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A BODIPY–indole conjugate as a colorimetric and fluorometric probe for selective fluoride anion detection

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ABSTRACT

A BODIPY–indole conjugate, **1**, behaves as a colorimetric and fluorometric probe for selective and sensitive detection of F^-. Compound **1** interacts with F^- in a 1:1 stoichiometry via a hydrogen bonding interaction between the indolic NH proton and F^-, leading to clear color change from blue to green and quenching of orange fluorescence.

Design and development of efficient probes for selective anion sensing have attracted a great deal of attention, since anions play fundamental and important role in chemical, biological, medical, and environmental processes.[1] Of particular interest is the design of probes for selective fluoride anion (F^-) detection because of its important roles in dental care[2] and in the treatment of osteoporosis.[3] Various colorimetric[4] or fluorometric[5] F^- probes have been proposed. For practical application, probes that can detect F^- by both colorimetric and fluorometric analyses are favorable due to their ease of use. Several dual-mode F^- probes have therefore been proposed so far,[6] and intensive researches have still been made by many researchers.

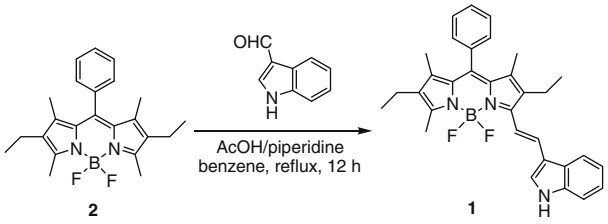
Boradiazaindacene (BODIPY)[7] is a dye being studied extensively because of its excellent photophysical properties, such as high fluorescence quantum yield, large extinction coefficient, high photostability, long absorption and fluorescence wavelengths. Recently, application of BODIPY to optical chemosensors,[8] fluorescent biolabeling reagents,[9] light harvesting materials,[10] and photodynamic therapy reagents,[11] has been studied extensively. In particular, metal cation sensors have attracted a great deal of attention.[8a–e] However, there are only a few reports of BODIPY-based anion sensors,[8f–k] where only two reports describe F^- probe.[8f,g]

Herein, we report that a new BODIPY-based probe (**1**) containing an indole moiety allows highly selective and sensitive F^- detection by both colorimetric and fluorometric analyses. The probe **1** shows F^--induced clear color change from blue to green and quenching of orange fluorescence. We describe that the F^--induced colorimetric and fluorometric responses of **1** are simply driven by hydrogen bonding interaction between the indolic NH proton of **1** and F^-.

Synthesis route of **1** is depicted in Scheme 1. Compound **1** is easily obtained by Knoevenagel-type condensation of a BODIPY derivative, **2**,[8d] with indole-3-carbaldehyde in a Dean–Stark apparatus (yield 34%).[12] The purity of **1** was confirmed by ^1H, ^{13}C NMR, and FAB-MS analyses (Supplementary data, Figs. S5–S7).

Figure 1 shows change in absorption and fluorescence (λ_{ex} = 605 nm) spectra of **1** (5 μM) measured in MeCN with respective anions as a *n*-Bu_4N^+ salt (200 equiv). As shown in Figure 1a, without anions, **1** exhibits an absorption band centered at 599 nm (ε = 57,600 M^{-1} cm^{-1}). F^- addition leads to a decrease in the 599 nm absorption, along with an appearance of red-shifted band at 718 nm (ε = 58,700 M^{-1} cm^{-1}). Accordingly, the solution color changes drastically from blue to green (Fig. 2a). In contrast, addition of other anions (Br^-, Cl^-, ClO_4^-, $H_2PO_4^-$, HSO_4^-, I^-, NO_3^-, SCN^-, and AcO^-) does not show change in absorption spectra (Fig. 1a).

As shown in Figure 1b, without anions, **1** shows strong fluorescence at 575–720 nm (fluorescence quantum yield: Φ_F = 0.353).[13] Addition of 200 equiv of F^-, however, leads to complete quenching of this fluorescence (Φ_F < 0.001). As shown in Figure 2b, bright orange fluorescence disappears completely by F^- addition. As shown in Figure 1c, ratio of the fluorescence intensity (FI_0/FI) measured at 624 nm with and without F^- is determined to be 378. This value is much higher than that obtained with early-reported fluorescent F^- probes.[6,8f,g] In contrast, addition of other anions shows almost no



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Scheme 1. Synthesis of BODIPY–indole conjugate, **1**.

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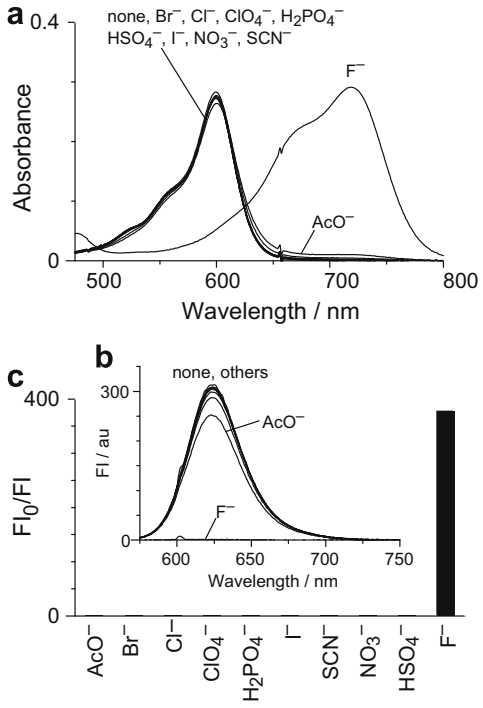

Figure 1. (a) Absorption and (b) fluorescence (λ_{ex} = 605 nm) spectra of **1** (5 μM) measured in MeCN with 200 equiv of respective anions as a *n*-Bu_4N^+ salt. (c) The ratio of the fluorescence intensity (FI_0/FI) of **1**, where FI and FI_0 are the fluorescence intensity monitored at 624 nm with and without anions.

change in fluorescence spectra (Fig. 1b). These findings suggest that **1** allows selective and sensitive F^- detection by both colorimetric and fluorometric analyses. It must be noted that the colorimetric and fluorometric responses of **1** to F^- are unaffected by other anions (Supplementary data, Fig. S1), indicating that **1** can detect F^- selectively even in the presence of other anions

Figure 3 shows the results of absorption titration of **1** with F^-. Addition of F^- leads to decrease in the 599 nm absorption, along with an increase in the 718 nm band. The spectral change almost stops upon addition of 150 equiv of F^-. The clear isosbestic points at 504 and 625 nm indicate that a single component is produced in response to the interaction between **1** and F^-. Figure 4 shows the results of fluorescence titration of **1** with F^-. Addition of F^- leads to continuous decrease in the 575–720 nm fluorescence. Complete fluorescence quenching takes place upon addition of 150 equiv of F^-, which is similar to the change in absorption spectra (Fig. 3). Based on the change in fluorescence intensity at 624 nm, the detection limit for F^- is determined to be 36 μM.[14]

The probe **1** associates with F^- in a 1:1 stoichiometry. This is confirmed by the Benesi–Hildebrand analysis.[8d,15] When assuming a 1:1 association between **1** and F^-, the Benesi–Hildebrand equation is given as follows:

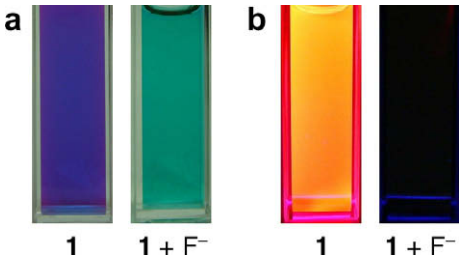

Figure 2. Change in (a) color and (b) fluorescence color of a MeCN solution containing **1** upon addition of F^-.

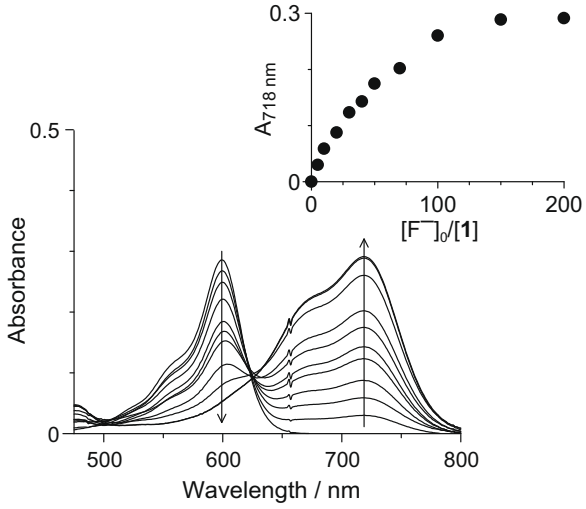

Figure 3. Change in absorption spectra of **1** (5 μM) in MeCN upon addition of 0, 5, 10, 20, 30, 40, 50, 70, 100, 150, and 200 equiv of F^- as a *n*-Bu_4N^+ salt. (Inset) Change in absorbance monitored at 718 nm.

$$\frac{1}{A-A_0}=\frac{1}{A_\infty-A_0}\left[\frac{1}{K[F^-]_0}+1\right] \quad (1)$$

A_0 is the absorbance of free **1**, A_∞ is the absorbance measured with excess amount of F^-, A is the absorbance measured with F^-, K is the association constant (M^{-1}), and $[F^-]_0$ is the concentration of F^- added (M). As shown in Figure 5, the plot of $1/(A-A_0)$ against $1/[F^-]_0$ shows a linear relationship (R = 0.998), indicating that **1** indeed associates with F^- in a 1:1 stoichiometry. The association constant, K, between **1** and F^-, is determined from the ratio of intercept/slope to be 7.8×10^2 M^{-1}.

The probe **1** associates with F^- via a hydrogen bonding interaction between the indolic NH proton of **1** and F^-. This is confirmed by ^{1}H NMR analysis. Figure 6 shows the results of ^{1}H NMR titration of **1** with F^- in CD_3CN. Upon F^- addition, the indolic NH proton of **1** (δ = 9.66 ppm) shows drastic downfield shift ($\Delta\delta$ = 0.63 ppm), indicating that F^- indeed interacts with the indolic NH proton. In contrast, the H_b–H_e protons on the indole moiety shift upfield. This is because the hydrogen bonding interaction leads to an increase in the electron density of the indole moiety (through-band effect).[4e,6k] In contrast, H_a proton of **1** shifts downfield. This is because the hydrogen bonding interaction leads to a polarization of the adjacent CH moiety and, hence, creates a partial positive charge

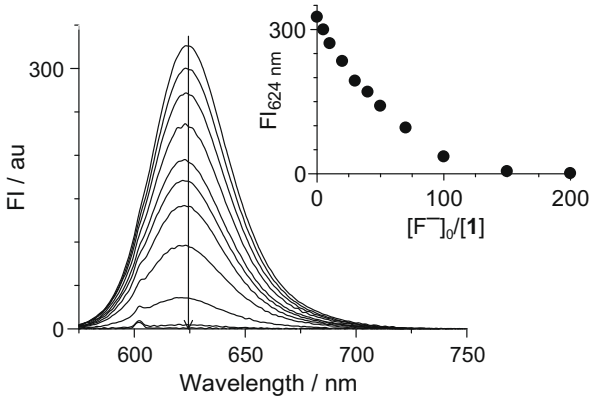

Figure 4. Change in fluorescence (λ_{ex} = 605 nm) spectra of **1** (5 μM) in MeCN upon addition of 0, 5, 10, 20, 30, 40, 50, 70, 100, 150, and 200 equiv of F^- as a *n*-Bu_4N^+ salt. (Inset) Fluorescence intensity monitored at 624 nm.

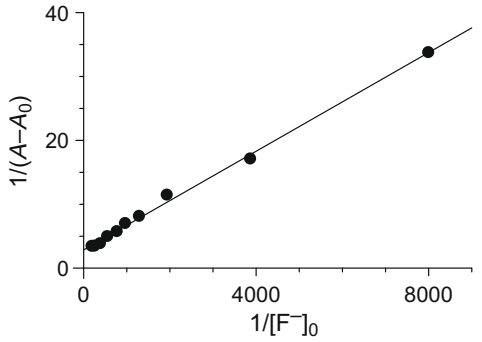

Figure 5. Benesi–Hildebrand plot (718 nm) using Eq. 1, assuming 1:1 stoichiometry for association between **1** and F^-.

on the H_a proton (through-space effect).[4e,6k] These ^1H NMR titration results clearly suggest that **1** associates with F^- via a hydrogen bonding interaction between the indolic NH proton and F^-.

The F^--induced shift of the absorption spectra is due to the charge-transfer character of the **1**–F^- complex. This is confirmed by absorption spectra of **1** and **1**–F^- complex measured in different solvents. Figure 7 shows the relationship between λ_{max} of the absorption spectra and dielectric constants, ε,[16] of the solvents. In the case of **1**, λ_{max} shows minor solvent-dependent shift. This indicates that dipole moments of the ground and excited states of **1** are similar and both states have minor charge-transfer character.[17] In contrast, λ_{max} of **1**–F^- shows stronger solvent dependence. This indicates that relatively large difference in the dipole moment exists between the ground and excited states of **1**–F^-, and the electronic excitation has a charge-transfer character.[18] The charge-transfer character of **1**–F^- is probably due to the positive charge on the indole moiety by the hydrogen bonding interaction. The dipole moment difference between the ground and excited states of **1**–F^- may therefore lead to a decrease in electronic transition energy, resulting in a red-shift of the absorption spectra (Fig. 3).

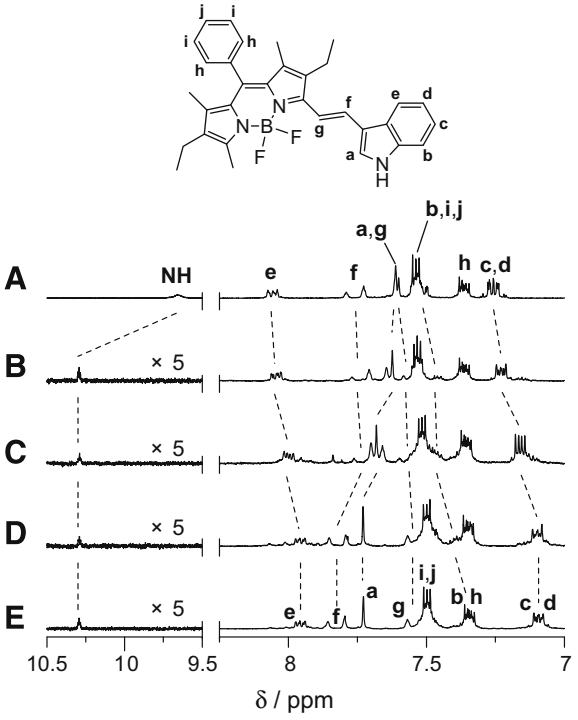

Figure 6. Change in partial ^1H NMR (270 MHz, 9.6 mM, CD_3CN) spectra of **1** upon addition of (A) 0, (B) 1, (C) 2, (D) 3, and (E) 5 equiv of F^-.

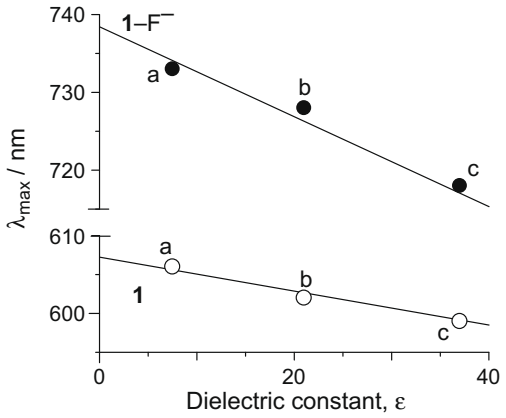

Figure 7. Relationship between λ_{max} of the absorption spectra of **1** (5 μM) obtained without (open keys) and with (closed keys) F^- and dielectric constants, ε, of the solvents. The solvents are (a) THF, (b) acetone, and (c) MeCN, respectively. The absorption spectra of the respective samples are summarized in Figure S2 (Supplementary data).

The **1**–F^- complex does not show fluorescence upon photoexcitation at 600–800 nm (Fig. S3, Supplementary data). As reported,[17b] excited state molecules with charge-transfer nature undergo nonradiative decay due to the acceleration of internal conversion. The no fluorescence of **1**–F^- complex is probably due to its charge-transferred excited state. As a result of this, the fluorescence intensity of the solution just depends on the absorbance of free **1** at the excitation wavelength (605 nm). This therefore results in fluorescence intensity decrease (Fig. 4) similar to the decrease in the absorbance of free **1** (Fig. 3).[19]

In summary, we found that a new BODIPY derivative, **1**, behaves as a highly selective and sensitive[20] F^- probe in both colorimetric and fluorometric analyses. The drastic color change and strong fluorescence quenching of **1** are simply driven by hydrogen bonding interaction between the indolic NH proton and F^-. The simple probe design presented here may contribute to the development of more efficient and more useful dual-mode anion probes.

Acknowledgments

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Supplementary data

Supplementary data (methods and Figs. S1–S7) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.05.018.

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12. *Synthesis of* **1**: **2** (0.2226 g, 0.59 mmol) and indole-3-carbaldehyde (0.0935 g, 0.64 mmol) were refluxed in a mixture of benzene (10 ml), AcOH (300 μl), and piperidine (360 μl) in a Dean-Stark apparatus for 12 h. The resultant was concentrated by evaporation, and the crude product was purified by silica gel column chromatography with CH_2Cl_2 and CH_2Cl_2/*n*-hexane mixture (3/1 v/v). The second fraction with red fluorescence was dried in vacuo, affording **1** as a red-purple solid (0.1022 g, 0.20 mmol, yield 34%). ^{1}H NMR (270 MHz, $CDCl_3$, TMS): δ (ppm) = 8.34 (br, 1H), 8.04 (t, J = 5,4 Hz, 1H), 7.78 (d, J = 8.1 Hz, 1H), 7.45–7.53 (m, 5H), 7.38 (t, J = 5,4 Hz, 1H), 7.24–7.33 (m, 3H), 2.59–2.69 (m, 5H), 2.32 (q, J = 8.1 Hz, 2H), 1.32 (s, 3H), 1.29 (s, 3H), 1.20 (t, J = 8.1 Hz, 3H), 0.99 (t, J = 8.1 Hz, 3H). ^{13}C NMR (68 MHz, $CDCl_3$, TMS): δ (ppm) = 151.0, 137.4, 136.7, 136.0, 132,8, 132.6, 131.8, 131,1, 128.8, 128.8, 128.4, 125.6, 125.0, 123.4, 123.3, 122.7, 120.9, 120.1, 116.5, 116.3, 111.3, 18.4, 17.1, 14.6, 14.1, 12.7, 11.6, 11.4. FAB-MS: Calcd for $C_{32}H_{32}BF_2N_3$: 507.4, found: m/z 507.6 (M, 100%).
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19. As shown in Figure S4 (Supplementary data), plots of the fluorescence intensity (λ_{em} = 718 nm) and the absorbance of free **1** at the excitation wavelength (605 nm) clearly show linear relationship.
20. A referee pointed out that the detection limit for F^- by **1** (36 μM) is relatively high as compared to that of the previously reported F^- probes (Refs. 6,8f,g). However, as shown in Figure 1c, the change in fluorescence intensity of **1** upon F^- addition (Fl_0/Fl = 378) is much larger than that of the previously reported probes (Refs. 6,8f,g). This suggests that **1** shows high 'sensitivity' to F^-.