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A colorimetric and fluorometric fluoride sensor based on a BODIPY-phenol conjugate

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A boradiazaindacenes (BODIPY)-phenol conjugate, **1**, can act as a colorimetric and fluorometric sensor for sensitive and selective measurement of F^- over AcO^- and $H_2PO_4^-$ in CH_3CN. Sensor **1** gives response to F^- in a 1:1 ratio via the deprotonation of the phenolic OH proton, which results in color change from pale yellow to light green and quenching of bright green fluorescence.

colorimetric, fluorescence, fluoride, sensor, BODIPY

1 Introduction

In recent years, the design and synthesis of sensors capable of binding and sensing fluoride selectively have drawn considerable attention in supramolecular chemistry [1], because fluoride anion plays very important roles in clinical treatments for osteoporosis and fluoride toxicity [2]. To date, considerable effort has been devoted to the development of artificial fluoride sensors through visible, optical and electrochemical responses [3–5]. Most of synthetic sensors generally involve the covalent linking of a signaling fragment to a neutral anion receptor containing urea, thiourea, amide, indole, or phenolic hydroxyl subunits, which can provide hydrogen-bond donor sites for selective binding some anions, especially these anions F^-, AcO^- and $H_2PO_4^-$. The selectivity can be related to the structure of the hydrogen bond complex and the basicity of the anions. Although some reported reaction-based sensors selectively recognize fluoride, the limit is lack of reversibility [6–9]. Alternatively, few sensors can selectively sense F^- over AcO^- and $H_2PO_4^-$, due to their similar basicity, based on hydrogen-bond or deprotonation [1, 10–14]. Thus, we expect to develop a selective anion sensor for fluoride through both the acid-base interaction and hindrance effect between anion and the binding site modified by the introduction of a larger bulky group.

As known, phenolic unit has been investigated widely as a good anion receptor via hydrogen bonding interactions or salt complex [15, 16]. Several phenol-based boradiazaindacenes (BODIPY) conjugates were reported as pH indicators [17, 18], but their potential capabilities as sensing anions are not extensively explored. On the other hand, BODIPY is an advantageous fluorophore with many excellent photophysical properties, and numerous BODIPY-based derivatives have been synthesized as anion, mental and pH probes [19].

Hence, we synthesized a BODIPY-phenol conjugate **1** and investigated its anion reorganization properties by UV-vis and fluorescence spectroscopy. With the larger bulky *tert*-butyl groups *ortho* to the phenolic OH, com-

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pound **1** was expected to trigger color and fluorescence changes upon complexation with fluoride over other large anions such as AcO^- and $H_2PO_4^-$. Moreover, a reference **2** was also prepared according to published procedures (Scheme 1) [20].

2 Experimental

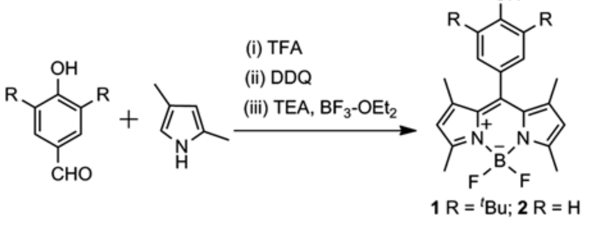
2.1 Materials and methods

All the tetrabutylammonium salts with different anions were purchased from Alfa Aesar Chemical Co., stored in a desiccator under vacuum, and used without further purification. CH_3CN used in the context was chromatographic pure. ^1H NMR and ^{13}C NMR spectra were performed on a Varian INOVA 400 MHz spectrometer in $CDCl_3$. ESI-MS studies were carried out using a Waters Micromass ZQ-4000 spectrometer. The fluorescence spectra were recorded on a Perkin Elmer LS55 spectrometer. UV-vis spectra were determined on a Perkin Elmer Lambda 35 spectrometer. C, H, N elemental analyses were made on a Vario-EL.

2.2 Synthesis

A solution of corresponding benzaldehyde (0.61 g, 2.62 mmol), 2,4-dimethyl pyrrole (0.52 g, 5.24 mmol) and one drop of trifluoroacetic acid (TFA) in dry CH_2Cl_2 (50 mL) was stirred overnight under N_2 atmosphere. After oxidation by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (0.59 g, 2.62 mmol), Et_3N (2 mL) and BF_3-OEt_2 (2 mL) were added in ice-water bath. After being stirred for 2 h, the mixture was washed with water several times, dried over $MgSO_4$, and concentrated at reduced pressure. The residue was purified by column chromatography (silica gel, CH_2Cl_2) to give the target compound.

Compound **1** yield 40%. ^1H NMR (400 MHz, $CDCl_3$) δ:1.408 (s, 6H, $2CH_3$), 1.433 (s, 18H, $6CH_3$), 2.557 (s, 6H, $2CH_3$), 5.368 (s, 1H, OH), 5.981 (s, 2H, 2CH), 7.032 (s, 2H, 2ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.34, 14.54, 30.41, 34.52, 120.92, 124.38, 125.52, 131.89, 137.08, 143.05, 154.29, 154.88. FT-IR (KBr): 1413.73, 1440.79, 1464.76, 1509.80, 1542.84, 2868.15, 2916.46, 2951.53, 3421.05 cm^{-1} ESI-MS: *m/z* (%) 453.4 ($M + H^+$, 100). Anal. calcd for **1** ($C_{26}H_{31}BF_2N_2O$): C, 69.11; H, 7.34; N, 5.83. Found: C, 68.93; H, 7.37; N, 5.79.



Scheme 1 The synthetic route of two compounds **1** and **2**.

Compound **2** yield 34 %. ^1H NMR (400 MHz, $CDCl_3$) δ: 1.441 (s, 6H, $2CH_3$), 2.550 (s, 6H, $2CH_3$), 5.301 (s, 1H, OH), 5.979 (s, 2H, 2CH), 6.943 (d, $J = 7.6$ Hz, 2H, 2ArH), 7.114 (d, $J = 7.6$ Hz, 2H, 2ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.56, 116.10, 121.13, 127.11, 129.35, 131.79, 141.73, 143.19, 155.28, 156.29. FT-IR (KBr): 1408.33, 1439.30, 1468.34, 1511.70, 1542.91, 1608.07, 2874.06, 2922.57, 2963.32, 3418.38 cm^{-1}. ESI-MS: *m/z* (%) 339.3 ($M - H^+$, 100). Anal. calcd for **2** ($C_{19}H_{19}BF_2N_2O$): C, 66.20; H, 5.38; N, 7.67. Found: C, 66.26; H, 6.32; N, 7.64.

3 Results and discussion

As shown in Table 1, both **1** and **2** show a typical narrow absorption band at approximately 500 nm, which corresponds to the $S_0 \rightarrow S_1$ transition of BODIPY subunits, and an emission band at about 510 nm in tested solvents, which is in keeping with classical BODIPY derivatives [21]. Fluorescein ($\Phi_f = 0.925$) in 1 $mol\,L^{-1}$ NaOH was used as a standard to estimate the fluorescence quantum yields Φ_f [22]. Compound **1** shows a relatively high fluorescence quantum yield compared to **2**, which can be ascribed to the introduction of bulky *tert*-butyl groups hindering π-π stacking of the fluorophore [23].

The interaction of sensor **1** with different anions was investigated in CH_3CN by observing the changes in the absorption spectra. Upon addition of anions such as F^-, $H_2PO_4^-$, Cl^-, Br^-, I^-, AcO^-, HSO_4^- and ClO_4^- (as their tetrabutylammonium salts) to sensor **1**, only F^- remarkably changed the absorption spectrum, whereas the other anions tested only induced negligible responses (Figure 1). During the titration of sensor **1** with F^- as shown in Figure 2, the absorption band at 496 nm decreased and two new bands emerged at 470 and 670 nm, which was responsible for simultaneously changing the solution of sensor **1** from pale yellow to light green (Figure 3). Two isosbestic points at 481 and 519 nm were observed, indicating the formation of F^--sensor complex. Two novel bands can be assigned to the deprotonated form of BODIP-phenolate as was confirmed by the Brønsted acid-base reaction of sensor **1** with a strong base $[Me_4N]OH$. According to the Job plot, sensor **1** interacted with F^- in a 1:1 ratio (Figure 2 inset). The equilibrium constant (or proton-dissociation constant) K for F^- was determined to be 1.65×10^4 at 496 nm and 1.66×10^4 at 670 nm [24]. In brief, sensor **1** can selectively bind F^- over other basic anions such as AcO^- and $H_2PO_4^-$, owing to the basicity and smaller radius of F^- and the larger steric hindrance of two *tert*-butyl groups.

For further investigation, the recognition properties of sensor **1** with various anions were conducted by fluorescence technology (Figure 4). In the presence of F^-, the fluorescence

Table 1 Spectroscopic characteristics of the two compounds **1** and **2** in different solvents

Compound	Solvent	λ_{Abs} (max/nm)	λ_{em} (max/nm)	Φ_f	$\varepsilon\times10^4$ (L mol^{-1} cm^{-1})
1	CH_3CN	496	509	0.525	8.84
	EtOH	497	512	0.574	9.48
	THF	499	511	0.873	8.67
	CH_2Cl_2	499	511	0.870	9.02
	cyclohexane	501	512	0.715	8.06
2	CH_3CN	497	511	0.420	3.66
	EtOH	498	511	0.458	2.80
	THF	500	513	0.429	7.22
	CH_2Cl_2	501	514	0.704	7.35
	cyclohexane	502	514	0.651	7.55

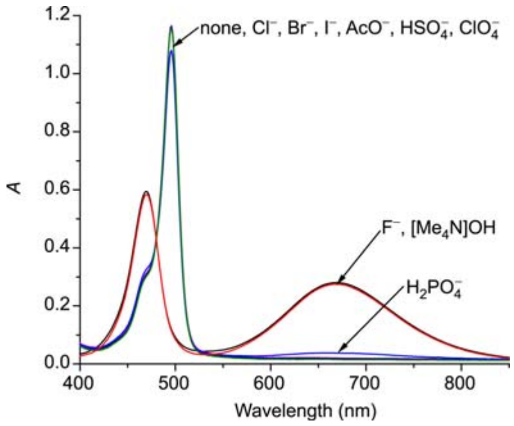


Figure 1 Absorption spectra of sensor **1** (3.1×10^{-5} mol L^{-1}) upon the addition of respective anions (4×10^{-4} mol L^{-1}).

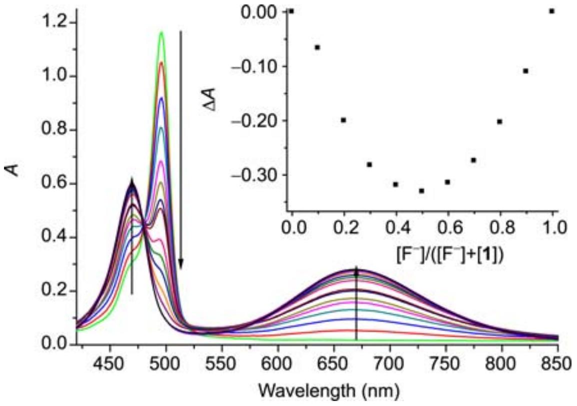


Figure 2 UV-vis titration of sensor **1** (3.1×10^{-5} mol L^{-1}) upon the addition of F^- (0–4×10^{-4} mol L^{-1}). Inset: A job plot of sensor **1** with F^- in CH_3CN.

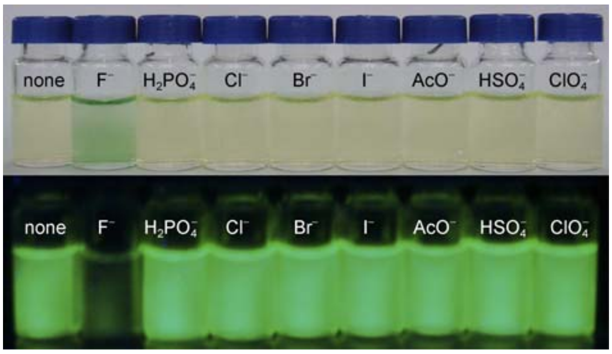


Figure 3 Color changes and fluorescence responses of sensor **1** (3.1×10^{-5} mol L^{-1}) with various anions (4×10^{-4} mol L^{-1}) in CH_3CN.

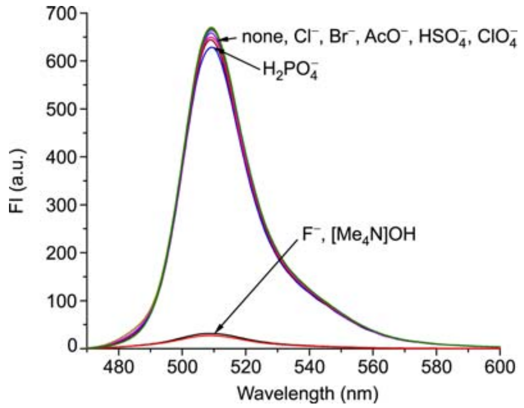


Figure 4 Fluorescence spectra of sensor **1** (3.1×10^{-6} mol L^{-1}) upon the addition of respective anions (6.9×10^{-5} mol L^{-1}). Excitation was at 496 nm.

intensity of **1** significantly decreased along with the bright green fluorescence quenching (Figure 3). Likewise, similar quenching was observed by addition of $[Me_4N]OH$. Quenching can be attributable to the occurrence of photoinduced electron transfer (PET) mechanism from the phenolate salt to the BODIPY core. No fluorescence change was observed for other tested anions. As shown in Figure 5, the intensity of the peak at 509 nm decreased upon gradual addition of F^- and complete quenching (Φ_f = 0.018) took place in the presence of 20 equiv of F^-. Based on the change in fluorescence intensity, the detection limit for F^- was determined to be 2.0×10^{-6} mol L^{-1} (based on $S/N = 3$).

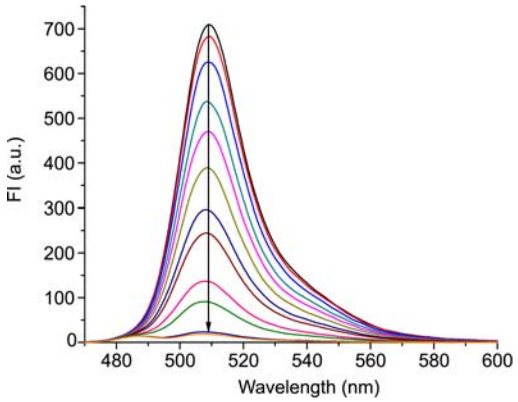


Figure 5 Fluorescence spectra of sensor **1** (3.1×10^{-6} mol L^{-1}) upon the addition of F^- ($0–6.9\times10^{-5}$ mol L^{-1}) in CH_3CN.

To firmly prove the interaction of sensor **1** with F^-, ^1H NMR experiments were conducted in acetonitrile-*d*$_3$ and $CDCl_3$ (5:1) solution, and addition of $CDCl_3$ was to improve the solubility of **1** in acetonitrile-*d*$_3$. A partial ^1H NMR spectrum of sensor **1** is shown in Figure 6. It was found that, upon gradual addition of F^-, the signal of the phenolic OH proton underwent downfield shift ($\Delta\delta = 0.34$) and disappeared with the addition of 5.0 equiv of F^-. The above-mentioned results indicate that sensor **1** can interact with F^- through deprotonation.

In Figure 7, control experiments were performed with compound **2**. In the presence of F^- or $[Me_4N]OH$, a slight response was developed in the absorption spectrum. Interestingly, compared to **2**, sensor **1** exhibited two novel absorption bands at 470 and 670 nm, respectively, which may be attributed to the two allotropic forms (**1a** and **1b**) of sensor **1** after deprotonation (Figure 8) [25, 26]. The donor ability of two *tert*-butyl groups can facilitate the formation of **1b**, which causes the increased degree of π-electron conjugation of the sensor. Besides, addition of AcO^- or $H_2PO_4^-$ to the solution of **2** also resulted in the decreased fluorescence intensity at 511 nm to some extent (Figure 7(b)). Namely, reference **2** not only gave the fluorescence response to F^-, but also AcO^- and $H_2PO_4^-$ under the similar experimental conditions. During the titration of **2** with F^- in Figure 9, fluorescence quenching was also observed upon gradual addition of F^- due to the occurrence of PET process after the deprotonation of **2**. These findings support that the existence of *tert*-butyl hindrance in molecule **1** can prevent the affinity of large basic anions. As a result, sensor **1** can allow sensitive and selective detection of F^- through color and fluorescence changes.

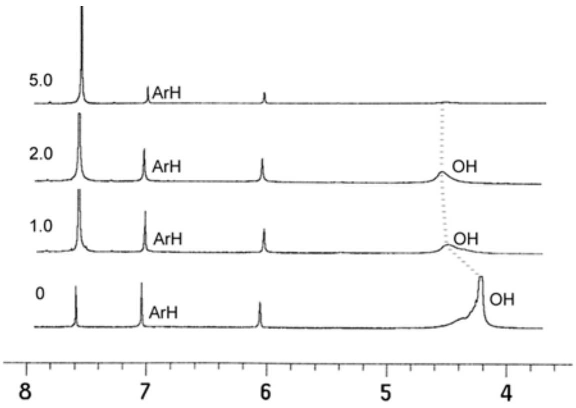


Figure 6 ^1H NMR spectra of sensor **1** in the presence of 0, 1.0, 2.0, and 5.0 equiv of F^-.

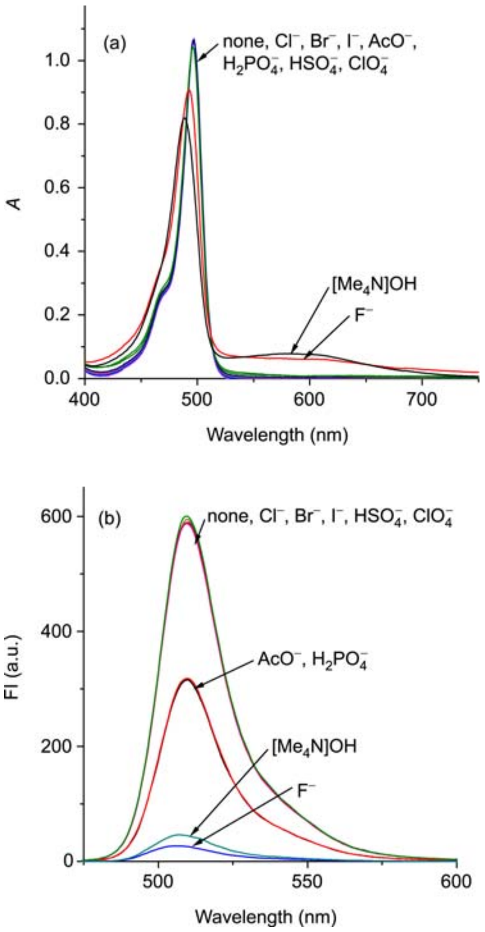


Figure 7 (a) Absorption spectra of **2** (3.1×10^{-5} mol L^{-1}) upon the addition of respective anions (4×10^{-4} mol L^{-1}); (b) fluorescence spectra of **2** (3.1×10^{-6} mol L^{-1}) upon the addition of respective anions (6.9×10^{-5} mol L^{-1}) in CH_3CN.

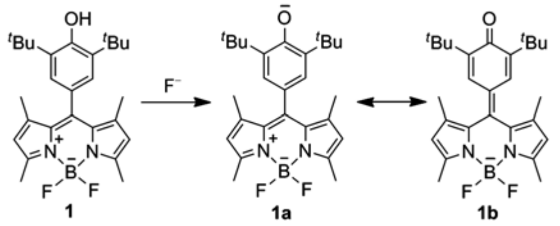


Figure 8 Proposed binding mechanism of sensor **1** with F^-.

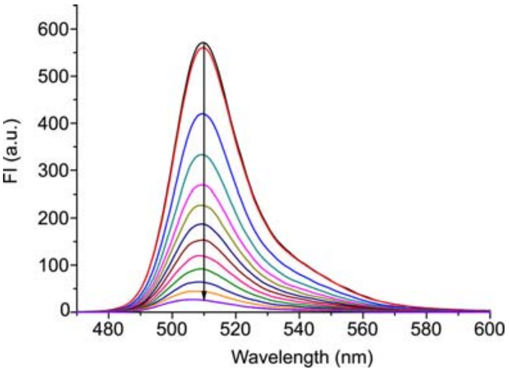


Figure 9 Fluorescence spectra of **2** (3.1×10^{-6} mol L^{-1}) upon the addition of F$^-$ ($0-6.9 \times 10^{-5}$ mol L^{-1}) in CH_3CN.

4 Conclusions

In conclusion, a BODIPY dye **1** incorporating *tert*-butylphenol unit has been investigated as a colorimetric and fluorometric sensor for fluoride based on the deprotonation mechanism. In the presence of F$^-$, sensor **1** shows naked eye-detectable color change from pale yellow to light green and obvious fluorescence quenching due to the PET process from the phenolate unit to BODIPY. The present study illustrates that the hindrance of the hosts and the basicity of the anions should be taken into consideration in the design of versatile anion probes.

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