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BODIPY-based fluorescent sensors with tunable binding ability to fluoride and hydrogen sulfate anions

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The binding and sensing abilities of BODIPY based fluorescent sensors **1** and **2** towards various anions have been studied by absorption, emission and ^{1}H NMR titrations spectroscopy. Sensor **1** shows selective response toward fluoride anions through hydrogen bonding interaction, while sensor **2** acts as a highly selective ''Off–On'' fluorescent sensor for hydrogen sulfate anion in DMSO solvent. The fluorescence response of sensor **2** towards HSO_4^- may be due to the suppressed PET (photo-induced electron transfer) process induced by the multiple hydrogen bonding interactions between sensor **2** and HSO_4^-.

Keywords: Fluorescent sensors, Off-On sensors, BODIPY derivatives, Hydrogen sulfate, Fluoride

Anion recognition and sensing is an area of great interest due to its vital role in environmental, clinical, chemical and biological systems[1-4]. Among various important anions, fluoride anions have gained great attention due to their role in preventing dental caries and osteoporosis. Excess of fluoride can cause dental or skeletal fluorosis, and is also associated with kidney failure and nephrolithiasis[5, 6]. Thus, considerable effort has been devoted to the development of techniques for detection and sensing of fluoride anions[7-12]. On the other hand, the hydrogen sulfate anion is especially important in biological and industrial areas. Recently, much attention has been focused on the development of techniques for detection and monitoring of hydrogen sulfate anions[13-23]. Among various methods, most of them are optical sensors and give fluorimetric/ colorimetric responses, which can be classified into two classes viz., non-Schiff bases and the Schiff bases.

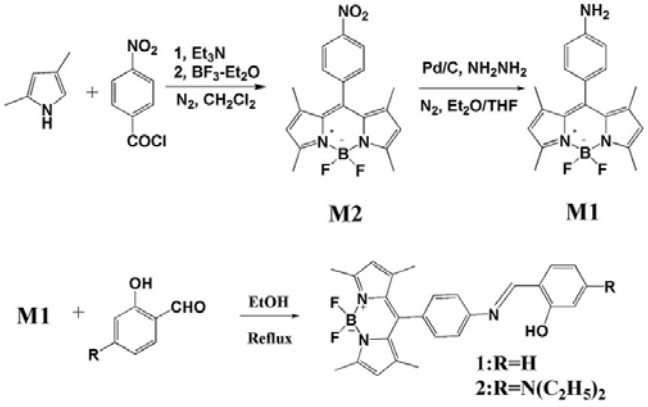
Fluorescent sensors appear as the most promising candidates for chemical sensing due to their simplicity, high degree of specificity and low detection limit[24, 25]. Among various fluorescent dyes, the BODIPY scaffold has been found to be as the most promising candidate for the fluorescent sensing and labeling due to its excellent photophysical properties, such as sharp absorption and fluorescence peaks, high stability and high fluorescence quantum yield[26-28].

Recently, Borisov and coworkers[29] presented highly sensitive ammonia sensors based on BODIPY dyes for environmental monitoring. The most sensitive sensor has a limit of detection (LOD) of 0.11 μg/L and the sensors show remarkable operational stability with no noticeable drift over a period of 2 weeks. Emrullahoglu and coworkers developed a BODIPY-based fluorescent probe with a phosgene-specific reactive motif, which shows remarkable selectivity toward phosgene. A prototypical handheld phosgene detector with a promising sensing capability that expedites the detection of gaseous phosgene without sophisticated instrumentation has been developed[30]. Our ongoing studies on the design, synthesis and evaluation of artificial fluorogenic and chromogenic probes for selective sensing of biological important species[31-34] have led us to design a new BODIPY based fluorescent sensors **1** and **2**. In our current study, sensors **1** and **2** can effectively recognize F^- or HSO_4^- via fluorescence and UV absorption changes.

Experimental

All reagents for synthesis obtained commercially were used without further purification. In the titration experiments, all the anions (in the form of tetrabutylammonium salts) were purchased from Sigma-Aldrich Chemical, stored in avacuum desiccator.

^{1}H NMR spectra were recorded in DMSO-d_6 solution on the Bruker 400 MHz instruments, and spectral data are reported in ppm relative to tetramethylsilane (TMS) as internal standard. HR MS were carried out on QTof-Micro YA 263 instrument. UV-vis spectra were recorded on a Perkin Elmer Lambda 35 UV/Vis spectrophotometer, while fluorescent spectra were recorded on a Perkin Elmer LS55 fluorescence spectrophotometer.



Synthesis of receptors 1 and 2

Scheme 1

Scheme 1 outlines the synthesis of sensors **1** and **2**. The intermediate M**2** was prepared through the condensation reaction of 4-nitrobenzoyl chloride with 2,4-dimethylpyrrole according to a published procedure[35]. Reduction of **M2** with Pd/C-NH_2NH_2 gave another intermediate **M1**, which was reacted with salicylaldehyde or 4(diethylamino)salicylaldehyde as given below to afford compounds **1** and **2**.

Compound **M1** (0.3 mmol), 2-hydroxy-benzaldehyde (0.3 mmol) and one drop of acetic acid in EtOH (20 mL) were stirred for 4 h at room temperature. After completion of the reaction, the obtained yellow precipitate was filtered and washed several times with cold ethanol to yield the pure compound **1**. Yield 85%. HR MS: Anal. (%): Calc. M+H=444.2053, found 444.2050; ^{1}H NMR (400Hz, DMSO-d_6), δ: 12.87 (s, 1H, OH), 9.06 (s,-N=CH,1H), 7.69-7.12 (d,1H), 7.59-7.61 (d, 2H), 7.43-7.47 (m, 3H), 6.97-7.01 (t, 2H), 6.19 (s, 2H), 2.49-2.50 (m, 6H), 1.42 (s, 6H). ^{13}C NMR: 155.661, 148.954, 142.972, 140.858, 133.625, 132.556,131.450, 129.184, 122.240,121.309. Anal. (%): Calcd. for $C_{26}H_{24}BF_2N_3O$: C, 70.44; H, 5.46; N, 9.48. Found: C, 70.53; H, 5.41; N, 9.51.

Compound **M1** (0.3 mmol), 4-(diethylamino)-salicylaldehyde (0.3 mmol) and one drop of acetic acid in EtOH (20 mL) were stirred for 4 h at room temperature. After completion of the reaction, the obtained yellow precipitate was filtered and washed several times with cold ethanol to yield the pure compound **2**. Yield 83%. EI-MS: (M+H) = 515.2. ^{1}H NMR (400Hz, DMSO-d_6), δ: 13.49 (s, 1H, OH), 8.80 (s, 1H, CH=N), 7.35-7.49 (m, 5H, ArH), 6.08-6.34 (m, 4H, ArH), 3.37-3.42 (m, 4H, CH_2), 2.45 (s, 6H, CH_3), 1.36 (s, 6H,CH_3), 1.04-1.14 (m, 6H, -CH_3). Anal. (%): Calcd. For $C_{30}H_{33}BF_2N_4O$: C, 70.04; H, 6.47; N, 10.89. Found: C, 70.11; H, 6.45; N, 10.77.

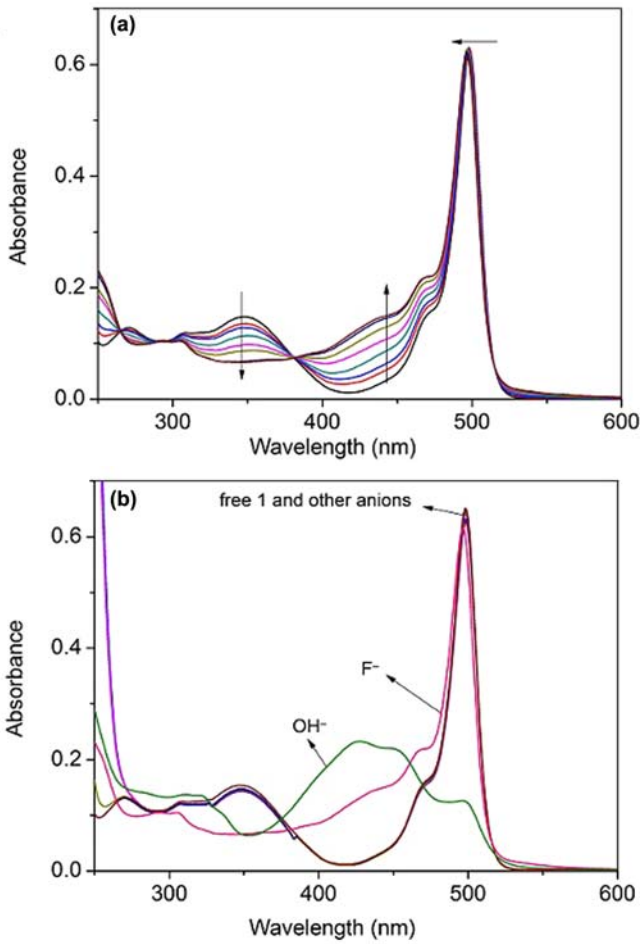


Fig. 1 – UV-vis spectra of **1** (5.0 μM) in DMSO solution upon addition of (a) 0–50 equiv. of F^-, and, (b) 50 equiv. of other anions (F^-, Cl^-, Br^-, I^-, AcO^-, ClO_4^-, HSO_4^-, $H_2PO_4^-$) and 5 equiv. of OH^-.

Results and discussion

The anion-binding properties of receptor **1** were studied in DMSO solution by UV-vis and emission spectroscopy. As shown in Fig. 1a, receptor **1** showed an intense absorption band at 499 nm and a weak absorption band at 348 nm. The band at 499 nm is the typical absorption band of BODIPY dyes, and the band at 348 nm is due to the existence of charge transfer transition within the whole molecule. The addition of fluoride anions to the solution of receptor **1** induced decreasing of the absorption peaks at 348 nm, but the main band at 499 nm had just a 3 nm

blue shift. The changes of absorption were saturated with the addition of 50 equiv. fluoride anions. During the titration process, a clear isosbestic point at 380 nm was observed, indicating a single component was produced. In contrast, the addition of other anions (Cl^-, Br^-, I^-, AcO^-, ClO_4^-, HSO_4^-, $H_2PO_4^-$) did not cause obvious changes in absorption (Fig. 1b).

In order to determine the nature of sensing process, titrations of receptor **1** with [Salt]+OH was carried out. The absorption spectral changes of receptor **1** upon addition of [Salt]+OH were different with that of upon addition of F^- (Fig. 1b), which indicating a hydrogen bonding process involved in the interaction between receptor **1** and F^-. As known to us, in a biological system, the hydrogen bond is the key interaction for proteins to selectively bind and transport a specific anion.

Receptor **1** shows a bright green fluorescence with an intense emission band at 516 nm (Φ= 0.55, excitation at 498 nm) in DMSO solution. Compared to the minimal changes in absorption, the changes in the emission spectrum of receptor **1** were remarkable. With the addition of fluoride anions, the emission at 516 nm was quenched efficiently with an unchanged peak position (Fig. 2a), which could be attributed to the PET (photo-induced electron transfer) process[36]. The anion selectivity of the fluorescent response of the receptor **1** was also investigated (Fig. 2b). In the presence of 50 equiv. of other anions, no significant changes in emission were observed, whereas on F^- addition, the ratio emission changed about 50 fold.

The protic solvents (H_2O) were added to the solution of receptor **1** to check the reversibility of the responses of the sensors. Interestingly, when a small amount of water (2%, v%) was added, the absorption and emission of receptors **1** changed back, which suggested that the protic solvents destroyed the hydrogen bonding between receptors **1** fluoride anions. The above results indicated that the interactions between receptors **1** and fluoride anions were hydrogen bonding interaction.

The binding stoichiometry of receptor **1** with fluoride anions was calculated through the Benesi-Hildebrand equation[37]. As shown in inset of Fig. 2a, the plot of $1/(FI-FI_0)$ against $1/[F^-]_0$ shows a linear relationship (R = 0.99), indicating that receptor **1** associates with F^- in a 1:1 stoichiometry. The association constant (K) of receptor **1** for fluoride anions was calculated to be 1.02×10^3 M^{-1}.

The anion-binding properties of receptor **2** were also studied in DMSO solution by UV-vis and emission spectroscopy. As shown in Fig. 3a, receptor **2** showed an intense absorption band at 499 nm and a weak absorption band at 380 nm. The addition of various anions to the solution of **2** shows that only HSO_4^- anions could cause obvious changes in absorption (Fig. 3a). Upon addition of HSO_4^- anions, the absorption peaks at 380 nm decreased, with a new band at 430 nm appeared.

The interaction of receptor **2** with HSO_4^- was further investigated in detail through UV-vis spectroscopic titrations. As shown in Fig. 3a, with the addition of HSO_4^- anions to the solution of receptor **2** from 0–20 equiv., the absorption band at 380 nm

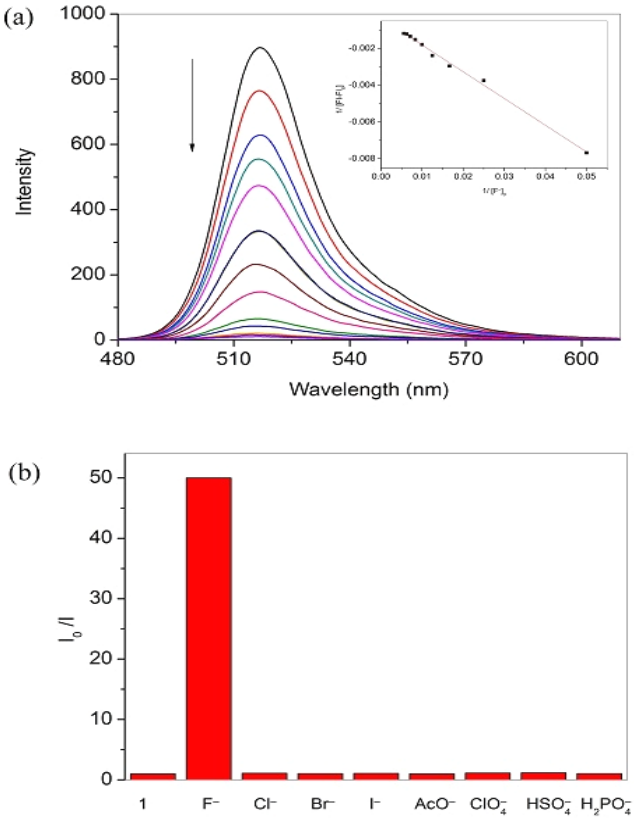


Fig. 2 – (a) Fluorescence spectra (excitation at 496 nm) of **1** (5.0 μM) in DMSO solution upon addition 0–50 equiv. of F^-. Inset: Benesi-Hildebrand plot assuming 1:1 stoichiometry for association between receptor **1** and F^- (516 nm). (b) Fluorescence quenching ratio I_0/I of receptor **1** (5.0 μM) at 516 nm on addition of 50 equiv. of various anions (F^-, Cl^-, Br^-, I^-, AcO^-, ClO_4^-, HSO_4^-, $H_2PO_4^-$).

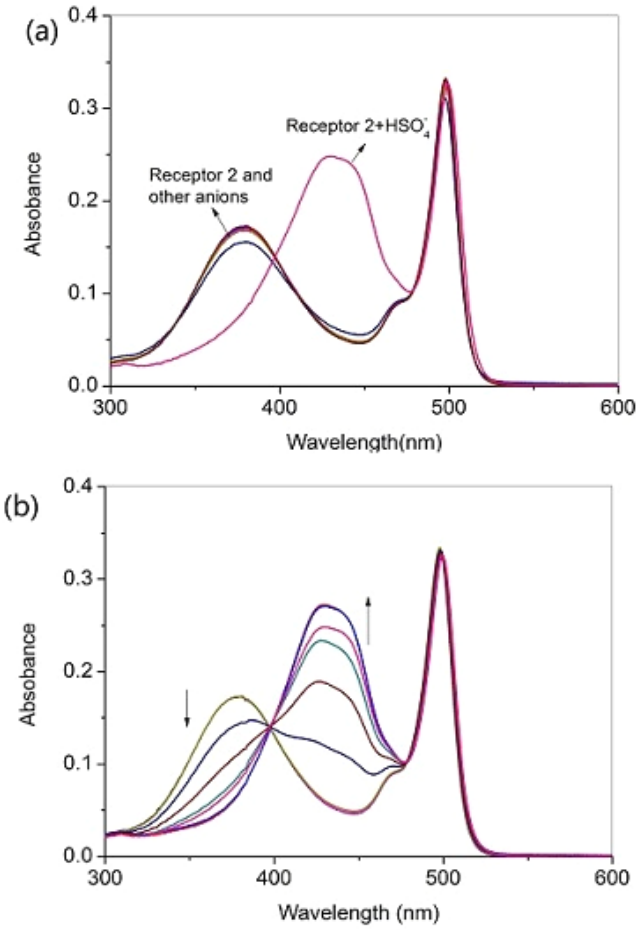


Fig. 3 – UV-vis spectra of **2** (5.0 μM) in DMSO solution upon addition of (a) 50 equiv. of various anions (F^-,Cl^-, Br^-, I^-, AcO^-, ClO_4^-, HSO_4^-, $H_2PO_4^-$), abd, (b) 0–20 equiv. of HSO_4^-.

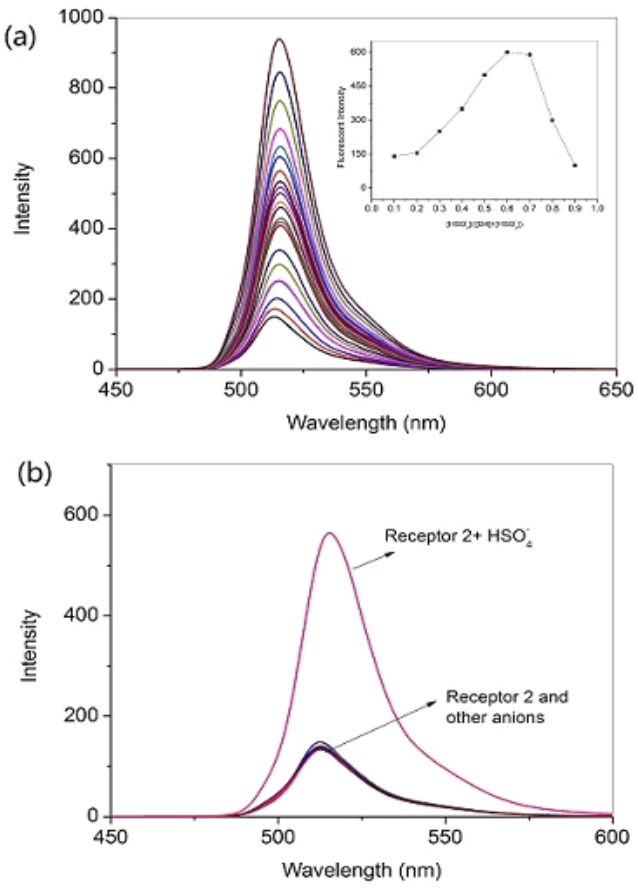


Fig. 4 – (a) Fluorescence spectra (excitation at 496 nm) of receptor **2** (5.0 μM) in DMSO solution upon addition 0–20 equiv. of HSO_4^-. [Inset: Job plot for receptor 2 and HSO_4^-]. (b) 20 equiv. of various anions (F^-, Cl^-, Br^-, I^-, AcO^-, ClO_4^-, HSO_4^-, $H_2PO_4^-$).

decreased and a new red shift band at 430 nm appeared with a clear isosbestic point at 395 nm.

The anion-binding properties of receptor **2** were studied in DMSO solution by emission spectroscopy. The receptor **2** showed quite weak fluorescence (Φ= 0.08, excitation at 496 nm) with an emission intensity at 512 nm due to the PET process from the lone pairs of electrons on the N atoms, which has inherent electron donating property, to the excited BODIPY fluorophore.

As shown in Fig. 4, the addition of HSO_4^- resulted in a remarkable fluorescence enhancement. With increasing HSO_4^- concentration, the emission intensity of receptor **2** increased gradually, and the solution gave green fluorescence emission accordingly. The method of continuous variation (Job's method) was used to determine the stoichiometry between receptor **2** and hydrogen sulfate anions (Inset of Fig. 4). The result

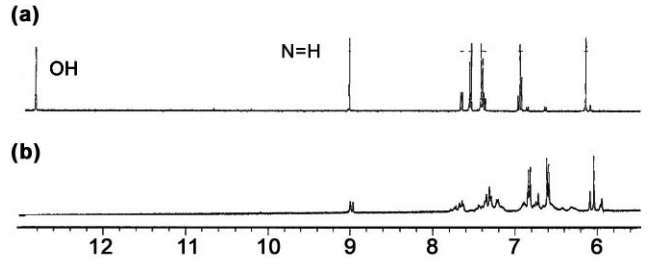


Fig. 5 – Partial ^{1}H NMR spectra of (a) receptor **1,** and, (b) receptor **1** + 2 equiv. of F^- in DMSO-d_6 solvent.

indicated a 2:1 stoichiometry of HSO_4^- to **2** in the complex. The anion selectivity of the fluorescent response of receptor **2** was also studied in DMSO solvent (Fig. 4b). In the presence of 20 equiv. of other anions (Cl^-, Br^-, I^-, AcO^-, ClO_4^-, HSO_4^-, $H_2PO_4^-$), no significant changes in emission of receptor **2** were observed.

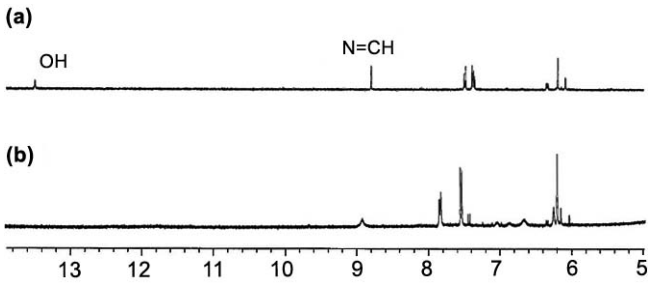
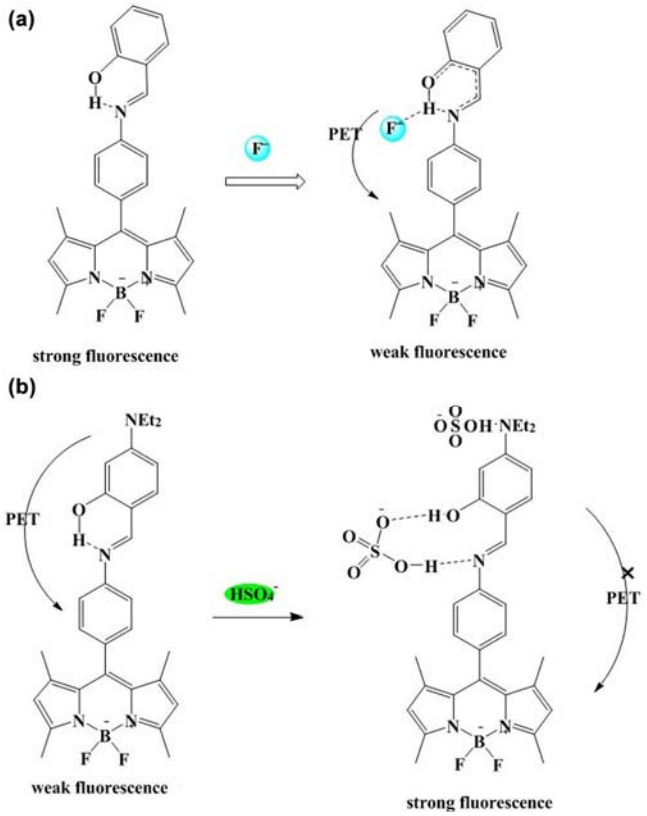


Fig. 6 – Partial ^{1}H NMR spectra of (a) receptor **2**, and, (b) receptor **2** + 2 equiv. HSO_4^- in DMSO-d_6 solvent.



Proposed interaction mode of (a) receptor **1** with F^- and (b) **2**+HSO_4^- anions

Scheme 2

The ^{1}H NMR titrations experiment was also carried out to clarify the sensing mechanism. From the ^{1}HNMR spectrum, we found that the chemical shifts of phenolic proton (OH) of receptors **1** and **2** were 12.87 and 13.49 ppm, respectively, which indicated intramolecular H-bonding with the imine nitrogen formed[38, 42].

As shown in Fig. 5, upon addition of 2 equiv. fluoride anions, the OH signal of receptor **1** disappeared completely, the CH=N signal split into two peaks along with a small upfield shift due to through-bond electronic propagation effect induced by the hydrogen bonding, other aromatic H signals shifted upfield or downfield.

As for receptor 2, upon addition of 2 equiv. HSO_4^-, the OH signal of receptor **2** disappeared completely and CH=N signal became broad and shifted down field (Fig. 6). From the above results, the F^- anions and HSO_4^- indeed interact with phenolic OH proton of receptors **1** and **2**, respectively, resulted in the changes in absorption and emission spectra.

The proposed mechanism for the fluorescence change of receptors **1**[39] and **2**[40-42] to F^- anions and HSO_4^- are shown in Scheme 2. The fluoride anions-triggered PET process of sensor **1** was responsible for the ON-OFF emission. As for sensor 2, upon binding the HSO_4^- anions, the PET process was prohibited, thus exhibiting OFF-ON fluorescent emission.

In summary, we have developed BODIPY-based fluorescent sensors with tunable anions binding ability for fluoride and hydrogen sulfate anions. Further, this study may contribute to the development of more efficient ‘‘Off–On’’ fluorescent anion sensors.

Supplementary data

Supplementary data associated with this article are available in the electronic form at http://www.niscair.res.in/jinfo/ijca/IJCA_57A(02)186-191_SupplData.pdf.

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References

1 Moragues M, Martínez-Máñez R & Sancenón F, *Chem Soc Rev*, 40 (2011) 2593.
2 Li A, Wang J, Wang F & Jiang Y, *Chem Soc Rev*, 39 (2010) 3729.
3 Duke R, Veale E, Pfeffer F, Kruger P & Gunnlaugsson T, *Chem Soc Rev*, 39(2010) 3936.
4 Gale P, *Chem Soc Rev*, 39(2010) 3746.
5 Kirk K, Plenum Press, New York) 1991.
6 *Environmental Health Criteria 227, IPCS International Programme on Chemical Safety*, (World Health Organization, New York) 2002.
7 Chen X X, Leng T H, Wang C Y, Shen Y J & Zhu W H, *Dyes Pigments*, 141 (2017) 299.
8 Jain A, Gupta R & Agarwai M, *Synth Commun*, 47 (2017) 1307.
9 Cametti M & Rissanen K, *Chem Comm*, (2009) 2809.

10 Yu G C, Zhang Z B, Han C Y, Xue M, Zhou Q Z & Huang F H, *Chem Comm*, 48 (2012) 2958.
11 Cao X W, Lin W Y, Yu Q X & Wang J L, *Org Lett,* 13 (2011) 6098.
12 Mashraqui S H, Ghorpade S S, Tripathi S & Britto S, *Tetrahedron Lett*, 53(2012) 765.
13 Yu T, Yin G X, Niu T T, Yin P, Li H T, Zhang Y Y, Chen H M, Zeng Y & Yao S Z, *Talanta*, 176 (2018), 1.
14 Li Q & Shao, S J, *Chinese J Anal Chem*, 45 (2017),1248.
15 Rull-Barrull J, d'Halluin M, Le Grognec E & Felpin F X, *Chem Comm*, 52 (2016) 2525.
16 Wang LY, Ou J J, Fang G P & Cao D R, *Sensors Actuators B: Chem*, 222 (2016)1184.
17 Kumar V, Kumar A, Diwan U & Upadhyay K K, *Chem Comm,* 48 (2012) 9540.
18 Yang S T, Liao D J, Chen S J, Hu C H & Wu A T, *Analyst,* 137 (2012) 1553.
19 Xue W J, Li L, Li Q & Wu A X, *Talanta,* 88 (2012) 734.
20 Li P, Zhang Y M, Lin Q, Li J Q & Wei T B, *Spectrochim Acta, Part A,* 90 (2012) 152.
21 Lu W, Chen D, Jiang H, Jiang L J & Shen Z Q, *J Polym Sci Part A: Polym Chem,* 50 (2012) 590.
22 Li Q, Guo Y & Shao S J, *Sensors Actuators B: Chem*, 173 (2012) 797.
23 Li Q, Guo Y & Shao S J, *Analyst,* 137 (2012) 4497.
24 Basabe-Desmonts L, Reinhoudt D N & Crego-Calama M, *Chem Soc Rev*, 36 (2007) 993.
25 Martinez-Manez R & Sancenon F, *Chem Rev,* 103 (2003) 4419.
26 Boens N, Leen V & Dehaen W, *Chem Soc Rev*, 41 (2012) 1130.
27 Ulrich G, Ziessel R & Harriman A, *Angew Chem Int Ed*, 47 (2008) 1184.
28 Loudet A & Burgess K, *Chem Rev*,107 (2007) 4891.
29 Strobl M, Walcher A, Mayr T, Klimant I & Borisov S M, *Anal Chem*, 89 (2017) 2859.
30 Emrullahoglu M, Sayar M, Karakuş E, Güner T, Yildiz B, Yildiz U H, *Chem Eur J*, 2018 In press (doi:101002/chem201705613).
31 Li Q, Wang Z Z, Xu J, Yue Y & Shao S J, *RSC Adv*, 4 (2014) 34470.
32 Xu J, Li Q, Yue Y, Guo Y & Shao S J, *Biosensors Bioelectron*, 56 (2014) 58.
33 Li Q, Guo Y & Shao S J, *Sensors Actuators B: Chem*, 171-172 (2012) 872.
34 Li Q, Xu J, Guo Y & Shao S J, *Sensors Actuators B: Chem,* 158 (2011) 427.
35 Ziessel R, Bonardi L, Retailleau P & Ulrich G, *J Org Chem*, 71 (2006) 3093.
36 Gabe Y, Urano Y, Kikuchi K, Kojima H & Nagano T, *J Am Chem Soc*, 126 (2004) 357.
37 Benesi H A & Hildebrand J H, *J Am Chem Soc,* 71(1949) 2703.
38 Peng X J, Wu Y K, Fan J L, Tian M Z & Han K L *J Org Chem,* 70 (2005) 10524.
39 Devaraj S, Saravanakumar D & Kandaswamy M, *Tetrahedron Lett*, 48 (2007) 3077.
40 Lu W, Zhou J T, Liu K Y, Chen D, J, L M & Shen, Z Q, *J Mater Chem B*, 1 (2013) 5014.
41 Xue W J, Li L, Li Q & Wu A X, *Talanta*, 88 (2012) 734.
42 Kim H J, Bhuniya S, Mahajan R K, Puri R, Liu H G, Ko K C, Lee J Y & Kim J S, *Chem Commun*, (2009) 7128.

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