BODIPY-based sulfoxide: Synthesis, photophysical characterization and response to benzenethiols

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A R T I C L E   I N F O

Keywords:
BODIPY-based sulfoxide
Benzenethiols
Ratiometric fluorescence response
Chemodosimeter
Chemospecific reduction
Hypsochromic shifts

Abstract

Two BODIPY dyes bearing a sulfur containing function at the 3-position are reported. The 3-benzylthio compound shows spectroscopic features of the classical BODIPY platform, showing minor solvent dependent spectral shift, a relative small Stokes shift and a high fluorescence quantum yield. Oxidation of the sulfur atom to the sulfoxide leads to a large hypsochromic shift in absorption and emission. We also demonstrated that the sulfoxide derivative can be used as a ratiometric fluorescent chemodosimeter for highly toxic benzenethiols in aqueous media. In this dosimeter the sulfoxide is chemospecifically reduced by benzenethiols to obtain the original oxidation state of the sulfur atom, accompanied with a drastic ratiometric fluorescence response. Furthermore, the probe features excellent selectivity over other competing analytes, moderate signal response times and a good linearity range for quantification. All these features render the sensor suitable for detection of benzenethiols in environmental settings.

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1. Introduction

BODIPYs (boron-dipyromethene dyes) are of special interest as chromophores due to their valuable photophysical characteristics [1]. Furthermore, the parent structure of BODIPY is easy to modify chemically for the preparation of various derivatives. The most commonly studied synthetic strategies available for the modification of the BODIPY core are: (1) nucleophilic substitutions of halogen atoms at the 3- and 5-positions [2,3], (2) condensation reactions [4], (3) substitution of the fluorescent atoms by C or O atoms [5–7], (4) transition-metal-catalyzed reactions through the use of halogenated BODIPYs [8], and (5) electrophilic substitutions at the 2- and 6-positions [9]. In particular, the facile introduction of different groups at the 3- and 5-positions by nucleophilic substitution of chlorine atoms could be used for fast and easy variation of the BODIPY core to optimize the spectroscopic properties. This approach has caught the attention of several research groups [10], and several BODIPYs, containing sulfur atoms at the 3- and 5-positions, have now been constructed to form thioether compounds [2a–c].

Although the sulfur substituted BODIPYs are known, the related fascinating compounds, aromatic sulfoxides, have not been investigated well, so far. Therefore, we initiated the investigation of new BODIPY dyes containing sulfoxide and the BODIPY derivative BODIPY-SO (Scheme 1) was selected for initial evaluation on the basis of ease of synthetic access. In organic compounds, sulfur can have a formal oxidation state ranging from −2 to +6 [11]. Previously studied BODIPYs are thioethers with oxidation state of −2, while the oxidation state of a sulfoxide is 0. The change in oxidation state would have sufficient effect on the photophysical properties. The electron-withdrawing nature of the oxidized thioether, sulfoxide, would lead to hypsochromic shifts in absorption and emission wavelength compared to that of the thioether. On the basis of this finding, we reasoned that the sulfoxide-sulfide interconversion could be used to construct a reaction-based probe and chemodosimeter.

Explorations of sulfoxides in synthesis hold great interest from both laboratory and biological perspectives [12]. Of special interest is the thiol-sulfoxide reactions previously investigated in detail [13]. Theoretically, an interaction between the two species should yield a sulfide, disulfide and water. It is also well known that thiol acidity is of major importance as far as the ease of oxidation is concerned.
The observed ease of thiol oxidation is ArSH > ArCH2SH >> RSH, and aromatic thiols are about 10³–10⁴ times more reactive than aliphatic thiols [13d]. Based on this background, a ratiometric fluorescent probe for benzenethiols, BODIPY-based sulfoxide BODIPY-SO, could be designed (Scheme 1). BODIPY-S and its analog BODIPY-SO are fluorescent chromophores with characteristics of BODIPYs. Sulfoxide BODIPY-SO undergoes a change in the electron-withdrawing nature of the S-group and should show a significant change in photophysical properties, such as a significant shift in emission wavelength. Thus a fluorescent ratiometric chemodosimeter could be obtained. Several fluorescent sensors that selectively respond to the presence of benzenethiols have been reported [14], most of which respond to benzenethiols with only fluorescence signal turned-on. Unfortunately, single-intensity-based sensing is compromised by the local distribution of probes, drift of light sources and detectors. New ratiometric fluorescent probes that can overcome the limitation of intensity-based probes and provide quantitative measurement are therefore in demand. To our best knowledge, few ratiometric fluorescent probes for benzenethiols have been constructed to date. Herein, we report the synthesis and photophysical properties of a new BODIPY dye, BODIPY-SO, and its potential application as a ratiometric fluorescent chemodosimeter for benzenethiols.

2. Experimental section

2.1. General methods and instruments

All chemicals were purchased from commercial suppliers and used without further purification unless otherwise specified. Anhydrous CH2Cl2 was dried and distilled immediately prior to use. 3-chloro-5,7-dimethyl-6-ethyl-8-phenyl-BODIPY [3b] was prepared according to literature procedures.

1H NMR and 13C NMR spectra were recorded on a spectrometer operating at 400 MHz and 100 MHz, respectively. Deuterated chloroform was used as the solvent, TMS as internal standard. Mass spectra were measured on an HP 1100 LC–MS spectrometer. UV–vis spectra were measured using a Shimadzu UV-2550 spectrophotometer. Fluorescence spectroscopic measurements were conducted on a Varian Cary eclipse fluorescence spectrophotometer. TLC analysis was performed on silica gel plates and column chromatography was conducted over silica gel (mesh 200–300), both of which were obtained from the Qingdao Ocean Chemicals.

For absorption or fluorescence measurements, compounds were dissolved in EtOH to obtain stock solutions (2–5 mM). These stock solutions were diluted with aqueous solutions to the desired concentration.

2.2. Synthesis

Synthesis of 3-Benzylsulfanyl-5,7-dimethyl-6-ethyl-8-phenyl-4,4-difluoro- 4-bora- 3a,4a-diaza-indacene (BODIPY-S). To a solution of 3-chloro-5,7-dimethyl-6-ethyl-8-phenyl-BODIPY (0.716 g, 2 mmol) in CH2CN (30 mL) was added z-tolueneethiol (0.298 g, 2.4 mmol) and Et3N (5 mL), and the reaction mixture was stirred for 3 h at room temperature. Excess CH2CN was removed under vacuum, and the residue was dissolved in ethyl acetate, washed with H2O and dried over Na2SO4. The crude product was purified by flash chromatography (silica gel, eluent: CH2Cl2/EtOAc = 40:1) to afford BODIPY-S (0.713 g, 80%), mp 169–173 °C; FTIR (BODIPY-S) 2963, 1542, 1380, 1189, 1141, 964, 728 cm⁻¹; 1H NMR (400 MHz, CDCl3) 7.43–7.50 (m, 5H), 7.27–7.34 (m, 5H), 6.29 (d, J = 4 Hz, 1H), 6.22 (d, J = 4 Hz, 1H), 4.29 (s, 2H), 2.62 (s, 3H), 2.36 (q, J = 7.6 Hz, 2H), 1.43 (s, 3H), 1.03 (t, J = 7.6 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 159.5, 150.2, 140.1, 139.0, 136.2, 136.0, 135.1, 134.4, 132.4, 129.5, 129.1, 128.9, 128.8, 128.3, 128.6, 128.3, 127.3, 127.1, 116.2, 38.0, 171.4, 143.3, 13.0, 12.1; HRMS (ESI+) calced for C26H24N2BF2S [M + H⁺]: 445.1721. Found: 445.1760.

Synthesis of 3-Benzylsulfinyl-5,7-dimethyl-6-ethyl-8-phenyl-4,4-difluoro- 4-bora- 3a,4a-diaza-s-indacene (BODIPY-SO). To a solution of BODIPY-S (0.446 g, 1 mmol) in dry dichloromethane (20 mL) was added 0.99 equivalents of m-CPBA (0.17 g, 0.99 mmol) at 0 °C. The reaction mixture was stirred for 30 min. Excess potassium carbonate was added to neutralize any acids, and washed with water. The organic layers were dried over anhydrous Na2SO4 and evaporated in vacuo. The crude product was further purified by flash chromatography (silica gel, eluent: CH2Cl2/EtOAc = 50:1) to afford BODIPY-SO (0.32 g, 70%), mp 180–183 °C; FTIR (BODIPY-SO) 1578, 1141, 1071, 1056 (S=O), 731 cm⁻¹; 1H NMR (400 MHz, CDCl3) 7.51–7.53 (m, 3H), 7.28–7.40 (m, 7H), 6.56 (d, J = 4 Hz, 1H), 6.26 (d, J = 4 Hz, 1H), 4.51 (d, J = 12.8 Hz, 1H), 4.22 (d, J = 12.8 Hz, 1H), 2.70 (S, 3H), 2.40 (q, J = 7.6 Hz, 2H), 1.51 (S, 3H), 1.07 (t, J = 7.6 Hz, 3H); 13C NMR (100 MHz, CDCl3) δ 166.2, 150.4, 143.6, 141.6, 137.7, 136.9, 134.7, 133.5, 130.6, 129.6, 128.8, 128.7, 128.6, 128.3, 128.1, 124.1, 115.5, 64.2, 17.2, 14.0, 13.6, 12.5; HRMS (ESI+) calced for C26H24N2BF2SO [M + H⁺]: 461.1670. Found: 461.1616.

3. Results and discussion

3.1. Synthesis of BODIPY-S and BODIPY-SO

BODIPY-SO was readily synthesized in two steps beginning with the key intermediate 1. The overall yield is 56% for two steps. Intermediate 1 was obtained in a one-pot, two-step procedure via condensation of 2,4-dimethyl-3-ethylpyrrole with 2-benzoyl-5-chloro-4-bora-4a-diaza-indacene. The structures of BODIPY-S and BODIPY-SO were fully characterized by 1H NMR, 13C NMR, and HRMS analysis.

3.2. Photophysical properties of BODIPY-S and BODIPY-SO

Spectroscopic evaluation of BODIPY-S and BODIPY-SO was performed in several solvents of varying polarity (Figure S1, Figure S2, Table S1 in supporting information). The optical features are characteristic of the classical BODIPY platform. As is evident from Figure S1, S2 and Table S1, BODIPY-S shows a narrow, strong absorption band around 545 nm and a shoulder at the short wavelength side in pure solvents. The S0–S1 absorption band shows
minor solvent-dependent variation, with the maximum being slightly shifted hypsochromically (~7 nm) when the solvent is changed from benzene (550 nm) to acetonitrile (543 nm), which is consistent with the general behavior of other BODIPY chromophores [15]. Similar to the absorption spectrum, the emission spectrum also shows minor solvent-dependent shift with a relative small Stokes shift (~15 nm) and a high fluorescence quantum yield (0.2–0.4).

Oxidation of BODIPY-S to the sulfoxide (BODIPY-SO) causes a large hypsochromic shift in absorption and emission relative to the parent compound. This blue shift in emission is accompanied by a decrease in \( \Phi_f \), which is consistent with the general behavior of other aromatic sulfur-containing compounds \[11b\] [16]. The emission maximum shifts from 561 nm for the unoxidized version to 537 nm for the sulfoxide (BODIPY-SO) in EtOH. The broad shape of the \( S_0 \rightarrow S_1 \) transition together with the hypsochromic shifts may be attributed to intramolecular charge transfer character resulting from the strong conjugation of the sulfoxide function with the BODIPY core. All these characteristics demonstrate that changing the oxidation state of the sulfur atom leads to productive changes in the photophysical properties. Ultimately, the fact that the interconversion of BODIPY-S to BODIPY-SO induces a dramatic shift in emission provides an opportunity for construction of ratiometric chemodosimeters. As sulfoxide reduction by aromatic thiols could yield the corresponding sulfide, the thiol-sulfoxide reactions were therefore chosen to prove the above concept and quantify the toxic benzenethiols.

3.3. Thiol-sulfoxide reaction based response of BODIPY-SO to benzenethiols

At first, the time course of the reaction between BODIPY-SO and p-thiocresol was studied by monitoring the variations in the ratios of fluorescence intensities of the reaction mixture at 568 and 536 nm (\( I_{568}/I_{536} \)) (Fig. 1). Under pseudo-first-order reaction conditions (10 \( \mu \)M BODIPY-SO and 1 mM p-thiocresol), an observed rate constant (\( k_{obs} \)) at pH 7.2 and 40 °C is found to be 1.7 min\(^{-1}\), indicating that BODIPY-SO reacted rapidly with p-thiocresol under the given experimental conditions.

Fig. 2 shows the sensory response of BODIPY-SO to various concentrations of p-thiocresol in buffer solutions at 40 °C. Upon addition of increasing concentrations of p-thiocresol to a solution of BODIPY-SO, a decrease in the absorption band at 484 nm and a concomitant increase of a new band at 546 nm were observed, with a distinct isosbestic point at 512 nm. In good agreement with the findings in absorption, the sensor exhibited a ratiometric fluorescent response to p-thiocresol. As shown in Fig. 2, addition of p-thiocresol elicited a dramatic change in the emission spectrum. The intensity of the emission at 536 nm decreased gradually with the simultaneous appearance of a new red-shifted emission band at 548 nm. Notably, the ratio of emission intensities at 568 and 536 nm (\( I_{568}/I_{536} \)) upon excitation at 484 nm increases from 0.67 in the absence of benzenethiols to 19.03 after complete conversion to BODIPY-S, showing a 28-fold ratiometric enhancement, indicative of an efficient ratiometric response of BODIPY-SO to p-thiocresol. A good linear calibration curve (\( R = 0.99 \)) of the emission response in the benzenethiols concentration range of 0–300 \( \mu \)M could be obtained (Fig. 3), indicating that BODIPY-SO would potentially be employed to quantitatively detect p-thiocresol concentrations. The detection limit of BODIPY-SO toward p-thiocresol is evaluated to be 2.1 \( \times \) 10\(^{-7}\) M, which is comparable or superior to most of the reported benzenethiol sensors.

The sensory response of BODIPY-SO to other benzenethiols such as thiophenol, 4-chlorobenzenethiol and 4-bromobenzenethiol was also studied. Predictably these benzenethiols induced a significant enhancement of the fluorescence ratio as p-thiocresol did,
indicative of an efficient ratiometric response of BODIPY-SO to benzenethiols.

Having determined the sensory process of BODIPY-SO to benzenethiols, we felt it desirable to gain insight into the sensing mechanism. Thus the reaction product of BODIPY-S + benzenethiols (100 equiv) was isolated by a silica gel column and was then subjected to standard characterization. Comparison of the 1H NMR (Figure S4), Mass (Figure S5), absorption and emission spectra of isolated compound with BODIPY-S indicates that, indeed, BODIPY-SO was converted to BODIPY-S by thiol - sulfoxide conversion consistent with the general mechanism of thiol oxidation by DMSO determined by Wallace and Mahon [13c–e].

BODIPY-SO is also highly selective for benzenethiols over other competing analytes in a buffer solution (Fig. 4). No obvious changes of the ratiometric emission ratio of BODIPY-S to BODIPY-SO were observed upon addition of the representative amino acids, sugar, vitamins, aromatic alcohols and amines. Although aliphatic thiols are known to be able to reduce sulfoxide, the aliphatic thiols are about $10^3$–$10^4$ times less reactive than aromatic thiols and the reaction process must proceed at elevated temperature. As expected, under the same experimental condition (in pH 7.2 sodium phosphate buffer/EtOH at 40 °C), aliphatic thiols did not undergo any appreciable reaction in the assay time period of 30 min. Even extending the reaction time to 10 h, no appreciable reaction occurred. Only addition of benzenethiols induced a significant enhancement of the fluorescence ratio. Moreover, no obvious interference was observed in the fluorescence spectra, while titrating the different mixtures of competing analytes and BODIPY-SO with benzenethiols. These results indicate the excellent selectivity of BODIPY-SO toward the benzenethiols over the other competitive species.

4. Conclusions

In summary, we have designed and synthesized sulfur substituted BODIPY fluorophores, BODIPY-S, and the derivative BODIPY-SO. BODIPY-S shows the general photophysical behavior of other BODIPY chromophores with a relatively small Stokes shift and a high fluorescence quantum yield. Conversion of BODIPY-S to BODIPY-SO causes a large hypsochromic shift in absorption and emission. This blue shift in emission is accompanied by a decrease in $\eta$. Based on the fact that the interconversion of BODIPY-S to BODIPY-SO induces a dramatic shift in emission, we applied BODIPY-SO as a ratiometric fluorescent chemodosimeter for benzenethiols. As expected, the probe exhibited a large red shift in absorption and a drastic ratiometric fluorescent response to benzenethiols with the emission intensity ratio ($I_{568}/I_{536}$) increasing from 0.67 to 19.03. In addition, the probe features excellent selectivity over other competing analytes, moderate signal response times and a good linearity range for quantification. We anticipated all these features render the sensor suitable for detection of benzenethiols in environmental settings.

Acknowledgments

We gratefully acknowledge the financial support by the National Science Foundation of China (grant no.: 20902021, 21172071, 21190033), the Scientific Research Foundation for the Returned Overseas Chinese Scholars (State Education Ministry) and the Fundamental Research Funds for the Central Universities.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.dyepig.2012.08.026.

References

(c) Fron E, Coutiño-Gonzalez E, Pandey L, Sliwa M, Van der Auweraer M, De


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