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Dual-mode chemodosimetric response of dibromo-BODIPY with anions

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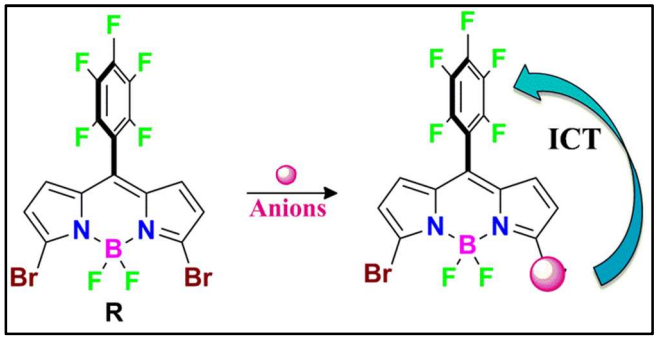
Aromatic nucleophilic substitution (Ar-S_N) reaction of 3,5-dibromopentafluorophenyl-BODIPY has been explored as a remarkable basis for selective discrimination of anions. Efficient and characteristic ability of anions to modulate absorption and emission properties of the dye provides an instantaneous distinction through dual-mode. For the first time, a novel platform to achieve dual-modal and promising recognition with discrimination of a series of anions differing in the nucleophilic atoms (F, O, C and N) has been taken into consideration. The behaviour of various anions with dibromo-BODIPY and vivid signal transduction has been fully established with absorption and emission spectroscopy. In addition to this, recognition events have been unambiguous characterized by ^{1}H, ^{19}F -NMR and single-crystal XRD.

Introduction

The dipyrromethene–BF_2 complexes (BODIPY) have attracted considerable attention of research community due to their interesting optical properties, thermal and photochemical stability.[1] Owing to its high fluorescence quantum yield, sharp absorption and emission properties, it is utilised in biological[2] and chemical applications.[3] Unlike absorption, the emission properties of BODIPY are found to be strongly depend on polarity of the solvent, pH, dielectric constant and substituents present on the chromophore.[4] Although BODIPY was reported in 1968 by Treibs and Kreuzer,[5] only in the last few decades it has been widely exploited by tuning its optical behaviour towards applications in photodynamic therapy,[6] sensors,[7] molecular switches,[8] bio-imaging[9] and protein labelling.[10] Its optical properties can be fine-tuned by functionalization at various pyrrolic positions on the BODIPY core.[11] In addition, *meso*- aryl functionalization plays an important role in the reactivity of BODIPYs because of electronic coupling with the BODIPY core.[12] Among other functionalization methods, BODIPY substitution at *α*- position is an effective way to tune the electronic properties. There are various synthetic procedures to functionalize these positions that includes aldehyde condensation,[13] transition metal catalysed cross-coupling reactions[14] and nucleophilic substitutions.[15] In this direction, aromatic nucleophilic substitution (Ar-S_N) reaction seems as an interesting way to functionalize *α*- dihalo-BODIPYs.

In this regard 3-halo and 3,5-dihalo-BODIPYs have been explored to achieve functional BODIPYs. Introduction of a heteroatom at the core of BODIPY derivatives results in bathochromic shift in both absorption and emission maxima, thus signalling potential exploitation for biomedical and near infra-red (NIR) applications.[16] Dehaen *et al.,* explored nucleophilic substitution reaction of a novel 3,5-dichloro-BODIPY with various nucleophiles.[17] The same group later extended this nucleophilic substitution reaction by an oxidative nucleophilic substitution of hydrogen (ONSH) without halogens at *α*-position.[18] Therefore, it is evident that the reactivity of these BODIPYs towards nucleophilic substitution mainly depends on the substituent present at the *meso*- position. Electron withdrawing aryl groups at *meso*- position are likely to enhance the electron deficiency on BODIPY chromophore for a facile Ar-S_N reaction at *α*- position. In continuation to our efforts for the synthesis of highly reactive BODIPYs toward Ar-S_N, we prepared an electron deficient BODIPY with pentafluorophenyl group at *meso*- position and bromine at α- positions. Aromatic nucleophilic substitution (Ar-S_N) on electron deficient pentafluorophenyl-dibromo-BODIPY (**R**) proceeds with efficient and rapid colorimetric and fluorescent response by intra molecular charge transfer shown in scheme 1. Hence, utilization of such a substitution reaction for selective discrimination of anions by taking into account of their characteristic nucleophilic character and modulation of electronic properties of BODIPY will be highly intresting.



Scheme 1. Nucleophilic substitution on BODIPY. The corresponding reaction products have been assigned as $\mathbf{R}_x$ where x is respective anionic substitution.

In short, sensing and quantification of anions are important areas of contemporary research.[19] The recognition behaviour has usually been achieved via hydrogen-bond acceptance,[20] by deprotonation,[21] excited state inter- or intramolecular proton transfer mechanisms (ESIPT, EIMPT).[22] In addition to this, reaction-based approaches for a few anions like desilylation for fluoride[23] and nucleophilic substitution for cyanide[24] are also known but only limited reports are available for sensing of anions based on nucleophilic substitution. In this regard, anions like cyanide, azide, fluoride and alkoxide are potentially strong nucleophiles towards a substitution reaction. Reaction of **R** with these anions will result in a BODIPY having heteroatoms attached to its core and therefore alteration in the photo physical behaviour, offering a visual display (Figure 2).

Keeping this in mind, a facile nucleophilic substitution reaction for aliphatic amine discrimination has been explioted.[25] Interestingly, reaction of 3,5-dibromo pentafluorophenyl-BODIPY (**R**) (ε=10300 M^{-1} cm^{-1}, Φ=0.37) with TBAF (Tetrabutylammonium fluoride) resulted in fascinating colorimetric and fluorimetric changes. It is then envisaged that the reactivity of the dye towards various anions possessing different nucleophilic donor atoms can be utilized for their discrimination.

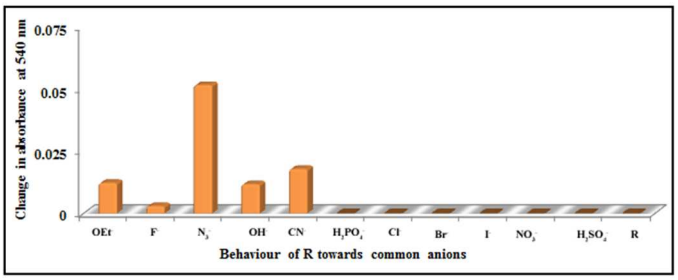


Figure 1. Decrease in absorbance of receptor **R** (1.2 μM) at 540 nm in presence of various anions with 10 mM concentrations in the form of TBA salts in DCM at room temperature.

In order to prove our hypothesis regarding exploration and development of **R** as a novel analytical tool for naked-eye anion discrimination, we carried out anion recognition studies with **R** in dichloromethane (DCM). **R** was synthesised via a reported procedure.[25] Initially, **R** was visually scanned by addition of various nucleophilic anions including F^-, Cl^-, Br^-, I^-, NO_3^-, ClO_4^-, HSO_4^-, CN^-, HPO_4^-, HO^-, N_3^- as their respective tetrabutylammonium salts (TBA) and alkoxides in the form of respective sodium salts. Noticeable changes were observed only in the presence of cyanide, fluoride, hydroxide, alkoxides and azide (Figure 1). Instantaneous and strong optical (colorimetric and fluorescent) read out were noticed, but fluorescent response are more prominent in this case (scheme 2).

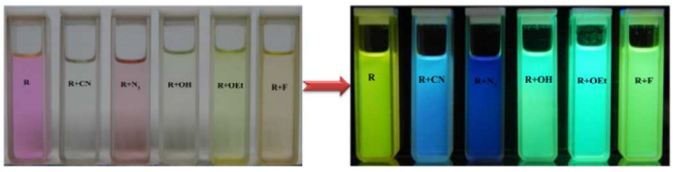
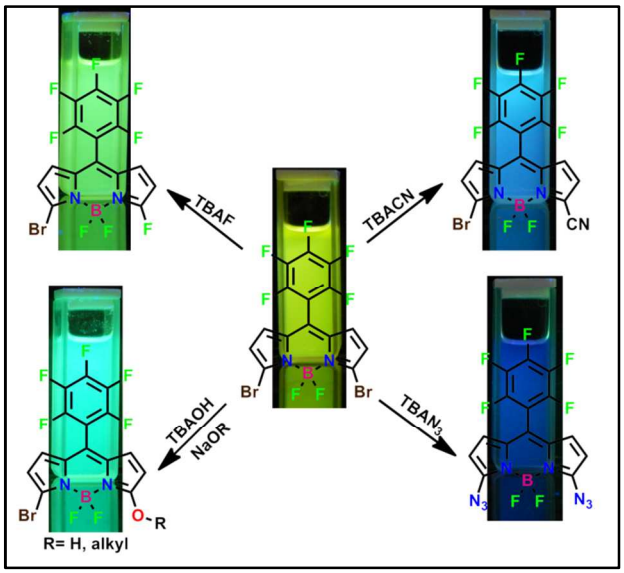


Figure 2. Absorption (left) and emission (right) changes of **R** after addition of various nucleophiles in DCM. Snap were taken within a minute after addition of anions.

Results and Discussion

In order to explore and comprehend this chemodosimetric reaction promoting a vivid colorimetric display with a range of anions, we carried out absorption and emission titration experiments of **R** with each anion. NMR titration studies were performed to understand the effect of anions. The changes were monitored with slow addition of various equivalents of nucleophiles to **R**.



Scheme 2. Nucleophilic substitution on BODIPY, with different nucleophiles.

Carbon as nucleophilic centre

The titration experiment of **R** proceeded with cyanide in DCM. The intensity of characteristic S_0 to S_1 transition of BODIPY (**R**) gradually decreased with increasing the equivalents of cyanide. At the same time a new intramolecular charge transfer (ICT) band was observed as a weak broad band around 400 nm through an isosbestic point. Because of weak absorption of the resultant product, $\mathbf{R_{CN}}$ appears colourless (Figure 2). Similarly in fluorimetric titrations, emission profile shows a gradual decrease in intensity was at 554 nm and in turn appearance of a new emission signal at 490 nm with a clear isosbestic point as shown in Figure 3.

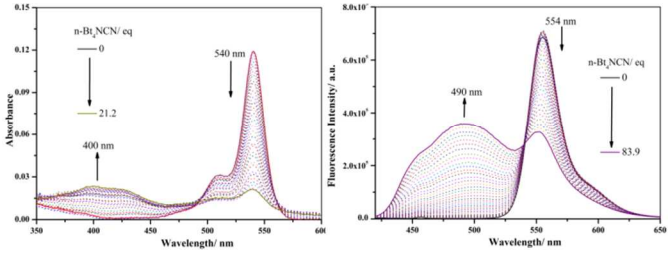


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Figure 3. Titration profiles of **R** (1.2 µM) upon addition of various equivalents of cyanide, (a) Absorption profile, (b)Emission profile in DCM.

Nitrogen as nucleophilic centre

The reactivity behaviour of azide with **R** was probed for its nucleophilic nature. The intensity of absorption band at 540 nm progressively weakened with the increase in azide concentration. This was accompanied simultaneously with an emergence of an ICT band at 485 nm. Visually, colour change from pale to dark pink was noticed (ESI). In the fluorescence studies, the emission intensity of BODIPY gradually decreases with increasing azide equivalents. However, at higher additions, a low intense peak emerged with a blue-shift, as depicted in figure 4b.

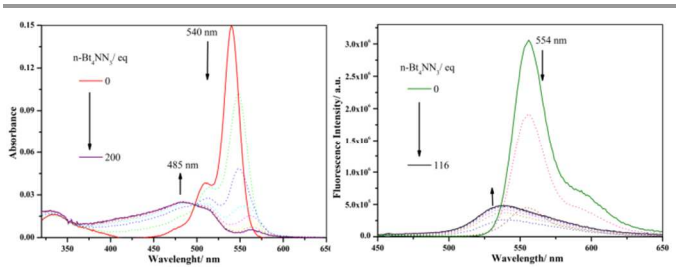

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Figure 4. Absorption (Left) and Emission titration profiles (Right) of **R** (1.2 µM) upon addition of various equivalents of azide in DCM.

Oxygen as nucleophilic centre

We investigated the nucleophilic effect of oxygen containing anions towards **R**. Hydroxide ion in the form of tetrabutylammonium salt was titrated with **R**. In absorption titration profile, a gradual decrease of BODIPY band (S_0 to S_1) at 540 nm upon continuous addition of OH^- was perceived. Simultaneously, a weak ICT band at 410 nm was noticed, which is responsible for the pale green colour shown in Figure 2. The recognition and consequences of hydroxide on **R** was further investigated by fluorescence studies. Emission band at 554 nm gradually decreased with increasing hydroxide concentration. This proceeds with a new emission band at 495 nm through an isosbestic point at 541 nm (Figure 5).

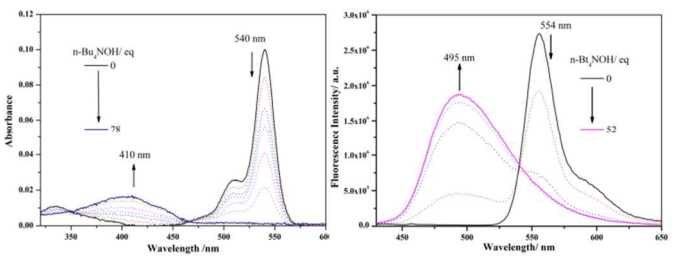

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Figure 5. Titration profiles of **R** (1.2 µM) upon addition of various equivalents of hydroxide anion (a) absorption profile, (b) Emission profile.

Surprisingly, absorption profile of alkoxides reveals a different behaviour compared to hydroxide. The titration experiment of **R** was carried out with ethoxide anion in the form of sodium salt, dissolved in ethanol. The intensity of S_0 to S_1 transition band decreased with the corresponding increment in equivalents of ethoxide. No changes were observed in the shoulder region of BODIPY. However, after a few sequential additions, the intensity of the shoulder band was reduced along with emergence of a new ICT signal at 438 nm. In the fluorimetric experiment of **R** with ethoxide, behaviour similar to hydroxide additions was revealed. The intensity of the emission band gradually decreased with increasing concentration of ethoxide in solution. This was concurrently seen with new emission band at 495 nm through a clear isosbestic point (Figure 6).

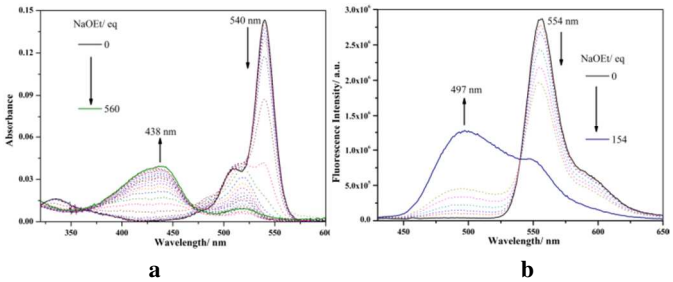

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Figure 6. Titration profile of **R** (1.2 µM) upon addition of various equivalents of Ethoxide anion (a) absorption profile, (b) Emission profile.

Fluoride as nucleophilic centre

Titration experiments were carried out with fluoride in the form of tetrabutylammonium salt to observe the modulation in

photophysical properties of **R**. Absorption profile shows reduction of spectral intensity of S_0 to S_1 band at 540 nm with increase in concentration of fluoride. This progressed with appearance of a new intramolecular charge transfer transition band at 430 nm through an isosbestic point at 490 nm. Similarly in emission spectra, a decrease in intensity of emission band was noticed with a gradual increment in equivalents of fluoride anion. This is concomitantly accompanied with a new emission signal emerged at 492 nm through an isosbestic point at 540 nm as shown in Figure 7.

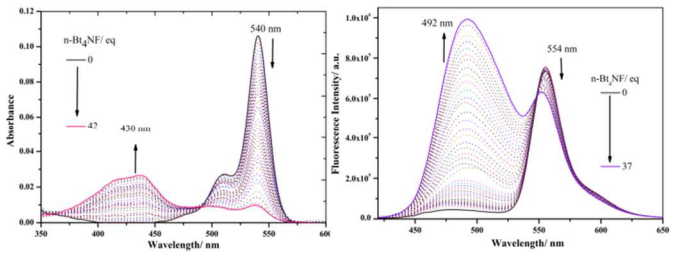

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Figure 7. Titration profiles of **R** (1.2 µM) upon addition of various equivalents of fluoride anion (a) absorption profile, (b) Emission profile.

NMR behaviour of R

The recognition mechanism of above anions was probed by NMR titration experiments. Addition of fluoride to **R** in $CDCl_3$ resulted in the appearance of four pyrrolic proton signals, which after higher additions of anions remain unaffected. It clearly indicates that completion of reaction and the formation of respective $\mathbf{R_F}$ (ESI) product. The NMR signal pattern can be attributed to the formation of an unsymmetrical structure due to the singly substituted product at 3-position of BODIPY (**R**), even at higher concentrations of fluoride. Thus, it revealed a 1:1 substitution reaction of **R** towards weak nucleophiles. In the case of azide addition at lower concentration singly substituted product $\mathbf{R_{N3}}$ formation was observed, while increasing the concentration of azide resulted in a pink solution attributed to di-substituted $\mathbf{R_{[N3]2}}$ (ESI). Further, for cyanide at higher concentration, decomposition of resultant $\mathbf{R_{CN}}$ was observed. In ^{19}F- NMR, deviation in chemical shifts of fluorine signals in **R** implicates a clear ICT modulation across the system due to the incorporation of nucleophile. In ^{1}H-NMR, along with four pyrrolic proton resonances, few less intense signals appeared in case of CN^-. These are probably attributed to the decomposition of resultant product. No decomposition was observed in the case of $\mathbf{R_F}$ (ESI).

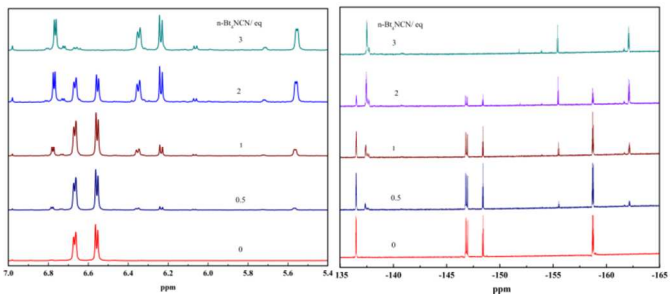

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Figure 8. ^{1}H- NMR (a) and ^{19}F- NMR (b) changes of **R** while titration with cyanide in $CDCl_3$.

In order to further validate the mechanism of the recognition behaviour of molecule **R**, chemical reactions were carried out between **R** and the selected nucleophilic anions in DCM. The stability of resultant product in these reactions depends on the electron withdrawing or donation ability of nucleophiles at 3-position. Thus product $\mathbf{R_F}$ was fully characterised by ^{1}H NMR, LR-MS and a single-crystal XRD, as reported earlier.[25] Further $\mathbf{R_{OMe}}$ was successfully characterized by NMR and single-crystal XRD (ESI). Single crystals suitable for x-ray diffraction were obtained for $\mathbf{R_{OMe}}$ from the slow evaporation of a methanolic solution.

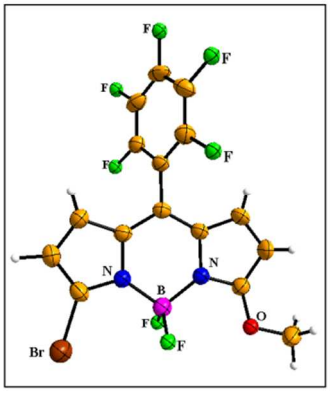

Figure 9. Single-crystal XRD structure of $\mathbf{R_{OMe}}$. (**CCDC** 1042078)

Stability of $\mathbf{R_{CN}}$ and $\mathbf{R_{[N3]2}}$

To prove our hypothesis regarding stability of products based upon the nature of nucleophilic anions incorporated, an in-situ preparation of compounds, $\mathbf{R_{CN}}$ were carried out. The products were analysed by NMR and other spectral studies. In absorption profile, progressive decomposition of CN substituted product with time was noticed. This can be correlated to the gradual decrease in characteristic $\mathbf{R_{CN}}$ absorption signal at 400 nm (Figure 10). In contrast, electron-withdrawing nucleophiles result in the formation of destabilized products with the electron-deficient BODIPY. In order to further accomplish this, an

experiment was performed with azides. The decomposition of the resultant product ($\mathbf{R_{[N3]2}}$) was observed with time. A sudden colour change from pink to yellow was detected with naked-eyes. The resultant events during the whole decomposition process were further visualized through digital video graphy (ESI).

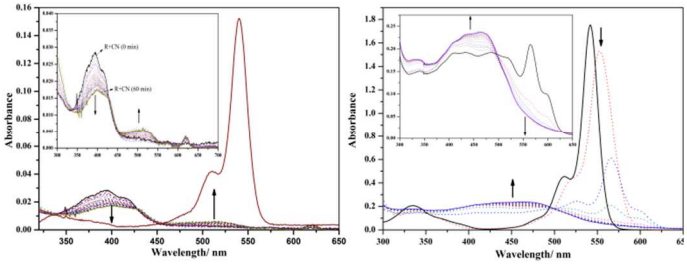

Figure 10. Decomposition of $\mathbf{R_{CN}}$ and $\mathbf{R_{[N3]2}}$ products with increasing time.

Materials and methods

All solvents and reagents were purchased from commercial sources and used without further purification except for dry THF which was further distilled over sodium metal. UV-Vis spectra were recorded on a Cary 100 spectrophotometer. Fluorescence emission spectra were recorded on a Horiba Jovin Vyon Fluoro log 3-111 spectrometer. Mass spectra were recorded on a Bruker QTOF-QII spectrometer. NMR spectra were recorded using a Bruker instrument operating at 400 MHz. Single-crystal data were collected on a Bruker APEX II diffractometer equipped with a graphite monochromator and Mo-Kα (λ = 0.71073 Å) radiation.

Spectrophotometric studies

UV-Vis and fluorescence titration experiments were carried out with a solution of **R** (1.2 μM) and gradual addition of anions for further analysis, prepared in dichloromethane (HPLC grade). In fluorescence experiment **R** was titrated with various equivalents of anions and excited at 400 nm. Experiments were carried out under ambient conditions. Spectra were recorded instantly after addition of analyte. All anions for the titration experiments were conducted with a stock solution in DCM. alkoxide stock solution was prepared in respective alcohols (HPLC grade) to avoid any solubility issues.

X- ray diffraction studies

Data collection was performed using φ and ω scans. The structure was solved using a direct method followed by full-matrix least square refinements against F2 (all data HKLF 4 format) using SHELXTL.[26] Subsequent difference Fourier synthesis and the least-square refinement revealed the positions of the remaining non-hydrogen atoms. Determinations of the crystal system, an orientation matrix, and cell dimensions were performed according to the established procedures. Lorentz polarization and multi-scan absorption correction applied. Non-hydrogen atoms refined with independent anisotropic displacement parameters and hydrogen atoms placed geometrically and refined using the riding model. All calculations were carried out using SHELXL 97,[27] PLATON 99,[28] and WinGXsystemVer-1.6414.

Table 1. Crystallographic data

	$\mathbf{R_{OMe}}$
CCDC	1042078
Formula	C_{16} H_7 B Br F_7 N_2 O
Formula mass (g/mol)	466.95
Crystal system	Monoclinic
Space group	$P_2(1)/c$
a(Å)	11.3455(12)
b(Å)	10.2153(10)
c(Å)	14.3393(13)
α(°)	90.00
β(°)	94.725(5)
γ(°)	90.00
V(Å ^{3})	1656.2(3)
$R_1[I>2\sigma(I)]^a$	0.0354
$R_w[I>2\sigma(I)]^b$	0.0944

$^aR_1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$, $^bR_w=[\Sigma\{w(F_o^2-F_c^2)^2\}/\Sigma\{w(F_o^2)^2\}]^{1/2}$

Experimental section

Preparation of Methoxide BODIPY ($\mathbf{R_{OMe}}$):

Pentafluorophenyl dibromo-BODIPY (100 mg) was dissolved in 10 ml of dry methanol. Then 2 equivalents of sodium methoxide salt was added to the reaction mixture at room temperature, stirred this mixture for 5 min in open atmospheric condition. The reaction mixture was concentrated by evaporation of solvent under reduced pressure. The crude mixture was subjected to silica column chromatography. The desired compound was purified using ethyl acetate and hexane as elutants as red colour powder. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 6.85–6.84 (d, *J*= 4.84, 1H), 6.41 (m, 2H), 6.26–6.25 (d, *J*= 4.84, 2H), 4.20 (s, 3H); ^{19}F NMR (376 MHz, $CDCl_3$): -*δ* 136.9-137.0 (2F, *ortho*), 147.45-147.67 (2F, BF), 149.75-149.87 (1F, *para*), 159.42-159.58 (2F, *meta*); ^{11}B NMR (128 MHz, $CDCl_3$): *δ* 0.64-0.21. MS (LR-MS): Anal. Calc. for $C_{16}H_7BBrF_7N_2O$ requires 466, found $-C_1H_3$ as 451.

Preparation of Azide BODIPY ($\mathbf{R_{[N3]2}}$):

Pentafluorophenyl dibromo-BODIPY (100 mg) was dissolved in 10 ml of dry chloroform. Then higher equivalents of tetrabutyl ammonium azide added to the reaction mixture at room temperature, stirred this mixture for 10 min in dark condition. Then solvent was evaporated under reduced pressure. By performing column chromatography we purified

desire compound by using ethyl acetate and hexane as elutants. The total procedure performed under dark condition, to avoid the decomposition of resultant product. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.69–6.68 (d, J= 4.83, 2H), 6.33–6.32 (d, J= 4.32, 2H), ^{11}B NMR (128 MHz, $CDCl_3$): δ 0.44-0.02. MS (HR-MS): Anal. Calc. for $C_{15}H_4BF_7N_8$ requires 388.0727, found $C_{15}H_4N_8BF_7$ + 4H-N_4 is 388.0746.

Detection limit calculations

After establishing the mechanistic aspects regarding the detection of anionic nucleophiles with **R**, we further explored the sensitivity and detection limits of each anion with **R**. Upon plotting change in the intensity of principal (S_0-S_1) band with different concentrations of each anion, a near-linear relation was achieved (ESI). This demonstrates a potential utility of **R** for quantification of corresponding anions. With the help of these plots, sensitivity was calculated as the slope of the calibration curve (θ), while limit of detection (LOD) was achieved using below equation:[29]

$$\mathbf{LOD} = 3\sigma/\theta$$

Where 'σ' refers to the standard deviation of blank measurements (n=3) and 'θ' indicates slope of the calibration curve.

Table 2. Sensitivity and detection limit of Analytes

Analyte	Sensitivity (θ)	Limit of Detection (μM)
N_3^-	0.0014	2.15
CN^-	0.0003	10
OH^-	0.0002	15
OEt^-	0.0002	15
F^-	0.00006	50

Conclusion

In summary, we have developed and explored an electron deficient BODIPY dye for nucleophilic anion recognition behaviour through absorption and emission spectroscopy. Explicitly, **R** is showing high selectivity and sensitivity towards azide and cyanide in presence of pool of anions. The recognition events can be easily marked by visual and instantaneous responses in colorimetric and fluorimetric studies. The basis for such a behaviour can be attributed to the typical aromatic nucleophilic substitution reaction (Ar-S_N) of highly electron deficient BODIPY (**R**). To the best of our knowledge, our reaction-based approach through a pentafluorophenyl-dibromo-BODIPY is a unique system deciphering nucleophilic anion discrimination even at very low concentrations (μM). We believe that the proposed BODIPY based nucleophilic substitution reaction approach adds another important and novel dimension to the sensing methodologies for the promotion of new and cost effective strategies. Further, biological imaging studies of this system will be an interesting aspect and studies towards this direction is in progress.

Notes and references

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Electronic Supplementary Information (ESI) available: [General Information, ^{1}H, ^{19}F and ^{11}B NMR titration experiments, absorption and calibration studies. For better visualization of all titration spectra we repeated in ESI]. See DOI: 10.1039/c000000x/

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