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The example of calix[4]pyrrole derivative containing Bodipy unit: Fluorometric and colorimetric sensor for F^- ion

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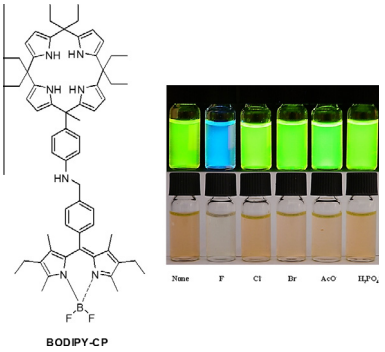
HIGHLIGHTS

- The anion recognition behavior of the **BODIPY-CP** containing four pyrrole-NH.
- **BODIPY-CP** showed to the colorimetric and 'turn-off' fluorescent responses.
- The rapid detection and identification of F^-anions.

GRAPHICAL ABSTRACT



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ABSTRACT

A novel chemosensor based on calix[4]pyrrole derivative modified by Bodipy unit has been synthesized, and its complexes with various anions were investigated. The results show that the receptors can selectively recognize biologically important fluoride ions. The binding affinity for fluoride ions was investigated by naked-eye color change, absorption, emission, proton nuclear magnetic resonance spectroscopy. The addition of fluoride ions to an acetonitrile solution of chemosensor can result in an obvious color change (brownish yellow color to straw yellow). The stoichiometries between the receptor and fluoride were determined from the molar ratio plots using the UV–visible spectra, which showed evident 1:1. The proton nuclear magnetic resonance spectral data supported the fluoride anion recognition with the disappearance of the amino proton peaks.

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Introduction

In recent years, there has been increasing emphasis on supramolecular chemistry on the development of new synthetic sensing receptors for recognizing anionic species [1–4]. It is commonly known that anions play an important role in numerous kinds of chemical and biological processes, and consequently the design and development of selective anion receptors is of great interest [5–8]. Among the various bioactive anionic analytes, fluoride is one of the biochemically important anions, which plays a key role in dental care and the treatment of osteoporosis [9–11]. Therefore the development of sensitive and selective chemosensors of fluoride ions has been an active research field over the past decade, and the colorimetric or fluorescent sensors of fluoride ions are intensifying and extensively investigated by virtue of their tender response, inexpensive instrumentation, simple detection procedure, and the potential of naked-eye recognition. A well-developed strategy is to couple a chromogenic or fluorogenic signaling unit to a receptor unit that can interact with fluoride ions via hydrogen bonding. A calix[4]pyrrole moiety was chosen for binding because

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it has good anion-binding capability both in solution and solid phases [12–16]. These macrocycles bind anions by means of hydrogen-bonding interactions between the polar NH units and the electron-rich guests [16–19]. One of the most attractive developments involves the construction of calix[4]pyrrole-based anion sensors in both the optical [20,21] and electrochemical realms, [22] which are of particular interest in the field of recognition and sensing of anionic analysts [23,24]. Like calix[4]pyrroles, Bodipy's (boron–dipyrromethene) are preferred for the detection of anions owing to their interesting photophysical properties. BODIPYs possess large molar extinction coefficients in visible or near infrared (NIR) region, high fluorescence quantum yields and sharp emission bands, excellent thermal and photochemical stabilities, as well as good amenability to structural modification. Therefore, many researchers have found wide applications in the labeling of proteins and DNA, luminescent devices, and chemical sensors [25–28]. Even though a great number of calix[4]pyrrole derivatives have been synthesized and reviews on synthesis and properties of calix[4]pyrrole derivatives have been published, to the best of our knowledge, studies on structural analyses of calix[4]pyrrole functionalized with Bodipy dyes in modern chemistry are very rare [29]. For that reason, we think that the synthesis of Bodipy's that function with calix[4]pyrrole derivative can generate new materials with interesting properties due to their above-mentioned specific complexation abilities with different anions.

In this study, we prepared to a selective fluorescent chemosensor based on calix[4]pyrrole and Bodipy for fluoride anion (Scheme 1) , which shows straw yellow fluorescence quenching in the presence of fluoride ions.

Experimental

Reagents

Unless otherwise noted, all chemicals are of analytical reagent grade obtained from commercial suppliers and are used without further purification. Chloroform ($CHCl_3$) were refluxed with calcium hydride and distilled under atmospheric pressure. Tetrahydrofuran (THF) was refluxed with Na metal and distilled under atmospheric pressure. Thin layer chromatography (TLC) analysis was performed on silica gel plates and column chromatography was conducted over silica gel (mesh 200–300). In titration, all the anions were added in the form of tetra-butyl ammonium (TBA) salts.

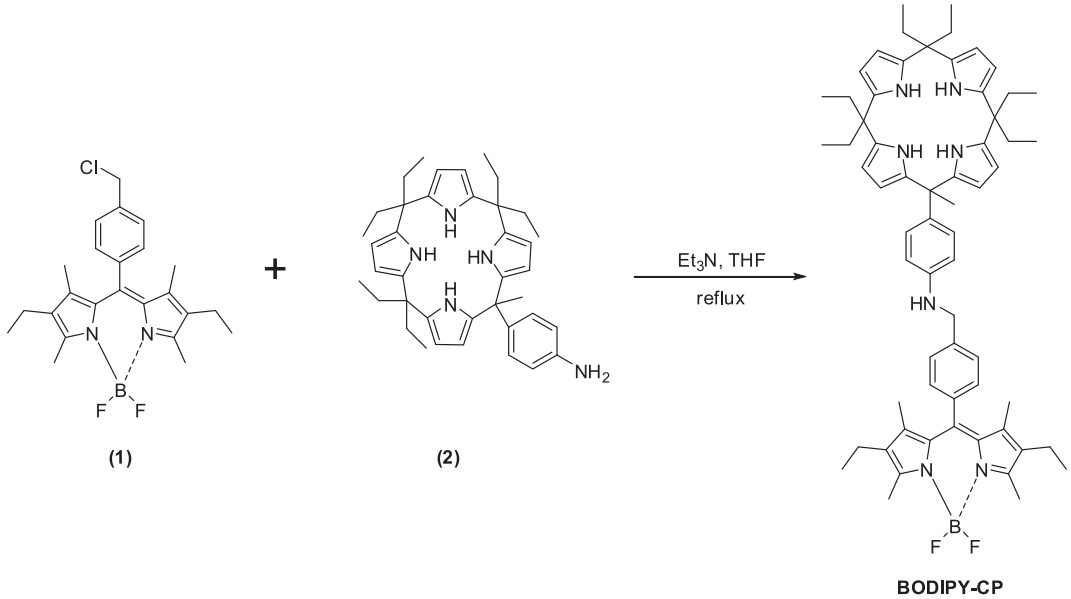
Apparatus

Elemental analyses (C, H, and N) were determined using a LECO-932 CHNSO model analyzer. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer in DMSO-d_6 as the solvent with Me_4Si as internal reference. UV–visible spectra were obtained using Shimadzu UV-1700 visible recording spectrophotometers. Fluorescence and excitation measurements were carried out in a PerkinElmer LS 55 spectrofluorimeter. The emission and excitation spectra were recorded in a 1 cm quartz cuvette at room temperature. The excitation and emission slits were set at 3 nm. Mass spectra were acquired in the linear mode with an average of 50 shots on a Bruker Daltonics Microflex mass spectrometer (Bremen, Germany) equipped with a nitrogen UV-Laser operating at 337 nm.

Synthesis methods

*The synthesis of 8-{4-(chloromethyl)phenyl}-2,6-diethyl-4, 4-difluoro-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene (**1**)*

1 was prepared according to known procedure [28] and used by purification techniques. To a stirred solution of 2,4-dimethyl-3-ethylpyrrole (2.5 mL) in dry dichloromethane (100 mL), 4-(chloromethyl)benzoyl chloride (1.875 g, 10 mmol) was added drop-by-drop at room temperature and under N_2. The solution was heated and stirred to 60 °C for 2 h. After cooling the solution, triethylamine (TEA) (5 equiv.) was added to the residual solid, the mixture was stirred at room temperature for 30 min under N_2, and boron trifuloride diethyl etherate (7 equiv.) was then added. The solution was stirred at 60 °C for 2 h and the final residue was purified by column chromatography (petrolium ether-EtOAc; in 8:1 ratio) and obtained as a red solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 7.41 (d, 2H, ArH), 7.18 (d, 2H, ArH) 4.63 (s, 2H, CH_2), 2.44 (s, 6H CH3) 2.21 (q, 4H, CH_2)1.27(s, 6H, CH_3) 0.89 (t, 6H, CH_3).^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) = 153.81, 139.42, 138.42, 136.12, 135.81, 132.83, 130.62, 129.02, 128.78, 45.59, 17.07, 14.43, 12.43, 11.62.



Scheme 1. The synthesis route of **BODIPY-CP**.

*Synthesis of meso-heptaethyl-calix[4]pyrrole-meso-4-aminophenyl (**2**)*

The benzyloxycarbonyl-protected calixpyrrole was synthesized by the co-condensation of Cbz-protected *p*-aminoacetophenone (11.4 mmol, 3.0 g), pyrrole (43.2 mmol, 3 mL), and 3-pentanone (45.6 mmol, 4.8 mL) in the presence of BF_3:Et_3O. Then, the benzyloxycarbonyl-protected calixpyrrole, (100 mg, 0.138 mmol) was dissolved in EtOH (10 mL). To this solution, 40% aqueous KOH solution (10 mL) was added, refluxed overnight, and then the organic materials were extracted with diethyl ether (50 mL) and washed with water (3 × 50 mL). The phase was concentrated under reduced pressure and the residue was subjected to column chromatography (1:3 EtOAc:hexane) and gave compound 2 (55 mg, 67.4%) as a white powder. ^{1}H NMR (400 MHz,$CDCl_3$): δ(ppm) = 7.17 (2H, s, pyrrole N–H), 7.00 (2H, s, pyrrole N–H), 6.81(2H, d, J = 8.4 Hz, phenyl C–H), 6.55 (2H, d, J = 8.4 Hz, phenyl C–H), 5.89–5.93 (m, 8H, CH), 3.53 (2H, br s, $–NH_2$), 1.87–1.45 (15H,m, $–CH_3$ and $–CH_2–$),0.66–0.60 (18H, m, $–CH_3$) ; ^{13}C NMR (400 MHz, $CDCl_3$): δ(ppm) = 144.6, 137.8, 137.1, 136.1, 135.9,135.8, 128.2, 114.4, 105.6, 105.4, 104.9, 43.9, 43.0, 29.2, 29.0, 28.8, 28.7, 8.1, 8.0.

*The synthesis of **BODIPY-CP** (based on calix[4]pyrrole and Bodipy)*

A solution of meso-heptaethylcalix[4]pyrrole-meso-4-aminophenyl (0.59 g, 1 mmol) in 10 mL dry THF was added to a mixture of 8-{4-(chloromethyl)phenyl}-2,6-diethyl-4,4-difluoro-1,3,5,7-tetramethyl-4-bora-3a,4a-diaza-s-indacene (0.42 g, 1 mmol) and triethylamine (0.14 mL, 1 mmol) in dry THF (20 mL). The mixture was refluxed at room temperature for 24 h and monitored by TLC. Then, ethyl acetate was added to the reaction mixture and the solution was washed with saturated NaCl (3 × 15 mL). The organic phase was collected, dried with Na_2SO_4, and the solvent was removed under reduced pressure. The product was purified by column chromatography (ethyl acetate/*n*-hexane, 1:1.5).

Yield 40%; mp >200 °C; Elemental analysis (Found: C, 77.12; H, 8.06; N, 10.05 %. Calc.: C, 77.04; H, 8.00; N, 9.98%); ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) = 0.51–0.62 (m, 18 H, CH_3), 0.90 (t, 6H, CH_3), 1.18(s, 6H, CH_3), 1.52–1.78 (m, 12 H CH_2 + CH_3), 2.21 (q, 4H, CH_2), 2.46 (s, 6H CH_3), 4.69 (s, 2H, CH_2), 5.57–5.90 (m, 8 H, pyr–CH), 6.48 (d, 2H, CH), 6.73 (d, 2H, CH), 6.94 (br s, 2H,NH), 7.13 (br s, 2H, NH), 7.21 (d, 2H, ArH), 7.41 (d, 2H, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) = 152.31, 144.33, 139.12, 138.82, 137.12 137.15, 136.44, 136.30, 135.79, 135.23, 135.18, 133.11, 130.65, 128.94, 128.66, 128.32, 114.42, 106.77, 105.34, 105.19, 48.59, 43.88, 43.22, 30.02, 29.55, 28.97, 28.67, 19.96, 15.43, 12.65, 11.67, 9.11, 9.05. MS for $C_{63}H_{78}N_7BF_2$ m/z: 982.28 $[M + H]^+$.

Results and discussion

The anion recognition properties of **BODIPY-CP** were firstly studied by UV–visible upon addition of tetra-n-butylammonium salt of F^-, Cl^-, Br^-, AcO^-, and $H_2PO_4^-$ in acetonitrile. The effect of various anions with different shapes and sizes on **BODIPY-CP** in acetonitrile is presented in Fig. 1. The most significant changes in the absorption spectra were observed only in the presence of F^- ion. The results, shown in Fig. 1, clearly demonstrate that the addition of F^- ion into acetonitrile solution of **BODIPY-CP** (1.0×10^{-4} M) causes strong changes in the absorption band at 521 nm which decreased while new maximum bands appeared at 419 and 443 nm.

Fig. 2 shows the absorption spectra of **BODIPY-CP** in acetonitrile in the presence of varied concentrations of F^-. Upon addition of F^-, a gradual absorbance decrease at 521 nm was accompanied by a gradual increase at 419 nm, and an isosbestic point appeared at 443 nm, indicating the formation of a new species, most likely resulting from the binding of F^- to **BODIPY-CP** via N–H. . .F hydrogen bonding. The selective sensing of F^- by **BODIPY-CP** may even be performed by naked eye. As shown in Fig. 3, the presence of 10 equiv. of F^- makes the acetonitrile solution of **BODIPY-CP** changed from brownish yellow color to straw yellow.

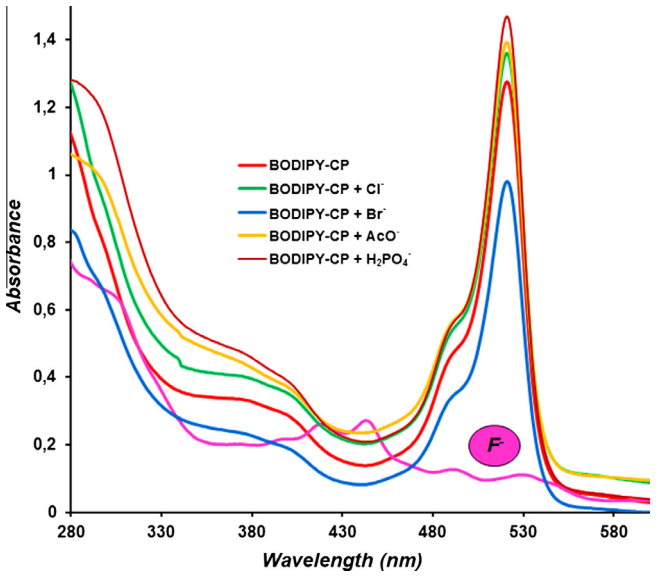


Fig. 1. Change in the UV–visible absorption spectrum of **BODIPY-CP** (1.0×10^{-4} M) in the presence of tetra-n-butylammonium salts of different anions in acetonitrile (10 equiv.).

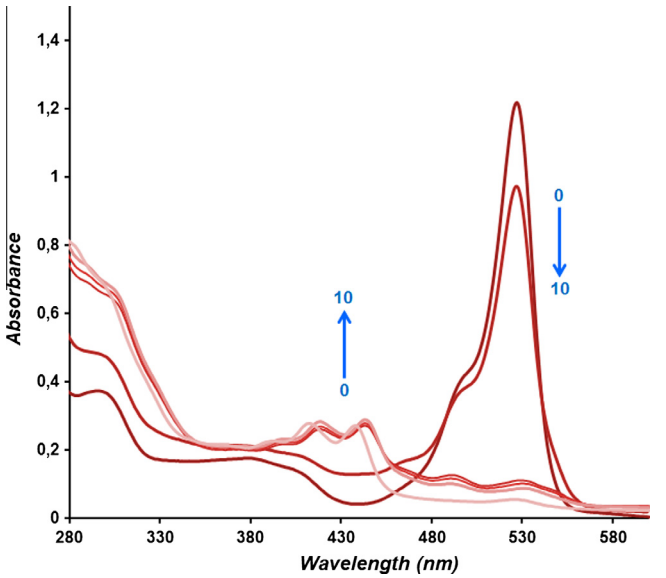


Fig. 2. Absorption spectra of **BODIPY-CP** (1.0×10^{-4} M) in acetonitrile in the presence of varied concentrations of F^- (0, 2, 4, 6, 10 equiv.).

In order to disclose the concrete binding sites within the **BODIPY-CP**, the ^{1}H NMR titration of the **BODIPY-CP** with F^- was conducted in DMSO-d_6 as an example (see Fig. 4). The **BODIPY-CP** displayed two sharp peaks at 9.76 and 9.26 ppm, attributed to pyrrole NH. With 1 equiv. amounts of F^- the signal of pyrrole NH protons disappeared until the new signals appeared at 12.41 ppm, which represented the formation of the stable complexes. The most significant changes in chemical shift values of the pyrrole CH protons were observed for pyrrole CH proton between NH moieties. The observed downfield shifts of the pyrrole NH resonances are an indication of hydrogen bonding to fluoride anion, as well as simplification of the pyrrole CH signals, a

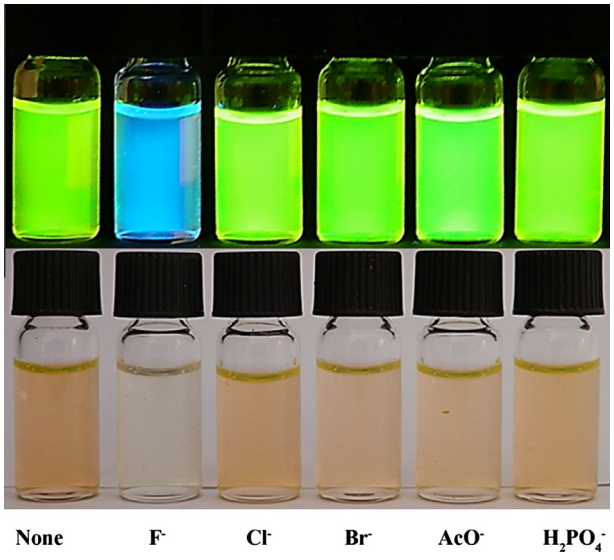


Fig. 3. The photographs of **BODIPY-CP** (1.0×10^{-4} M) solutions in acetonitrile in the presence of various anions (10 equiv.), taken either under day light (down) or in the dark and lightened by 365 nm light from a hand-held UV lamp.

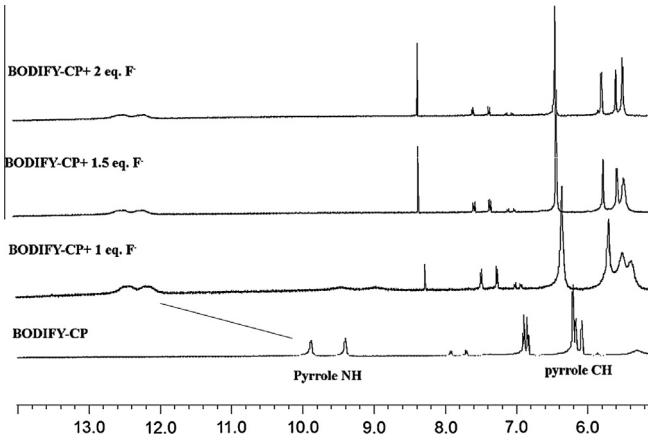


Fig. 4. Partial ^{1}H NMR spectra of the **BODIPY-CP** in DMSO-d_6 upon addition of F^- (0, 1, 1.5, 2 equiv.).

characteristic for transition from 1,3 alternate to a symmetrical cone-like conformation.

The emissions and excitations of **BODIPY-CP** in presence of various anions just as UV–visible were investigated by fluorometer. Observable color changes took place in acetonitrile. Upon addition of 10 equiv. of fluoride ions, the brownish yellow solutions of the dye became straw-yellow more in acetonitrile. No color changes of the receptor in acetonitrile were observed in the presence of chloride, bromide, and dihydrogen phosphate anions (Fig. 3). The anions were added as tetrabutylammonium salts (10 equiv.) to 1.0×10^{-7} M solutions of **BODIPY-CP**. The emission spectrum of the fluorescent dye shows three transitions in acetonitrile. Fig. 5 shows that the **BODIPY-CP** has a strong emission band entered at 532 nm (exc: 410 nm) due to its characteristic Bodipy emission band and two hills appear between 450 and 480 nm due to calix[4]pyrrole unit. Upon the addition of anions, only F^- gave increase/decrease to changes in calix[4]pyrrole emission bands and Bodipy emission band, respectively. But no detectable spectral changes were observed even in the presence of larger excess of hundred equivalents of other anions, which made it clear that the fluorescent dye could sense F^- over studied other anions. This quenching effect can be attributed to the smaller size and higher

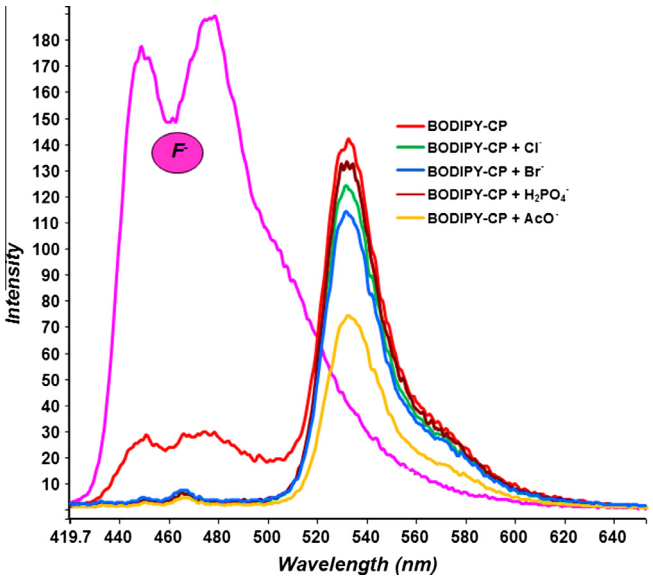


Fig. 5. Emission spectra of **BODIPY-CP** in acetonitrile (1.0×10^{-7} M) in the absence and presence of various anions. The amount of added anions is 10 equiv. (Excitation: 410 nm).

electronegativity of the F^- compared to the other anions. The diversity of these emission hills implies that pyrrole-NH fragments of calix[4]pyrrole unit were involved in F^- binding and the deprotonation of the amino moiety by F^- rather than hydrogen bonds. Here, the fluorescence intensity of the **BODIPY-CP** is effectively quenched or completely 'turn off' after the addition of 10 equivalents of F^-.

Fig. 6 shows the spectral changes in emission spectra of the **BODIPY-CP** depending on increasing of F^- anion. Once the concentration of F^- increased, the intensity of the peaks in shorter wavelength enhanced whereas the intensity of peak in longer wavelength decreases. This is attributed to more efficient energy transfer between anion and receptor. The changes in the emission spectra of the fluorescent dye upon titrating with F^- (1, 2, 4, 6, 8

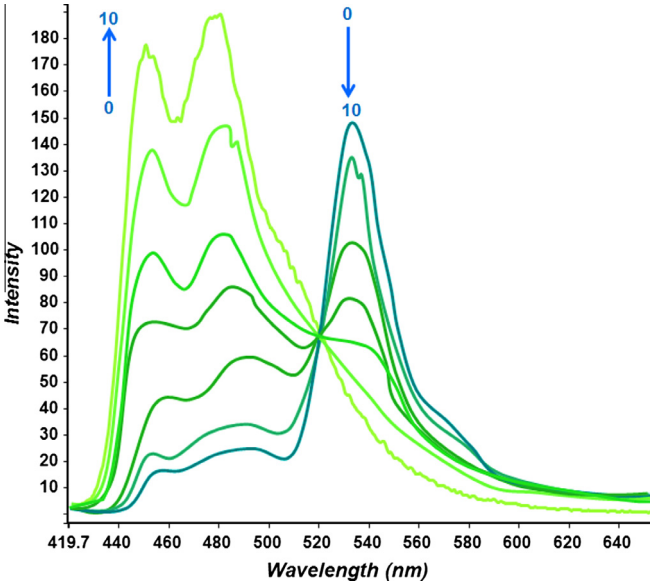


Fig. 6. Change in emission spectra of **BODIPY-CP** in presence of F^- anion (1, 2, 4, 6, 8, 10 equiv. in acetonitrile).

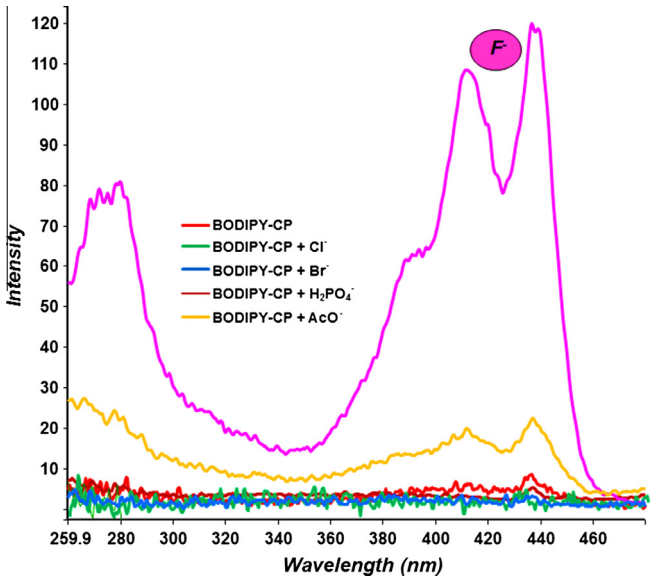


Fig. 7. Excitation spectra of **BODIPY-CP** in acetonitrile (1.0×10^{-7}) in the absence and presence of various anions. The emission data were collected at 500 nm.

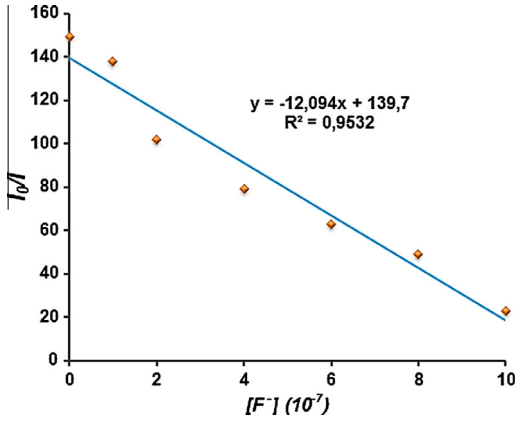


Fig. 8. The fluorescence variation of **BODIPY-CP** by F^- for Stern–Volmer plot in acetonitrile (emission: 532 nm, excitation: 410 nm).

and 10 equiv.), shown in Fig. 6, clearly demonstrate by the formation of a clear isosbestic point at 521 nm.

The excitation measurements of receptor solution and receptor–anion mixtures were performed at 500 nm emission. Fig. 7 shows a pronounced selectivity and sensitivity for F^- anion. The excitation graphs of other anions give similar curves such as receptor (almost a linear curve) while the addition of fluoride anion gives an enormous increase in excitation intensity. The increase of excitation wavelength of **BODIPY-CP-**fluoride indicates the energy transfer efficiency due to broader spectral overlaps between the donor and receptor when the fluoride anion is bound to the calix[4]pyrrole unit. The excitation spectrum of only **BODIPY-CP**-fluoride mixture compared to that of the **BODIPY-CP** and **BODIPY-CP**-anion mixtures presents an effective energy transfer within the target compound. Similarly, some little changes were recorded for acetate anion in excitation curve. As shown, acetate anion has a weaker quenching effect onto fluorescence of **BODIPY-CP**.

Stern–Volmer equation was utilized to quenching of fluorescence in the bonding of fluoride anions. The plots obtained emission intensities (I_0/I) against fluoride concentration and showed a negative linear graph (Fig. 8).

$$I_0/I = 1 + K_{sv}[M]$$

In the above equation, I_0 is the emission intensity of **BODIPY-CP** in the absence of F^-; I is the emission intensity of **BODIPY-CP** in the presence of F^-; and K_{sv} is the static quenching constant. Linear behavior was shown in graphic. The static quenching constants (K_{sv}) are calculated as 5.48×10^7.

Conclusions

The anion recognition behavior of the **BODIPY-CP** containing four pyrrole-NH, as anion-binding units was investigated toward anions, such as F^-, Cl^-, Br^-, AcO^-, and $H_2PO_4^-$. It was reported that the receptor showed colorimetric and 'turn-off' fluorescent responses in the presence of high electronegative and small-size anions F^- because of their ability to form intermolecular hydrogen bonding pyrrole-NH proton.

Acknowledgments

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