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Communication

# Development of aryl-containing dipyrrolyldiketone difluoroboron complexes (BONEPYs): Tune the hydrogen bond *o*–C—H···F for fluoride recognition

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ABSTRACT

Dipyrrolyldiketone difluoroboron complexes (BONEPYs) were synthesized by condensation of the corresponding pyrroles and malonyl chloride followed by treatment with $BF_3{\cdot}OEt_2$. The aryl-substituted pyrrole is introduced to form a cyclic system in order to investigate anion binding studies. In BONEPYs **1–3** the *o*-H of the aryl group forms hydrogen bonding with $F^-$ to give a more table complex. In contrast, the intramolecular hydrogen-bonded BONEPY endo-**4** is more stable than its *exo* isomer. While adding $F^-$, the hydrogen bonds must be broken first to give **4**·(3)$F^-$. Owing to the electron-rich group (-OMe), the *o*-H of the phenyl group can hardly interact with $F^-$ *via* hydrogen bonding to give the less stable complex **4**·(5)$F^-$. The energy differences between the different conformations were calculated using DFT methods, which is consistent to the experimental observations.

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The proper ingestion of the fluoride anion ($F^-$) is useful to human health [1]. However, many diseases have been assigned to an abnormal concentration of $F^-$. The over dosage of $F^-$ has a serious pathological impact, such as promoting tooth, skeletal fluorosis and osteosarcoma [2]. Therefore, the detection and quantification of fluoride in feeding and drinking water are of great importance. Among the available methods to detect and quantify $F^-$, luminescent methods have been extensively pursued owing to their simplicity and high sensitivity [3–12]. A fluorescent probe for $F^-$ consists of two parts: a receptor and a chromophore. The former is an ion antenna, typically composed of various better hydrogen-bond donors, such as pyrrole, and imidazole [13]. The latter could convert a test signal into an optical signal detected by the naked eye and simple instrumentation [14]. But, because $H_2PO_4^-$ and $CH_3COO^-$ possess similar basicity as $F^-$ and easily form the hydrogen bonds, only a few of probes are capable of distinguishing fluoride ion effectively from these ions [15,16]. Therefore, the development of specific optical $F^-$ sensing is still a challenge.

Traditional classical difluoroboron ($BF_2$) complexes, such as BODIPY/aza-BODIPY [17–21], POPHY [22,23], and BOPPY [24], usually act as a chromophore, and widely applied in probing, molecular imaging, photodynamic therapy, laser generation, and electroluminescent devices, *etc.* (Fig. 1). And, such dyes have been attracting increasing interest, and were investigated thoroughly for a long time [25]. Furthermore, difluoroboron ($BF_2$) complex of dipyrrolyldiketone as a probe was first reported by Maeda *et al.*, and show an excellent characteristic in recognition of anions such as halide [26–28].

Dipyrrolyldiketone difluoroboron complexes (BONEPY) could bind anions using two pyrrole N—H groups and bridging C—H with the pyrrole rings' inversion. Herein, the aryl-substituted pyrrole is introduced to form a cyclic system in order to investigate anion binding studies. Based on the electronegative difference of the aryl moiety, the aryl *o*-H could be fine-tuned by anion binding. Electron donating/withdrawing substituents can affect the aryl *o*-H, which could form the extra binding to anions in addition to the bridging C—H and pyrrole N—H in this new BONEPY. Our recent research interest lies in fluorescent dyes and chemosensors [29–31]. Therefore, herein we conceived that the aryl moiety, incorporated dipyrrin nitrogens, would provide a new set of BONEPY analogues that would act as the more efficient probes for detecting the halide ion.

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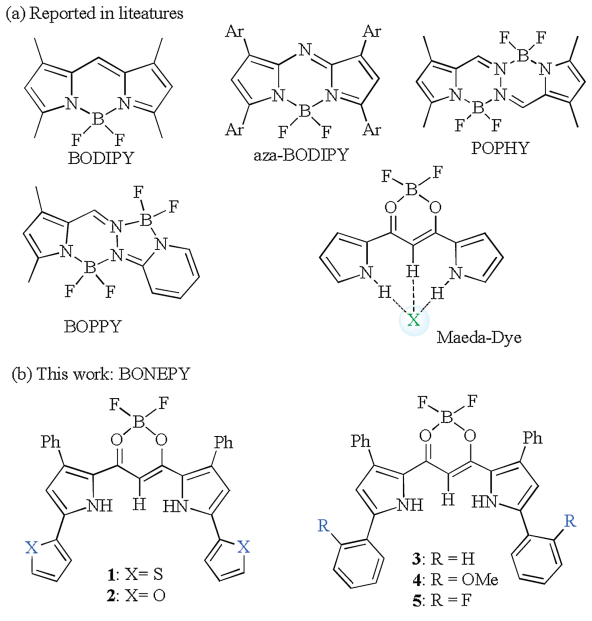
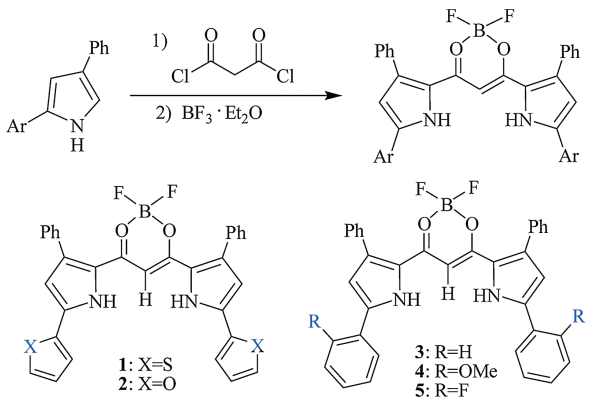



**Fig. 1.** Design strategies for BONEPYs for detecting the halide ion.




**Scheme 1.** Synthesis of the aryl-containing BONEPYs **1–5**.

To achieve a cyclic space for strongly binding ions, an aryl-containing pyrrole [32,33] was employed. BONEPYs **1–5** were smoothly obtained by condensation of the corresponding pyrroles and malonyl chloride followed by treatment with $BF_3{\cdot}OEt_2$ (Scheme 1). The structures of BONEPYs were confirmed by NMR and HRMS (Supporting information). Moreover, the solid-state structure of **1** was confirmed by X-ray crystallographic analysis (Fig. 2). In the solid-state structure, the thiophene, the pyrrole and the core $BF_2$ unit are almost coplanar (Supporting information), owing to the extension of $\pi$-$\pi$ conjugation.

In view of Maeda's papers [26–28], the complexation of BONEPY **1** with $Cl^-$ was first investigated. The binding with $Cl^-$ occurs at the bridging C—H and the pyrrole N—H. The strength of binding is weak, as it hardly affects the absorption intensity even with 90 equiv. of $Cl^-$ being added (Fig. S1 in Supporting information). Therefore, the response of BONEPY **1** towards $F^-$ was next carried out.

Upon addition of $F^-$ to BONEPY **1**, a stepwise decrease of the absorption intensity was observed, and BONEPY **1** is highly sensitive to $F^-$ (Fig. 3a). When treated with 0–1 equiv. of $F^-$, the absorption band at 545 nm decreased, accompanied by the emergence of a new absorption band around 528 nm, affording

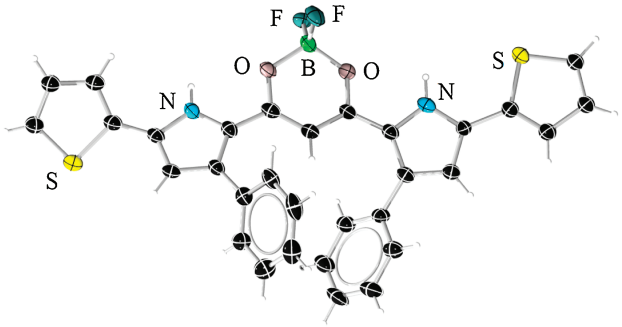


**Fig. 2.** Molecular structure and conformation for **1** (CCDC No. 1921407).

a blue-shift of 17 nm. However, with continuous addition of $F^-$, the formation of a new band at 563 nm was observed unexpectedly, affording a red-shift of 35 nm. The absorption intensity reached the maximum when 90 equiv. of $F^-$ was used. This change in absorption is remarkably different to those of Maeda's dyes [26–28]. Moreover, the binding stoichiometry (1:1) was determined by Job plots of **1** and $F^-$ (Fig. S2 in Supporting inforamtion).

We nervily propose that in this process, the tricoordinate complex **1**·(3)$F^-$ (red curve in Fig. 3a and Fig. 4) was generated first, which slowly became the pentacoordinate complex **1**·(5)$F^-$ (green curve in Fig. 3a and Fig. 4) [34]. Thereupon, density functional theory (DFT) calculations of **1**, **1**·(3)$F^-$ and **1**·(5)$F^-$ were carried out to gain insight into the conformation-dependence of the absorption spectrum (Fig. 5). Using DFT at the B3LYP/6–31 G(d) level, the molecular geometries of **1**, **1**·(3)$F^-$ and **1**·(5)$F^-$ were optimized. Comparing to **1**·(3)$F^-$, the most stable structure of **1**·(5)$F^-$, optimized at B3LYP/6–31 G(d), exhibited distorted conformation, wherein *o*-C–H in the thiophene of **1**·(5)$F^-$ showed effective interactions for $F^-$ (Fig. 4). The difference between the relative energies of *endo*-**1** and *exo*-**1** is 0.88 kcal/mol (Fig. 5). However, upon $F^-$ binding to form **1**·(3)$F^-$ and **1**·(5)$F^-$, the energy difference is increased to 6.76 kcal/mol. In addition, **1**·(3)$F^-$ shows a hypochromatic shift ($\lambda_{abs}$ = 528 nm) and **1**·(5)$F^-$ has a remarkable bathochromic shift ($\lambda_{abs}$ = 563 nm) in comparison with that of BONEPY **1** ($\lambda_{abs}$ = 545 nm) as described above. These experimental and theoretical results indicated that the extra hydrogen bonding C–H···F in **1**·(5)$F^-$ further stabilize this structure and lead to a lower relative energy of **1**·(5)$F^-$, comparing to that of **1**·(3)$F^-$. So, **1**·(3)$F^-$ and **1**·(5)$F^-$ are thought to be the solution-state [1 + 1]-type complex in this work, which are good agreement with the recent reported paper (Fig. S3 in Supporting information), even though containing a [2 + 1]-type complex in the solid state wherein the hydrogen bonding *o*—C—H···Cl really exist [35]. Moreover, the $^1$H NMR spectra exhibited more evident anion-binding modes of **1** upon the addition of TBAF in $CD_2Cl_2$ at 20 °C (Fig. 6). Due to the shield from the full effect of the applied field by their surrounding electrons [36], the chemical shifts in **1**·(3)$F^-$ and **1**·(5)$F^-$ are well-known to be lower than those in $^1$H NMR spectrum of dye **1** (Fig. 6). By increasing the amounts of the added $F^-$ (up to 4.0 equiv.), two kinds of gradual shifts of the bridging $CH_a$ and the thienyl $CH_b$ signals were obviously observed, and were shifted by anion binding to the downfield region. The bridging $CH_a$ and the thienyl $CH_b$ signals between dye **1** and pyrrole-inverted complex **1**·(3)$F^-$ were shifted from 6.35 and 7.13 ppm to 7.49 and 7.63 ppm, respectively, upon the addition of 0.50 equiv. of TBAF, and upon the addition of 4.0 equiv. of TBAF, to 7.81 and 7.91 ppm for **1**·(5)$F^-$, respectively, with increasing integrals. Addition, in comparison with the hydrogen signals for two aromatic rings of dye **1** in the $^1$H NMR spectrum, the complexes (**1**·(3)$F^-$ and **1**·(5)$F^-$) showed three sets of distinct hydrogen signals ($H_{d\text{-}f}$).

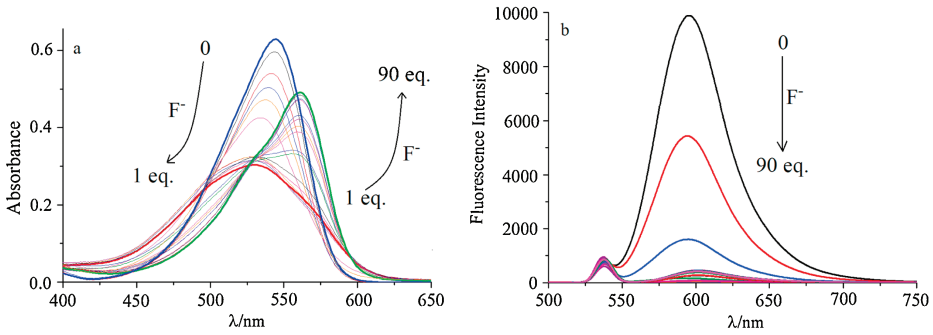



**Fig. 3.** Absorption (a) and fluorescence (b) response of $1 \times 10^{-5}$ mol/L BONEPY **1** upon addition of 0, 0.05, 0.1, 0.3, 0.5, 0.6, 1, 2, 3, 5, 7, 8, 10, 12, 15, 18, 20, 25, 30, 40, 50, 60, 70, 80 and 90 equiv. of $Bu_4NF$ in $CH_2Cl_2$ at 25 °C.

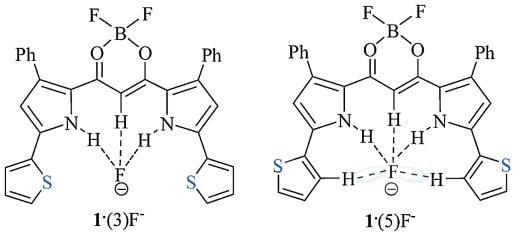



**Fig. 4.** Structures of the tricoordinate complex **1**·(3)$F^-$ and the pentacoordinate complex **1**·(5)$F^-$.

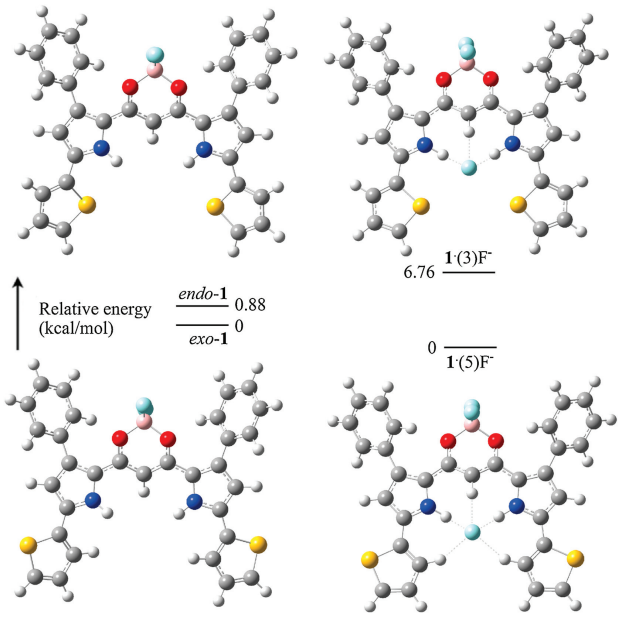



**Fig. 5.** Conformations of *exo*-**1**, *endo*-**1**, **1**·(3)$F^-$ and **1**·(5)$F^-$ according to the orientations of pyrrole and aryl moieties and the energy diagram of diverse conformations at the B3LYP/6–31 G(d) level with Gaussian 09.

Next, the sensitivity of BONEPY **1** was studied by its fluorescence response towards various concentrations of $F^-$ (Fig. 3b). BONEPY **1** exhibits fluorescence emission at 600 nm, and its fluorescence quantum yield is 0.71. A distinct response of **1** ($1 \times 10^{-5}$ mol/L) to $F^-$ in the concentration range of 0–90 equiv. was observed. Upon the addition of 0.3 equiv. of $F^-$, the emission of **1** is almost quenched by $F^-$, owing to the intramolecular electron-transfer. Further increase of $F^-$ concentration did not lead to the remarkable decrease of fluorescence intensity. And, BONEPY **1** could serve as a naked-eye indicator for $F^-$ from its color change from bright orange yellow to pink (Fig. 7).

As a homologue of the thiophene-substituted BONEPY, the optical properties of furan-substituted BONEPY **2** with $F^-$ was measured too. Similar to **1**, a similar synchronous effect with increasing amount of $F^-$ in solution was also shown from the absorption and emission spectra of **2** (Fig. S4 in Supporting information), which demonstrates that **2** was sensitive to $F^-$ as a turn-off fluorescent probe.

By changing the heterocyclic substituents to phenyl groups, we found that the absorption and fluorescence spectra of **3** are similar to those of **1** and **2**. However, the absorption spectra between **3** and the *ortho*-methoxy-substituted analogue **4** are distinct (Figs. 8a and c). BONEPY **3** absorbs at 525 nm, and a new band **3**·(3)$F^-$ grew at 516 nm, followed by generation of the final band **3**·(5)$F^-$ at 550 nm with a dropwise addition of $F^-$ (Fig. 8a and Fig. S5 in Supporting Information). The $^1H$ NMR spectra show that in contrast to that of BONEPY **3** ($\delta$ 9.62 (br s, 2 H)) in the high field, BONEPY *endo*-**4** showed the singlet hydrogen signals for pyrrole N—H ($\delta$ 10.81 (br s, 2 H)) in the low field (Supporting information), indicating that the hydrogen bond (N—H···O) was formed in solvent (*endo*-**4** of Fig. 9). Hence, the intramolecular hydrogen-bonded BONEPY *endo*-**4** ($\lambda_{abs}$ = 536 nm) is more stable. While adding few $F^-$, the hydrogen bonds have to be broken to give **4**·(3)$F^-$ (Fig. 8a). Owing to the electron-rich substituent (-OMe), the *o*-H of the phenyl group hardly associate with $F^-$ to give the hydrogen bond for forming the unstable complex **4**·(5)$F^-$ (Fig. 9). Therefore, upon addition of an excess of $F^-$, the final complex **4**·(3)$F^-$ ($\lambda_{abs}$ = 525 nm) was slowly generated instead of **4**·(5)$F^-$. This may attribute to the distinct absorption spectra of **3** and **4** upon addition of $F^-$. In addition, the synchronous effect was also shown in the emission spectra, and the fluorescence intensity is gradually decreased while adding $F^-$ (Figs. 8b and d). In contrast, the *o*-H of the phenyl group bearing the electron-withdrawing substituent (-F) could combine $F^-$ to produce the hydrogen bond for forming the stable complex **5**·(5)$F^-$ (Fig. S6 in Supporting information). Based on MO calculations, the values for *exo*-**4** are larger by 6.56 kcal/mol than those for *endo*-**4** (Supporting information), and the structure of *endo*-**4** is indeed a stable configuration owing to the intramolecular hydrogen bond (Fig. 9). Moreover, the values for the hypothetical complex **4**·(5)$F^-$ are indeed larger by 12.47 kcal/mol than those for **4**·(3)$F^-$ (Fig. 9 and Supporting information).

Additionally, the selectivity of BONEPY **1** towards various analytes was investigated. As shown in Fig. 10, in all cases BONEPY **1** was highly selective to $F^-$ with remarkable fluorescence intensity decrease. It is probably due to the $F^-$ electronegativity and its suitable size to a cyclic system of **1**, comparing to the other halogen anions. Moreover, the sensitivity for $F^-$ in a complex background of

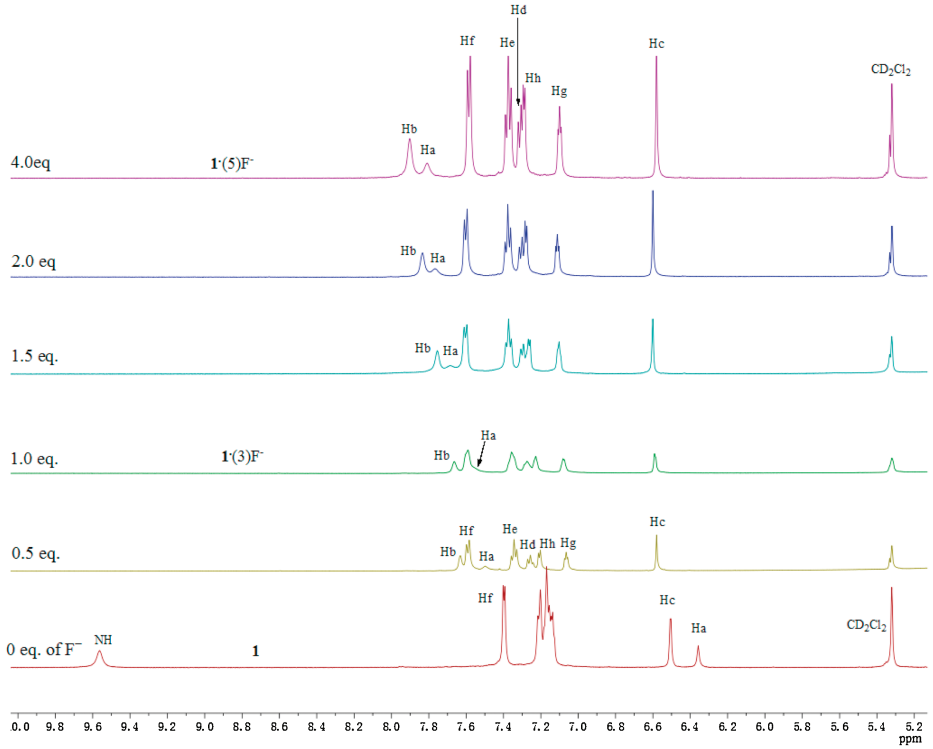



**Fig. 6.** $^{1}$H NMR of **1** ($2.0 \times 10^{-3}$ mol/L) upon the addition of $F^-$ as a TBA salt in $CD_2Cl_2$ at 20 °C.

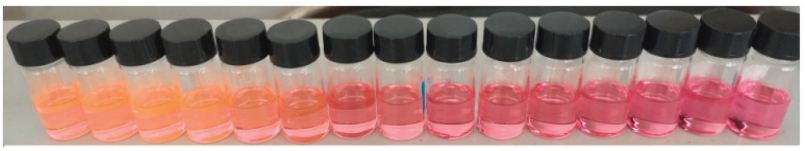


**Fig. 7.** Photograph of solutions of $1 \times 10^{-5}$ mol/L BONEPY **1** upon addition of 0, 0.05, 0.1, 0.3, 0.5, 1, 2, 3, 5, 10, 20, 30, 40, 50 and 90 equiv. of $F^-$ (from left to right) in $CH_2Cl_2$ under normal room illumination.

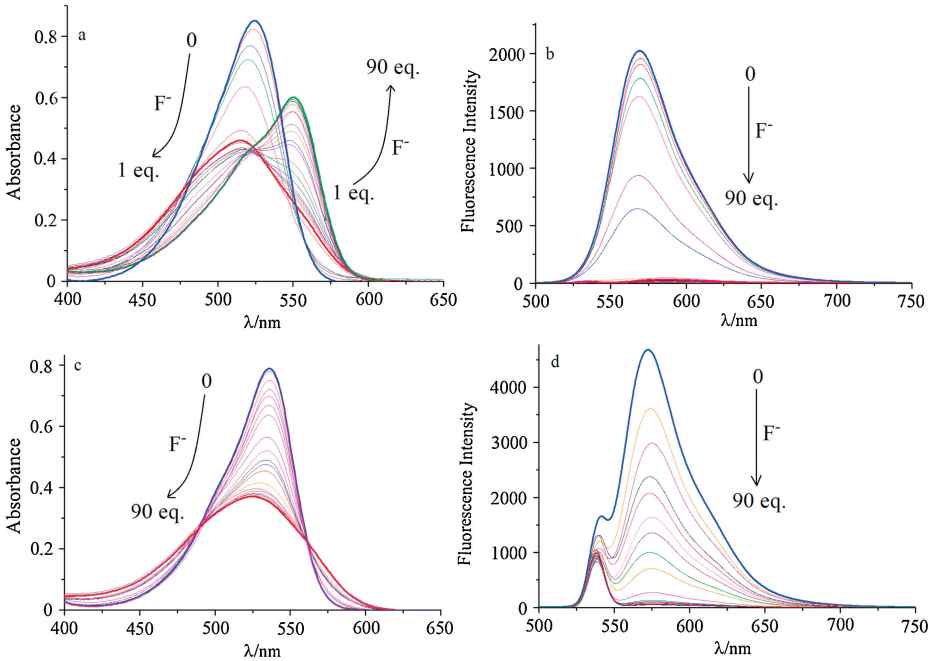



**Fig. 8.** Absorption and fluorescence response of $1 \times 10^{-5}$ mol/L BONEPYs **3** (a, b) or **4** (c, d) upon addition of 0, 0.1, 0.3, 0.5, 0.8, 1, 2, 3, 5, 7, 8, 10, 12, 15, 18, 20, 25, 30, 40, 50, 60, 70, 80 and 90 equiv. of $F^-$ in $CH_2Cl_2$ at 25 °C.

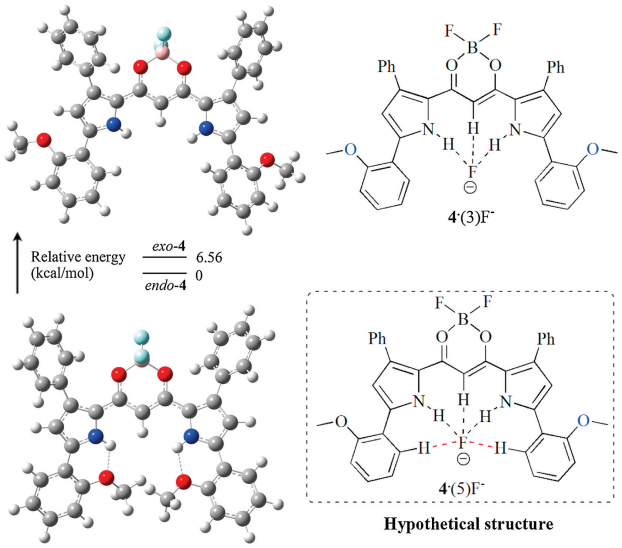



**Fig. 9.** Conformations of *exo*-**4**, *endo*-**4**, **4**·(3)$F^-$ and hypothetical complex **4**·(5)$F^-$.

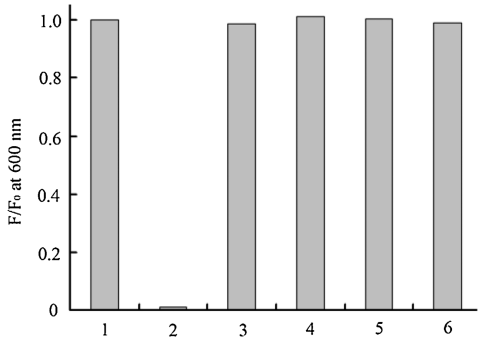



**Fig. 10.** Fluorescence intensity of **1** ($1 \times 10^{-5}$ mol/L) toward various analytes ([$Bu_4N$]R: R = $F^-$, $Cl^-$, $Br^-$, $H_2PO_4^-$ and $CH_3COO^-$, 30 eq.) in $CH_2Cl_2$. (1) **1** alone; (2) **1**+ $F^-$; (3) **1**+ $Cl^-$; (4) **1** + $Br^-$; (5) **1** + $H_2PO_4^-$, (6) **1** + $CH_3COO^-$.

the potentially competing species was measured. Based on Fig. S7 (Supporting information), we observed that there was no interference in the detection of $F^-$ in the presence of the interfering ions, and their fluorescence intensity was almost identical to that obtained in the presence of $F^-$ alone.

In conclusion, BONEPYs **1**–**4** were synthesized in 55%–67% yields by condensation of the corresponding pyrroles and malonyl chloride followed by treatment with $BF_3{\cdot}OEt_2$. Based on the electronegative difference of the aryl moiety, the aryl *o*-H could be fine-tuned by anion binding. Electron donating/withdrawing substituent affect the aryl *o*-H, which could form the extra binding with anions, in addition to the bridging C—H and pyrrole N—H in BONEPY. In BONEPYs **1**–**3** the *o*–H of the aryl group form hydrogen bonding with $F^-$ to form a more table complex, and are sensitive to $F^-$. In contrast, the intramolecular hydrogen-bonded BONEPY *endo*-**4** is more stable than its *exo* isomer. While adding $F^-$, the hydrogen bonds must be broken first to give **4**·(3)$F^-$. Owing to the electron-rich group (-OMe), the *o*-H of the phenyl group can hardly interact with $F^-$ *via* hydrogen bonding to form the less stable complex **4**·(5)$F^-$. The shapes of the absorption spectra of **3** and **4** are distinct to each other with respect to an increasing concentration of $F^-$. The energy differences between the different conformations were calculated using DFT methods, which is consistent to the experimental observations. BONEPY could serve as a naked-eye indicator for $F^-$ from its color change from bright orange yellow to pink. The fluorescence intensity of BONEPY is gradually decreased while adding $F^-$, and BONEPY was sensitive and selective to $F^-$ as a turn-off fluorescent probe. Further efforts for modifications in water-soluble BONEPYs are ongoing in our laboratory.

## Declaration of competing interest

The authors declare no competing financial interest.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2019.09.053.

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