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RAPID COMMUNICATION

Detection of hydrogen sulfide using BODIPY based colorimetric and fluorescent on-off chemosensor

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Abstract. A colorimetric and fluorescence turn-off probe 10-(4-azido phenyl)-5,5-difluoro-5h-dipyrrolo[1,2-c:1',2'-f][1,3,2] diazaborinin-4-ium-5-uide, **1**, for selective detection of H_2S is reported. The probe displayed a robust decrease in fluorescence intensity with high sensitivity, specificity and least toxicity to detect exogenous H_2S and also in live normal human oral fibroblast cells loaded with probe **1**. The detection limit of probe **1** being 0.17 μm for H_2S.

Keywords. BODIPY; H_2S sensing; Fluorescent probe; Cell imaging; Naked eye detection.

1. Introduction

Hydrogen sulfide plays a cell signalling role endogenously similar to NO and CO.[1,2] Unlike NO, it does not generate the toxic reactive oxygen species, but rather shows anti-inflammation effects and acts as an antioxidant. The role of CO is a smooth gaseous neurotransmitter agent at very low concentration. The signalling processes by H_2S are mediated most likely by HS^- but the role of H_2S cannot be eliminated. These active species are controlled by a prototropic equilibrium defined by pK_1 of 6.9 and pK_2 of 19 of H_2S at a physiological pH of 7.4.[3,4] The level of H_2S in the central nervous system lies in the range of 50–160 μM and the sulfide concentration in blood varies in the range of 10–100 μM, though some authors have reported lower sulfide concentrations.[10] The biological processes mediated by H_2S includes angiogenesis, vasodilation, neuromodulation and anti-inflammation.[5–9] Any misregulation in endogenous concentration levels of H_2S has been correlated with ailing conditions such as hypertension, Down's syndrome, diabetes and also liver cirrhosis.[11–14] To monitor such H_2S based activity, it requires the development of good analytical methods to rapidly identify and quantify its presence. Some methods based on colorimetry, electrochemical analysis, chromatography, metal-induced precipitation and fluorescence spectroscopy are known.[15–27] Sometimes, quick recognition of H_2S by visual sensing is important especially when its role as pollutant is suspected. Such method could be adopted by any non-expert at the initial stage to decide to seek other help based on sophisticated analytical techniques.

For such a strategy, the use of dual colourimetric-fluorescent probes will be helpful because this will offer convenient visual sensing by the 'naked eye', followed by sensitive detection using fluorescence response. To address this problem, we use the specific property of HS- which effectively reduces azide to amine.[28] BODIPY (5,5-difluoro-5H-dipyrrolo[1,2-c:1',2'-f][1,3,2]diazaborinin-4-ium-5-uide) based dyes

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find preference in these studies because of their high photo-stability with high molar extinction coefficients. Recent efforts have been made to explore BODIPY 'turn-on' probes that function in NIR region.[23–27,29–37] Most of them exhibit poor detection limit. Only a few functionalized BODIPY's have been studied which show fluorescence 'on-off' on exposure to H_2S and show a gain in fluorescence due to restriction in molecular rotation with time as cellular apoptosis increases viscosity within cellular fluid.[38,39] However, it is unclear if all cell types undergo apoptosis in the presence of exogenous H_2S with time.[40] This initiated us to develop the probe, 10-(4-azidophenyl)-5,5-difluoro-5H-dipyrrolo[1,2-c:1',2'-f][1,3,2]diazaborinin-4-ium-5-uide, **1**, by diazotization of 10-(4-aminophenyl)-5,5-difluoro-5H-dipyrrolo[1,2-c:1',2'f] [1,3,2] diazaborinin-4-ium-5-uide, **2**, as shown in Scheme 1. Probe **1**, has been characterized by ^{1}H NMR, and HRMS and by X-ray crystallography (Figures S5, S6 and S7, Supplementary Information).

2. Experimental

2.1 *General*

All reactions were conducted under the argon atmosphere using Schlenk line technique. $NaSH.xH_2O$, was purchased from Sigma Aldrich. Sodium azide, Fe-metal, and sodium nitrite were purchased from Merck Industries. All other chemicals and solvents were procured from Spectrochem Ltd. and used as received. Column chromatography was performed on Merck silica gel (60–120 mesh). TLC was carried out with E. Merck silica gel 60-F254 plates. All stock solutions were freshly prepared in deoxygenated and argon purged solvents. The concentration of NaSH solutions were calibrated using freshly prepared solutions of sodium nitroprusside before use.

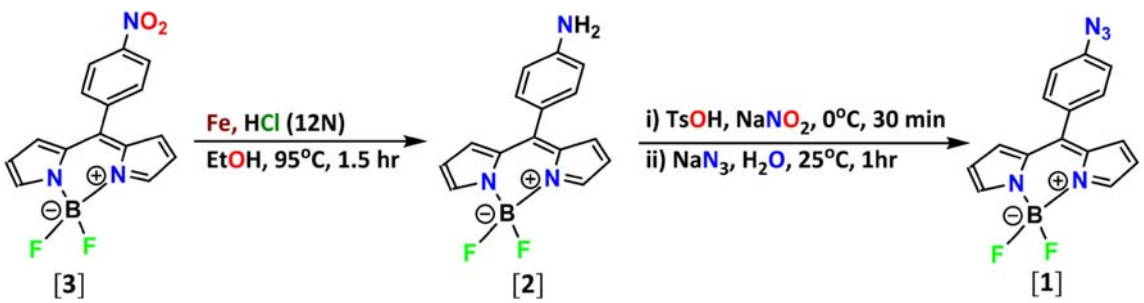
The ^{1}H and ^{13}C spectra were recorded on 400 MHz Jeol ECS-500 spectrometer. The chemical shifts (δ) are reported in ppm. The following abbreviations are used: m (multiplet), s (singlet), br s (broad singlet), d (doublet), t (triplet) dd (doublet of doublet). High-resolution mass spectra were obtained from MicroMass ESI-TOF MS spectrometer. Electronic absorption spectral measurements were performed in a Jasco V-630 UV/Vis Spectrometer. The IR spectra were taken using a JASCO FT-IR–460 plus infrared spectrometers in the 4000–400 cm^{-1} frequency range, using powered samples diluted in KBr pellets. Fluorescence experiments were performed using a PTI LPS –220B fluorescence spectrophotometer and using a fluorescence cell with a 10 mm path.A specimen of $C_{15}H_{11}BF_2N_5$ was used for the X-ray crystallographic analysis in a Bruker AXS KAPPA APEX II system, manufactured by Bruker Analytical X-ray Systems.

2.2 *Synthesis of 10-(4-nitrophenyl)-5,5-difluoro-5H-dipyrrolo[1,2-c:1',2'-f][1,3,2]diaza-borinin-4-ium-5-uide;* ***3***

10-(4-nitrophenyl)-5,5-difluoro-5H-dipyrrolo[1,2-c:1',2'-f][1,3,2]diazaborinin-4-ium-5-uide; **3** was prepared using the reported procedure.[1] Molecular Wt. 313; Molecular Formula: $C_{15}H_{10}BF_2N_3O_2$; ν_{max}(KBr)/cm^{-1} 1525, 1347 (nitro group).^{1}H NMR ($CDC1_3$): δ 6.602 (d, 2H, CH), 6.855 (d, 2H, CH), 7.773 (d, 2H, phenyl), 8.007 (s, 2H, CH), 8.423 (d, 2H, phenyl). MS (ESI), *m/z*: 312.0[$M-H]^-$ 312.0842. Elemental analysis: calculated (found) in % for $C_{15}H_{10}BF_2N_3O_2C$ 57.55 (57.56); H 3.22(3.20); N 13.42(13.40).

2.3 *Synthesis of 10-(4-aminophenyl)-5,5-difluoro-5H-dipyrrolo[1,2-c:1',2'-f][1,3,2]diazabor -inin-4-ium-5-uide;* ***2***

To an ethanol (30 mL) solution of **3** (0.313 g; 1 mmol) were added Iron powder[2] (0.35 g; 7.037 mmol), water (5 mL), and HCl (100 µL, 12N) consecutively. After stirring at 95 °C for 90 min, the reaction mixture was filtered in hot condition. Following an ethanol wash, the filtrates were combined and the solvent was removed under vacuum. Purification was done by column chromatography (silica gel, 1:5 Hex/ DCM) afforded the title compound as an orange red colour precipitate (0.24 g; yield: 88.88%). $R_f = 0.52$ in DCM. Molecular Wt 298; Molecular Formula:



Scheme 1. Synthesis of probe **1**.

$C_{15}H_{12}BF_2N_3$. ν_{max} (KBr)/cm^{-1} 3480, 3393 (amino group). UV/Vis λ_{max} 494 nm; HRMS (*m/z*) [M+H] 284.11; ^{1}H NMR ($CDCl_3$): δ 7.88(2H,s); 7.45–7.43(2H,d); 7.02–7.01(2H;d); 6.79–6.77(2H;d); 6.54–6.53(2H,d). Elemental analysis: calculated (found) in % for $C_{15}H_{12}BF_2N_3$ C 63.64 (63.66); H 4.27(4.25); N 14.84(14.82).

2.4 *Synthesis of 10-(4-azidophenyl)-5,5-difluoro-5H-dipyrrolo[1,2-c:1',2'-f][1,3,2]diazabor -inin-4-ium-5-uide;* ***1***

To an acetonitrile (30 mL) solution of **2** (0.14 g, 0.5 mmol) cooled to 0–5 °C were added 1 equivalents of p-toluenesulfonic acid, 2.5 equivalents of sodium nitrite and stirred for 30 min in ice bath. To these 2 equivalents of NaN_3 was added and stirred for one hour. Then the reaction mixture was washed with saturated $NaHCO_3$ solution and the organic layer was dried over sodium sulphate. Purification was done by column chromatography (silica gel, 1:1 DCM/Hex) afforded the title compound as an orange colour precipitate (0.1 g; yield: 71%). R_f = 0.34 in DCM/ Hexane (1:1 v/v).Molecular Wt 309; Molecular Formula: $C_{15}H_{10}BF_2N_5$. ν_{max}(KBr)/cm^{-1} 2130 (azido group). UV/Vis λ_{max}; 498 nm. HRMS(*m/z*) [M+H] 310.10 ^{1}H NMR($CDCl_3$): δ 7.94(2H,s); 7.60–7.57(2H,d); 7.26–7.20(2H;d); 6.92(2H;s); 6.56–6.55(2H,d). Elemental analysis: calculated (found) in % for $C_{15}H_{10}BF_2N_5$C 58.29 (58.32); H 3.36(3.28); N 22.66(22.62). [X-ray data deposited, **CCDC No. 1456824**].

3. Results and Discussion

The synthesized compound **1** was dissolved in CH_2Cl_2 and layered with hexane, which on standing at room temperature for a few days resulted in the formation of orange-coloured diffraction quality crystals. The structure of **1** is shown in Figure 1. IR spectrum of **1**, shows stretches at 2089 and 2130 cm^{-1} corroborating the presence of azide functionality (Figure S8c, SI).

To explore the potential application of **1** as a sensor material for the visual detection of H_2S, we found a color change of **1** (50 μM) towards NaSH, from pale yellow to orange in methanol–PBS buffer mixture (1:2v/v) (Figure 2a). Under UV lamp (λ=365 nm) it was found that a discernible color change in the solution of **1** from fluorescent green to violet-blue occurred only in the presence of NaSH (Figure 2b).

The absorption spectrum of 1 exhibited λ_{max} = 498 nm in methanol-PBS buffer mixture (pH = 7.4, 10 mM) (1:2 v/v) with a molar extinction coefficient ε = 57763 M^{-1} cm^{-1} with a distinct shoulder at 477 nm (Figure S2, SI). The fluorescence spectra acquired for 1 show a strong fluorescence emission at λ_{em} = 516 nm when excited at 495 nm (Figure S3, SI). In contrast compound 2 shows an absorption band centered at λ_{max} = 493 nm, with molar absorption coefficient ε = 52175 M^{-1} cm^{-1}, (Figure S2, SI) but no significant fluorescence was observed when excited at λ_{ex} = 495 nm under identical conditions (Figure S3, SI). These photophysical data reveal that probe **1** can act as an efficient turn off fluorometric chemodosimeter for H_2S detection. The above choice of solvent buffer system was made after studying the fluorescence emission spectra of probe **1** in various solvent and solvent buffer mixtures (Figure S1, SI).

When the spectral changes with time was monitored after treating probe **1** (5 μM) with NaSH under pseudo first order reaction conditions we find that the absorbance at λ_{max} = 498 nm for **1** gradually decreases with concomitant formation of **2** and λ_{max} = 493 nm. In order to decipher the response time of probe **1** towards

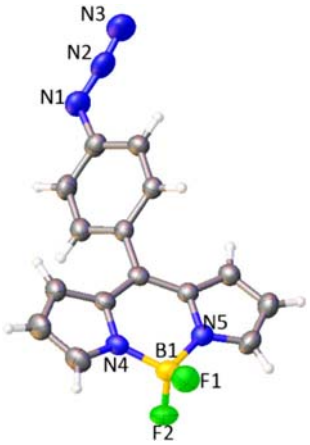


Figure 1. The perspective view of **1**, with thermal ellipsoid drawn at 50% probability level solvent molecules have been omitted for clarity; nitrogen (blue); carbon (grey); boron (yellow); fluorine (green).

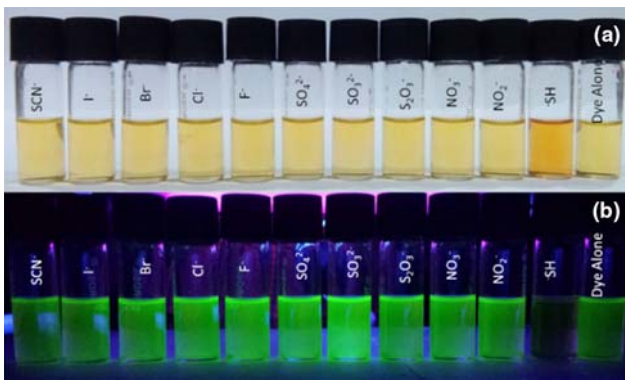


Figure 2. Photograph of culture tubes with probe **1** (50 μM) in the presence of different analytes (yellow colored) and in NaSH (orange colored) in MeOH-PBS buffer (1:2 v/v) taken (a) under ambient light; (b) taken under handheld UV lamp (λ = 365 nm).

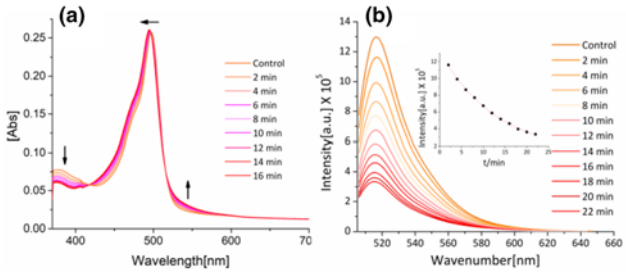


Figure 3. (a) UV-visible spectra of probe **1** (5 μM) with (30 μM) of NaSH in MeOH-PBS buffer (1:2 v/v) after 2, 4, 6, 8, 10, 12, 14 and 16 min; (b) Fluorescence responses of probe **1** (5 μM) to NaSH (30 μM) after 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 and 24 min. Inset: time dependence of fluorescence intensity, recorded at 520 nm in MeOH-PBS (1:2 v/v; 10 mM, pH = 7.4).

H_2S, time dependent fluorescence spectra were acquired. The probe **1** (5 μM) on treatment with NaSH (30 μM) in MeOH-PBS buffer (pH = 7.4; 10 mM) shows gradual decrease in fluorescence intensity with increasing time (Figure 3b).

To further check the full conversion of probe **1** to **2** under the reaction conditions, ESI MS of the authentic **2** matched with that of the peak at m/z = 284.1314 observed with **1**, when treated with NaSH. This confirms that **1** under reduction by NaSH produces the reduced product as **2** (Figure S7, SI).

The probe **1** was absorbed on Whatmann 1 grade paper and on silica coated TLC strips for the visual detection of H_2S. The change in color is nicely visible (Figure 4 inset). The selectivity and sensitivity of probe **1** towards H_2S in the presence of various analytes were examined (Figure 2). In each case, probe **1** (5 μM) was treated separately with 50 μM of each analyte (either F^-, Cl^-, Br^-, I^-,

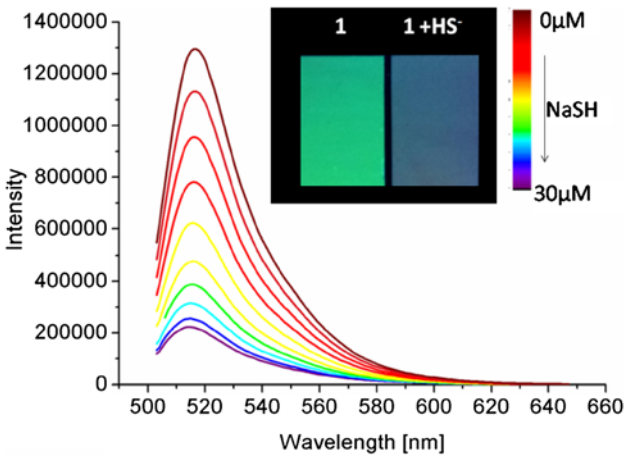


Figure 4. Fluorescence spectra of probe **1** (5 μM) with increasing concentrations (0 to 30 μM) of NaSH in PBS buffer (10 mM, pH = 7.4). The inset shows a fluorometric test kit; Photographs of the TLC plate coated with **1** used for the detection of SH^- ions in solution.

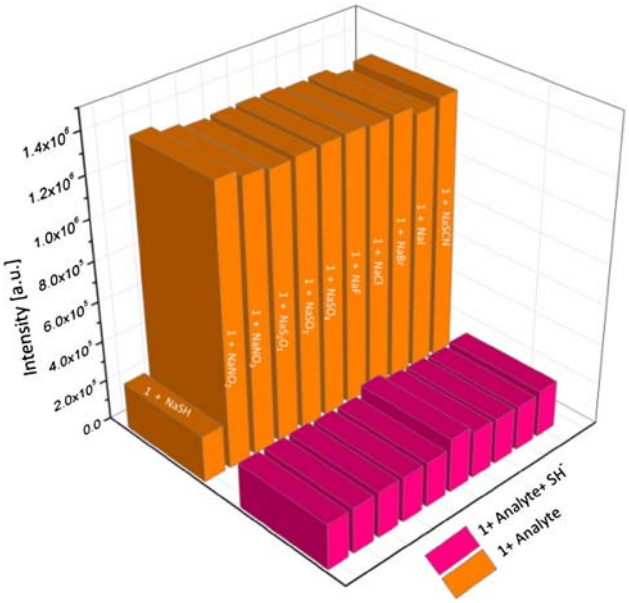


Figure 5. Fluorescence intensity diminution [I] at 516 nm for probe **1** (5 μM) towards NaSH (30 μM) in MeOH-PBS (1:2 v/v) buffer. Front row: NaSH was added in the presence of the respective analyte; back row changes in intensities in the presence of various analytes (50 μM).

NO_2^-, NO_3^-, $S_2O_3^{2-}$, SO_3^{2-}, SO_4^{2-}, SCN^-) in MeOH-PBS buffer (1:2 v/v; 10 mM, pH = 7.4) and fluorescence spectra were recorded at room temperature. However, no significant fluorescence diminution (at λ_{em} = 516 nm) were observed for all the analytes (Figure 5). But when NaSH (30 μM) was added in the presence of the individual analytes then a significant decrease in fluorescence intensity was observed in all the cases. This depicts that the probe can be used to selectively detect H_2S in the presence of competing analytes. A comparison with the structurally characterised different probes in the turn-off mode showed the detection limit of 4 μM;[41] 23.42 μM;[42] for complexes with Zn^{2+} = 7.9 μM and for Cd^{2+} = 0.2 μM;[43] 8.3 μM[44] and these data are not better than the present study. Sometimes the turn-on mode provided better resolution but with the structurally characterised two recent reports the identification limit of 2.6 μM;[45] and 0.5 μm[46] also poorer than 0.17 μM which has been the limit of identification in the present study.

The MTT assay showed that probe **1** is non-toxic in nature to normal human oral fibroblast (NHOF) cells and can be used for biological studies (Figure S9, SI). The NHOF cells were first incubated with the probe **1** for 20 min at 37 °C. The comparisons with control show that probe **1** treated NHOF cells are highly fluorescent on treatment with 10 μM NaSH. The fluorescence intensity decreases with time as the exogenous added H_2S react with probe **1** (Figure 6). The fluorescence intensity falls further on increasing the incubation time period and the rate of fluorescence diminution

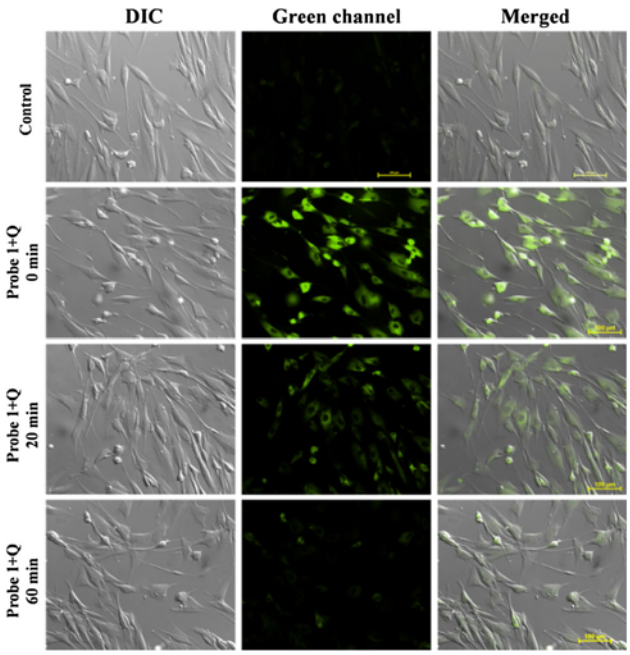


Figure 6. Cell images of NHOF cell lines. Cells were treated with probe **1** (1.0 μM) for 20 min and then incubated with H_2S (10 μM) for 0, 20, 60 min. Images were taken at FITC filter (excitation range 465–495 nm and emission range 515–555 nm).

increases with a higher concentration of NaSH. But, no cellular apoptosis was observed for NHOF cells within the above conditions.[21] Besides, both probe **1** and **2** show enhancement of fluorescent intensity in methanol on increasing the viscosity of the medium with increasing glycerol fractions (Figure S10, SI). Probe **1** is found to be ~100 folds more fluorescent than **2** under similar concentrations in methanol/glycerol fraction.

4. Conclusions

In conclusion, a BODIPY based colorimetric and fluorescent turn on-off probe has been developed for H_2S detection in methanol-PBS buffer at physiological pH. The probe provides detection of H_2S by chemical reaction with the HS^- *via* conversion of azide to amine. The detection limit of probe **1** is found to be 0.17 μM for H_2S. The fluorescence intensity of the probes decreases by nine-fold when NaSH is added at pH 7.4. The probe can be used on silica plate strips to detect H_2S in rusted water pipeline or from wastewater in the presence of other analytes and this also detect exogenous H_2S in NHOF cells.

Supplementary Information (SI)

Table S1 and Figures S1-S11 available at www.ias.ac.in/chemsci.

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