength of the absorption isosbestic point (546 nm), the fluorescence spectra of **Bodipy-2** exhibited a phenol/phenolate-dependent blue−red switching, as shown in Figure 1b. When the pH value was increased from 5 to 9, the spectrum showed a decrease of the emission band at 565 nm and a simultaneous increase of the emission band at 629 nm. The likely characteristic isoemission point at 602 nm makes **Bodipy-2** an excellent ratiometric pH indicator. More importantly, the characteristic two emission bands between pH values 5 and 9 make **Bodipy-2** a very interesting fluorophore. Along with its releasing during the sensing process, the pH-dependent blue−red switching emission appears, and the emission intensity ratio of the two bands remain unchanged as the pH value is constant.

Design and Synthesis of a Fluorescent Probe for Thiols. One significant advantage of **Bodipy-2** is the facile synthesis of derivatives by modification of the phenol function. Using this strategy, we designed and synthesized **Bodipy-1**, which was achieved by reaction of **Bodipy-2** with 2,4-dinitrobenzenesulfonyl chloride in the presence of Et_3N in dichloromethane to afford the target probe **Bodipy-1** in 86% yield (Scheme 3). The 2,4-dinitrobenzenesulfonyl (DNBS) group was chosen as protection group due to its unique and high reactivity toward thiolate anions to release the fluorophore.[2f,8a,13−15,18]

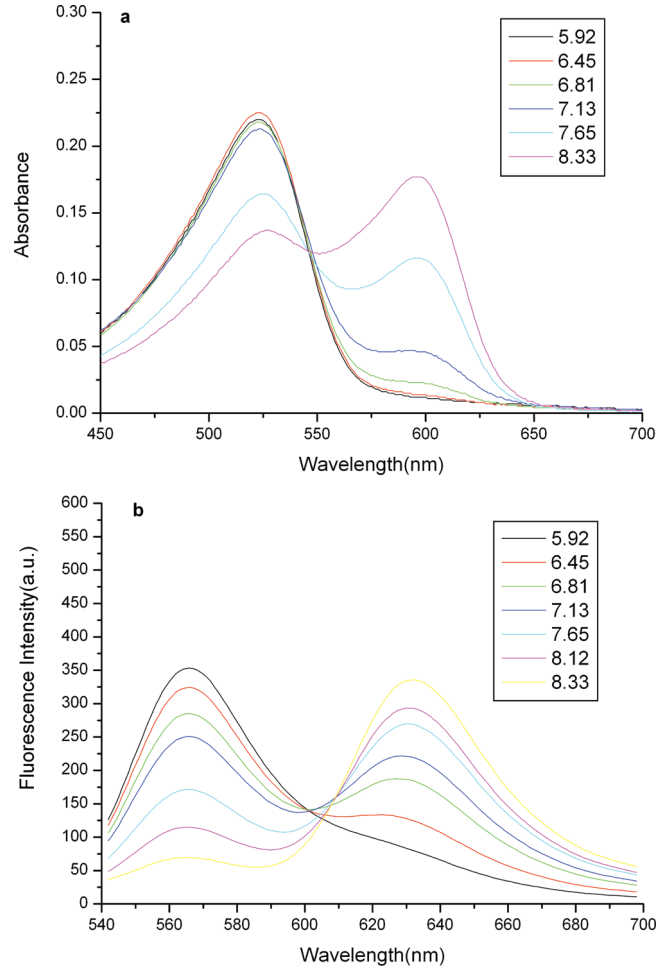
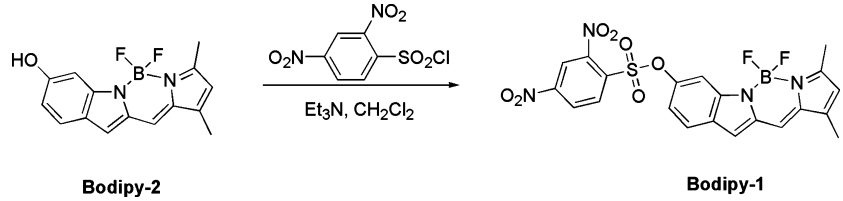


Figure 1. (a) Absorption spectra of **Bodipy-2** in buffer solution as a function of pH. (b) Corresponding emission spectra (λ_{ex} = 546 nm). The pH was adjusted by NaH_2PO_4 and Na_2HPO_4.

Sensing Properties of Bodipy-1 to Benzenethiols. The fluorescent response of **Bodipy-1** to benzenethiols was first performed in a sodium phosphate buffer solution with pH 7.4, containing **Bodipy-1** at a concentration of 4×10^{-6} M. The fluorescence spectra were recorded at several intervals during the reaction of **Bodipy-1** with benzenethiols. As expected, **Bodipy-1** displayed fluorescence ($\lambda_{em} \sim 530$ nm) with a very low quantum yield in the absence of thiols (Figure 2a). In sharp contrast to **Bodipy-2**, almost no change in fluorescence intensity was observed for **Bodipy-1** over the pH range from 5 to 9. Additionally, a negligible percentage of **Bodipy-1** decomposed to the corresponding **Bodipy-2** after 1 h of incubation in buffer solution at room temperature. However, upon addition of benzenethiols to the buffer solution, immediately, a dramatic change in the fluorescence spectra was observed, and two new peaks of the phenol/phenolate state of **Bodipy-2** at 565 and 629 nm appeared, resulting from the generation of **Bodipy-2** by the reaction of **Bodipy-1** with benzenethiols. The intensity of the peaks increased rapidly and reached a maximum after about 20 min. Therefore, in this work, an assay time of 20 min was adapted as the optical measurement condition. Notably, the intensity ratio of I_{565}/I_{629} remained unchanged (Figure S1, Supporting Information) after all **Bodipy-1** was consumed, which indicated that the ratio of phenol and phenolate is constant

SCHEME 3: Synthesis of Bodipy-1



Bodipy-2 **Bodipy-1**

under the measurement condition. On the other hand, once varying the pH to another measurement condition, the intensity ratio of I_{565}/I_{629} changed immediately and kept constant as the measurement condition did not change anymore (Figure S1, Supporting Information). When the pH value was increased from an acidic to a basic condition, the ratio of I_{565}/I_{629} decreased accordingly, which indicated that, in a basic condition, the phenolate form is the dominant species. On the basis of this observation, we next tested the ratiometric detection of benzenethiols by varying the pH value as shown in Figure 2b. The ratio of two emission band intensities (I_{565}/I_{629}) upon excitation at 520 nm varies from 2.0 in the presence of benezenethiols at pH 6.6 to 0.3 at pH 8.8 after complete conversion to **Bodipy-2**, a ca. 7-fold emission ratio change.

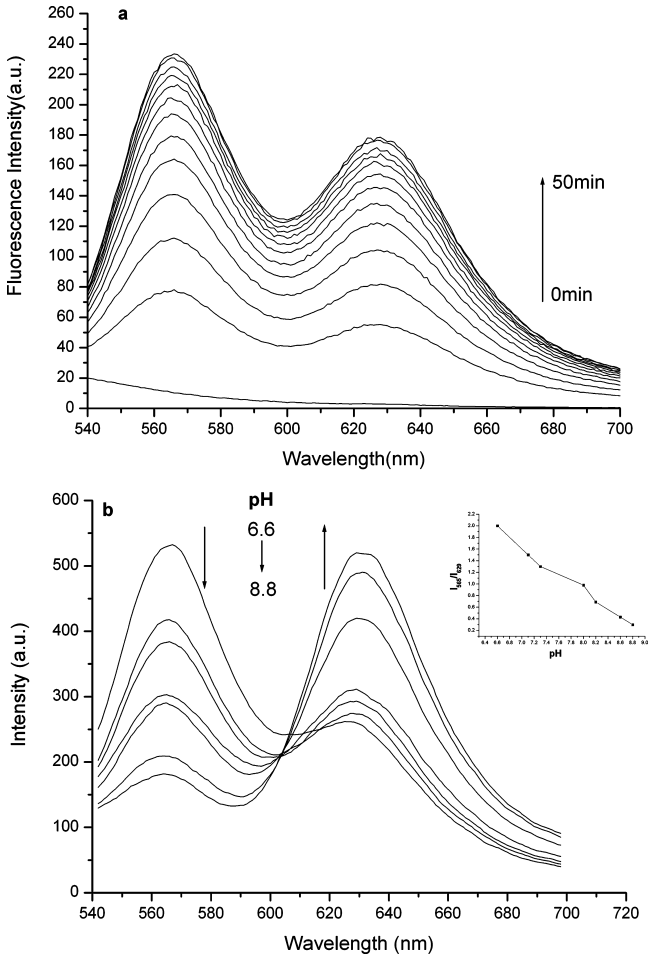


Figure 2. (a)Time course for the change in the fluorescence intensities of **Bodipy-1** (4 μM) in the presence of 2 equiv of benzenethiols, such as CH_3PhSH, in the neutral aqueous conditions (0.2 M phosphate buffer, pH 7.4). (b) Response of **Bodipy-1** (4 μM) to 2 equiv of benzenethiols, such as CH_3PhSH, at different pH values. The spectra were obtained 20 min later after addition of thiocresol. The pH value was adjusted by NaH_2PO_4 and Na_2HPO_4. Inset: the ratiometric fluorescence change as a function of pH.

The reported examples of fluorescent sensing of benzenethiols function by just the enhancement of fluorescence signals. However, as the change in fluorescence intensity is the only detection signal, factors, such as instrumental efficiency, environmental conditions, and the probe concentration, can interfere with the signal output. The probe reported here gave ratiometric emission properties after the interaction with benzenethiols by varying the pH value, so **Bodipy-1** can eliminate these ambiguities by self-calibration of the two emission bands.

We then study the fluorescence sensitivity of **Bodipy-1** to various concentrations of benzenethiols (Figure 3). When higher concentrations of benzenethiols was used, a more dramatic enhancement of the two peaks at 565 and 629 nm was observed, and the enhancement of fluorescence intensity reached the maximum as 4 equiv of benzenethiols was used. Further using higher concentrations than 4 equiv of benzenethiols did not result in additional enhancement of fluorescence intensity while a negligible decrease was promoted (Figure S2a, Supporting Information). The detection limit for benzenethiols was determined as 9.5×10^{-7} M under the experimental conditions (Figure S2b, Supporting Information),[4a,15,20] which is sufficiently low to allow the fluorogenic detection of micromolar concentrations of benzenethiols.

Although the above studies have indicated that the sensing response of the probe to benzenethiols is due to the thiolysis of ester **Bodipy-1** to **Bodipy-2**, further evidence should be provided. It is well known that the 2,4-dinitrobenzenesulfonyl ester can be readily cleaved by a thiolate anion through nucleophilic aromatic substitution, releasing the unprotected dye.[2f,8a,13−15,18] In our case, HPLC analysis was first performed to confirm the production of **Bodipy-2** in the reaction. As shown in Figure 4, the retention times of standard **Bodipy-2** and *p*-thiocresol were at 5.35 and 11.61 min, separately. The process of the thiolysis reaction was also monitored by HPLC at different

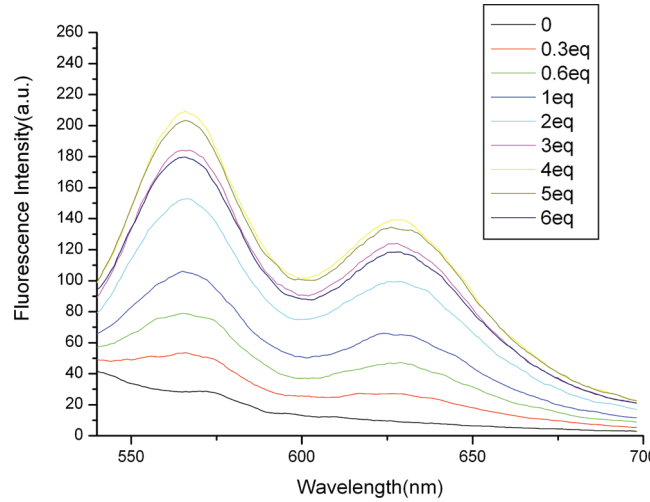


Figure 3. Emission spectra of **Bodipy-1** (4 μM) after addition of different concentrations of benzenethiols, such as *p*-thiocresol (0−6 equiv), in a phosphate buffer (0.2 M, pH 7.4) at room temperature.

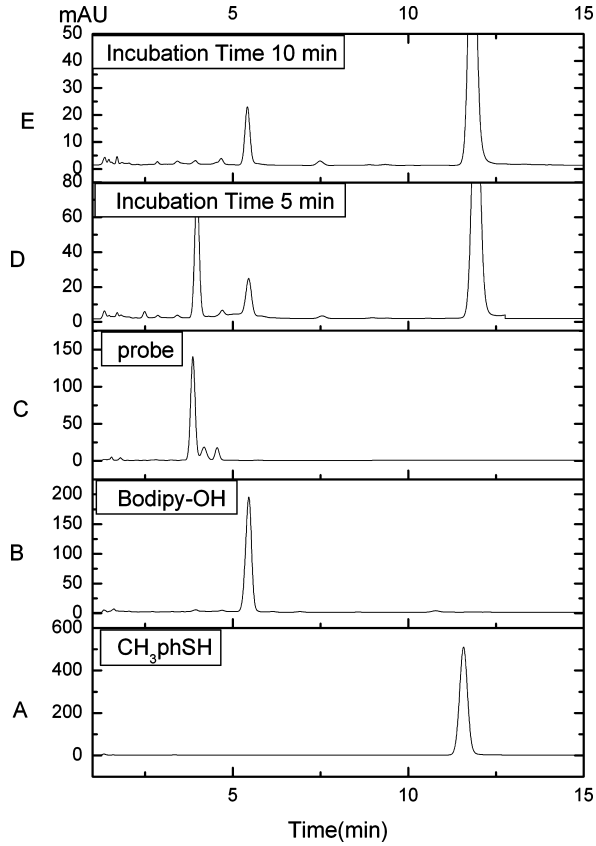


Figure 4. Chromatographic profile of (A) CH_3PhSH, (B) **Bodipy-2**, and (C−E) **Bodipy-1** in the absence and presence of 2 equiv of CH_3PhSH as a function of incubation time on the Agilent Eclipse XDB-C18: 5 μm, 4.6 × 150 mm column. Incubation time: (C) 0 min, (D) 5 min, (E) 10 min. Solvent: 60:40 (v/v) = methanol/buffer solution (18 g of NaOAc in 9.8 mL of acetic acid and 1000 mL of H_2O), pH 5.0.

time courses. In the absence of *p*-thiocresol, **Bodipy-1** gave a retention time at 3.89 min. However, upon addition of *p*-thiocresol, the peak at 3.89 min decreased in intensity until it disappeared after 10 min; meanwhile, a new peak with the retention time at 5.35 min appeared, coming from the formation of **Bodipy-2**.

Further support for the identity of the released **Bodipy-2** comes from the comparison of the emission spectra of the reaction mixture with the standard **Bodipy-2**. We found that they have the identical spectra. Furthermore, the pH titration displayed that they have the same behavior (Figure S3, Supporting Information). All the results of these experiments indicated that the reaction product was indeed the **Bodipy-2**. Finally, mass spectrometry analysis of the mixture of **Bodipy-1** with benzenethiols in buffer solutions was adopted. The mass spectrum displayed two peaks at *m*/*z* 124.0350 and 290.0359, consistent with that of *p*-thiocresol and 2,4-dinitrobenzene *p*-methylbenzene sulfide, respectively. Although attempts to get that of **Bodipy-2** were unsuccessful, the formation of 2,4-dinitrobenzene *p*-methylbenzene sulfide indeed indicated the deprotection of DNBS as reported by the literature.[2f,8a,13−15,18]

To confirm the key role of the 2,4-dinitrobenzensulfonyl (DNBS) protecting group in the sensing process, compound **11**, with a trifluorosulfonyl protecting group instead of DNBS, was synthesized. Different from that for **Bodipy-1**, compound **11** showed almost no fluorescence and fluorescence change in the absence and presence of benzenethiols under the same measuring conditions (Figure S4, Supporting Information), which means that compound **11** showed no response to benzenethiols.

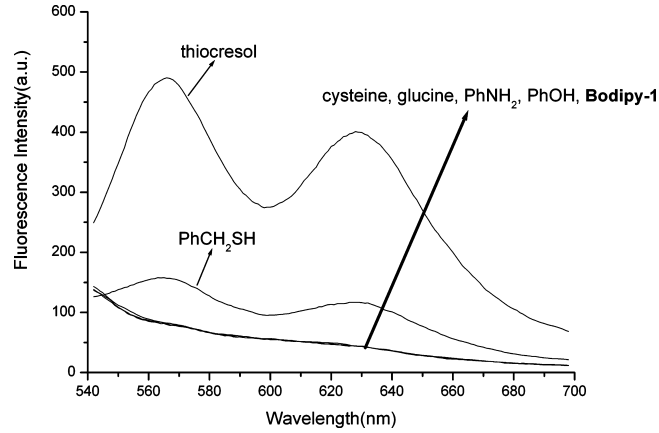


Figure 5. Fluorescence responses of **Bodipy-1** (4 μM) in the presence of 2 equiv of various analysts (phNH2, phOH, glucine, cysteine, $PhCH_3SH$, and *p*-thiocresol) in a phosphate buffer (0.2 M, pH 7.4) at room temperature. The spectra were obtained 20 min later after addition of analysts.

These results demonstrated that the DNBS groups serve as a key part in the probe sensing process.

Selectivity Studies of Bodipy-1 toward Benzenethiols. Fluorescence spectroscopy was employed to investigate the selectivity of **Bodipy-1** for benzenethiols over relevant aliphatic thiols and other common nucleophiles. Shown in Figure 5 are the fluorescence change of the probe upon the addition of CH_3PhSH, glucine, $PhNH_2$, PhOH, cysteine, and $PhCH_2SH$ at pH 7.4. The fluorescence spectra were obtained by excitation at 520 nm. As expected, **Bodipy-1** displays selective fluorescence enhancement in the presence of CH_3PhSH, whereas a negligible fluorescence enhancement is promoted by $PhCH_2SH$. On the other hand, no noticeable change was observed for the addition of the representative nucleophiles, such as glucine, $PhNH_2$, PhOH, and cysteine. The reactivity in the order of $CH_3PhSH > PhCH_2SH >$ cysteine can be rationalized according to the change of the fluorescence above. This order indicates that the degree of thiol dissociation is important for **Bodipy-1** to function as a thiol probe. The nucleophilic thiolate is an essentially reactive form for the thiolysis of ester **Bodipy-1** to **Bodipy-2**. The pK_a value of thiophenols is around 6.5, whereas that of aliphatic thiols is about 8.5. In a neutral reaction medium at pH 7.4, the high degree of dissociation of thiophenols results in the predominant generation of the corresponding thiolate anions, which can effectively react with 2,4-dinitrobenzenesulfonate. However, under the same reaction conditions, the aliphatic thiols remain as a less reactive neutral form and thus the cleavage of the sulfonate is very slow, which indicates that careful selection of the reaction pH would allow **Bodipy-1** to discriminate benzenethiols from aliphatic thiols. Moreover, **Bodipy-1** can readily detect CH_3PhSH in the presence of glucine, $PhNH_2$, PhOH, and cysteine (Figure 6), indicating that these relevant components will not interfere with **Bodipy-1** detection of benzenethiols at pH 7.4.

Conclusions

A novel fluorescent probe, **Bodipy-1**, containing an indole-based Bodipy as a fluorophore and the strongly electron-withdrawing 2,4-dinitrobenzenesulfonyl group as a recognition unit was synthesized. The probe displayed fluorescence ($\lambda_{em} \sim$ 530 nm) with a very low quantum yield due to the quenching effect by the DNBS. However, the Bodipy group in the prepared probe was selectively released immediately upon addition of

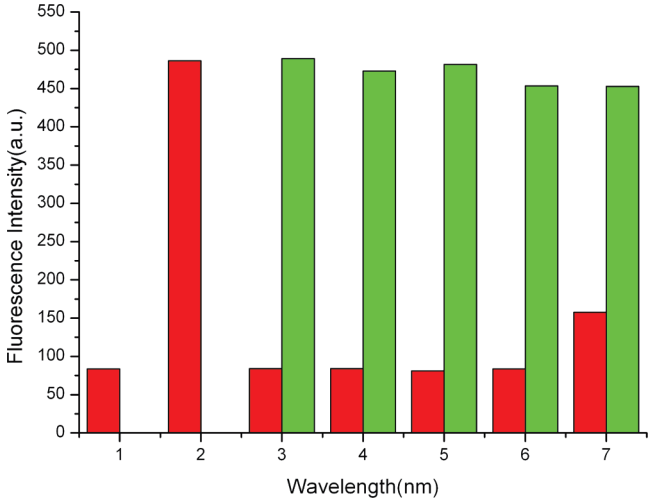


Figure 6. Selectivity of **Bodipy-1** toward *p*-thiocresol and other nucleophiles: (1) **Bodipy-1** only, (2) CH_3PhSH, (3) glucine, (4) $PhNH_2$, (5) PhOH, (6) cysteine, and (7) $PhCH_2SH$. Red bar: the furorescence intensity of only a single analyte (2 equiv) with **Bodipy-1** (4 μM). Green bar: the fluorescence intensity of a mixture of a nucleophilic reagent (2 equiv) and CH_3PhSH (2 equiv) with **Bodipy-1** (4 μM).

benzenethiols to the buffer solution, and a dramatic change with a higher quantum yield and a phenol/phenolate-dependent blue−red switching was observed. That is, two new peaks of the phenol/phenolate state of **Bodipy-2** at 565 and 629 nm appeared in the emission spectrum and two at 520 and 600 nm in the absorption spectrum, resulting from the generation of **Bodipy-2** by the reaction of **Bodipy-1** with thiolate anions from benzenethiols. By varying the pH value, the intensity ratio of I_{565}/I_{629} changed immediately and kept constant as the measurement condition did not change anymore. The ratio of two emission band intensities (I_{565}/I_{629}) upon excitation at 520 nm varies from 2.0 in the presence of benezenethiols at pH 6.6 to 0.3 at pH 8.8 after complete conversion to **Bodipy-2**, a ca. 7-fold emission ratio change. This ratiometric emission property makes **Bodipy-1** a promising probe to discriminate benzenethiols over aliphatic thiols by careful selection of the reaction pH. The reported examples of the fluorescent sensing of benzenethiols function by just the enhancement of fluorescence signals. However, as the change in fluorescence intensity is the only detection signal, factors, such as instrumental efficiency, environmental conditions, and the probe concentration, can interfere with the signal output. The probe reported here gave ratiometric emission properties after the interaction with benzenethiols by varying the pH value, so **Bodipy-1** can eliminate these ambiguities by self-calibration of the two emission bands.

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Supporting Information Available: A detailed description of the synthesis and photophysical data of **Bodipy-1** and **Bodipy-2**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

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