

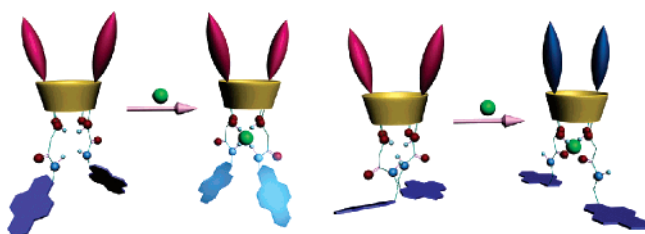
Fluoride-Sensing Calix-luminophores Based on Regioselective Binding

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Bifunctional (fluorescence and visible light absorption) anion-sensing compounds **1** and **2** based on calix[4]arene platform with 4-nitrophenylazo and pyrene moieties have been developed. The two NHs of the amide groups of **1** bind the fluoride anion through the H-bonding. This changes the characteristic excimer emission and forms a new emission peak from a *static* excimer. In **2**, two OHs bind the fluoride anion, and this changes the characteristic absorption spectrum. The DFT calculation supports the regioselective binding of the fluoride anion, which is responsible for the different sensing property.

Anions play a major role in a wide range of chemical and biological systems.^{1a-e} Among the anions, fluoride ion is of particular interest because of its role in preventing dental caries, and treatment of osteoporosis.² However, an excess fluoride anion can lead to fluorosis,^{3a,b} which is a type of fluoride toxicity. This diversity of function, both beneficial and detrimental, necessitates the development of systems capable of detecting the fluoride anion.

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Calix[4]arenes have a high selectivity and binding efficiency for both cations and anions.^{4a-c} Furthermore, calixarene-based chromogenic sensors have attracted attention due to their ability to visually detect analytes.⁵ Most chemosensors developed to date function either by a marked change of fluorescence or marked change of absorption. Previous studies revealed that the excimer band of pyrene pendant in the calix[4]arene family can be a fluorescent fluoride chemosensor.⁵ It was also noted that the nitrophenylazo moieties on the upper rim of the calix[4]-crown had a chromogenic role.⁶ Therefore, we thought it would be interesting to design calix-luminophores (**1** and **2**) as fluoride chemosensors bearing both pyrene pendants with amide linkages and 4-nitrophenylazo group (Figure 1). The introduction of a 4-nitrophenylazo group to the calixarene platform is aimed to enhance the colorimetric property, while incorporation with a pyrene unit is expected to enhance the fluorescent property. These compounds are expected to recognize the F⁻ at the receptor sites and display concomitant changes in their photo-physical properties. In **1**, the -NH is directly connected to the pyrene moiety, while in **2**, there is an additional methylene spacer between -NH and pyrene. The methylene spacer in **1** was introduced to investigate the resonance effect, when the amide proton is partly deprotonated upon the addition of fluoride anion.

Compounds **2** and **3** were synthesized by adapting the procedures that were previously described.^{6,7} Compound **1** was synthesized by the reaction of **4** with 1-aminopyrene in the presence of triethylamine in THF (Scheme 1). The presence of the doublets (or broad singlets) at 4.5 and 3.5 ppm in the ¹H NMR and two methylene bridge resonances at about 33 ppm in the ¹³C NMR spectra provide clear evidence that **1-3** have the cone conformation.

The characteristic UV-vis absorption and fluorescence changes have been investigated upon the addition of tetrabutylammonium salts of F⁻, Cl⁻, Br⁻, I⁻, CH₃CO₂⁻, HSO₄⁻, and H₂PO₄⁻ to a MeCN solution of **1** and **2**. Among the anions tested, it was found that **1** and **2** selectively bind F⁻ anion. The UV-vis spectra show that **1** leads to the red shift by 54 nm in the presence of F⁻, while in the case of **2** a bathochromically shifted band is observed at 614 nm (Figure 2). The red shift of **1** upon the F⁻ complexation can be explained by the photoinduced charge transfer (PCT).⁵ The PCT might have its origin in the interaction between F⁻ and the amide proton (-NH). This leads to an enhanced π electron density at the nitrogen atom, which is mediated through the pyrene ring.⁵ However, the appearance of the peak at ~600 nm of **2** upon the F⁻ complexation is related to the conversion of phenolic to phenolate forms. It should be noted that F⁻ interacts with the

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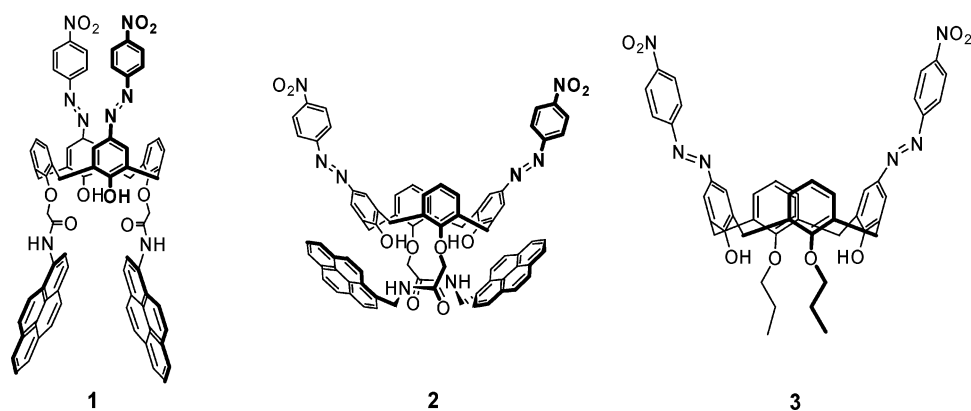
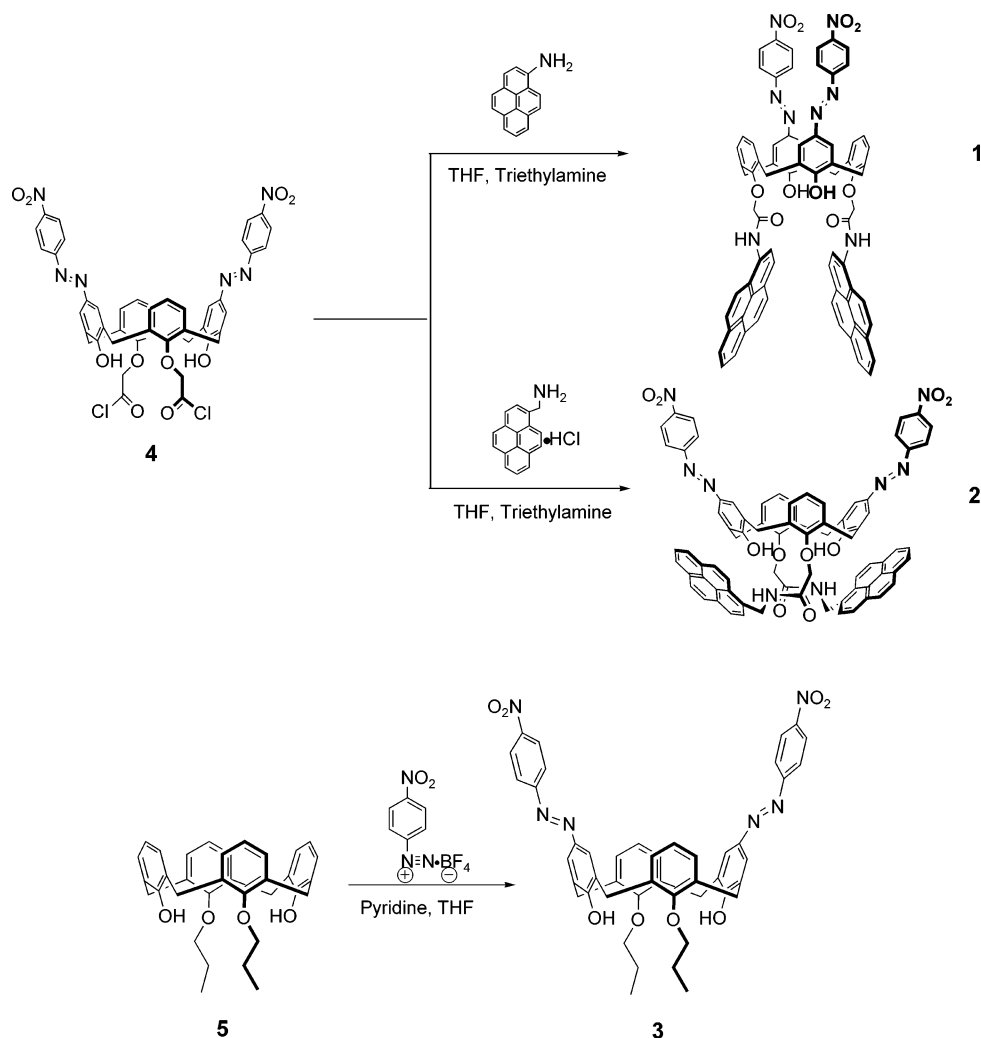


FIGURE 1. Structures of colorimetric and fluorescent sensors 1–3.

SCHEME 1. Synthetic Route of 1–3



amide protons of **1**, while it interacts with the phenolic protons of **2**. We observed two distinct absorption bands at 356 nm (pyrenemethyl amide) and 380 nm (4-nitrophenylazo) in **2**. Thus, **1** and **2** could be selective colorimetric sensors toward F^- anion even though the fluoride anion has similar basicity as $CH_3CO_2^-$ or $H_2PO_4^-$ anions.⁸

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When **1** is excited at 343 nm, it gives a characteristic emission band at 480 nm. As was previously noted for a similar compound, this emission band originates from the excimer (Py·Py*) formed by the ground-state pyrene (Py) and photoinduced excited-state pyrene (Py*).⁷ On the other hand, **2** does not exhibit such an excimer emission band. This is interesting because the main difference between **1** and **2** is the elimination of methylene spacer between the pyrene moiety and amide group from **2** to

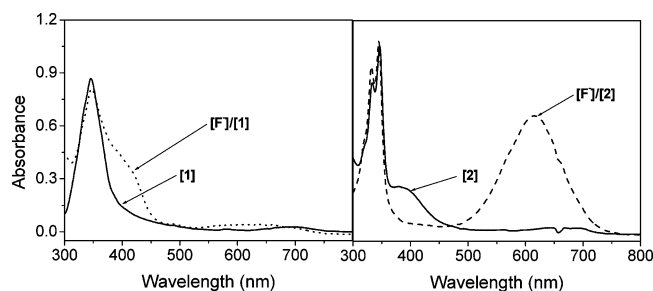


FIGURE 2. UV spectra of **1** and **2** in MeCN and their complexes with F^- .

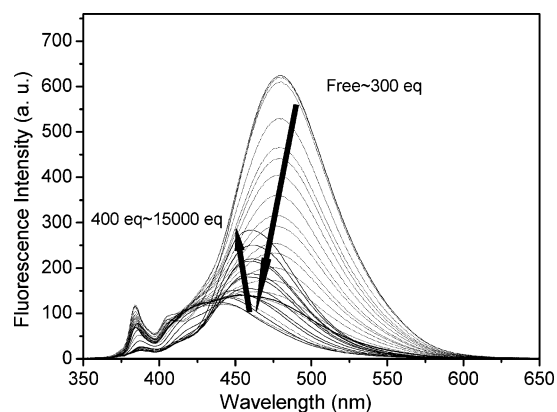
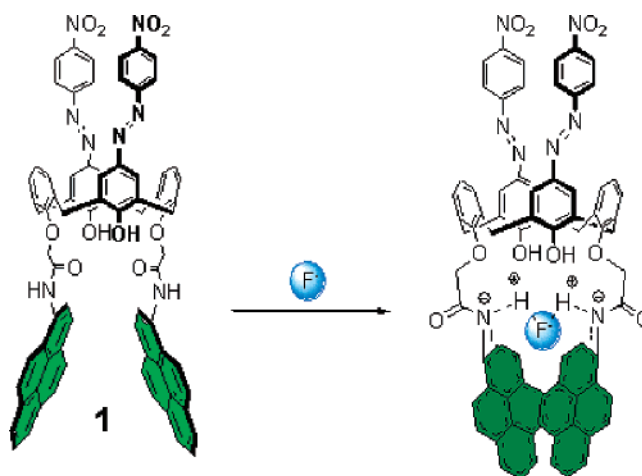


FIGURE 3. Fluorescence spectra of **1** ($6.0 \mu\text{M}$) upon titration with $\text{Bu}_4\text{N}^+\text{F}^-$ in MeCN. Excitation wavelengths were 343 nm.

form sensor **1**. The reason for this difference is because two pyrene moieties have an arrangement incapable of excimer formation as seen in our previous X-ray crystal structure of an analogue of **2**.⁷ As a matter of fact, the two pyrenes are orthogonal to each other in **2**. This prevents the formation of $\text{Py}\cdot\text{Py}^*$ dimeric HOMO–LUMO stable interaction which is responsible for the dynamic excimer.⁵ In the presence of F^- , the excimer band of **1** is blue-shifted by 20 nm, whereas Cl^- , Br^- , I^- , HSO_4^- , CH_3CO_2^- , and H_2PO_4^- give negligible changes in the emission bands, indicating the selective binding of **1** to F^- (Figure S3, Supporting Information). The fluorescence changes of **2** also exhibit the selective binding to F^- , but in a different manner (Figure S6, Supporting Information).

Titration of the fluoride anion to the solution of **1** yielded two characteristic emission bands at 385 and 460 nm (Figure 3). Addition of 300 equiv of F^- gives a quenched excimer emission which is presumably due to the photoinduced electron transfer (PET) from F^- to the pyrene moieties. Further addition of more than 300 equiv of F^- leads to the development of a new excimer band at 460 nm with a concomitant decrease of the monomer emission at 385 nm. This observation suggests that in the presence of an abundant amount of the fluoride anion, the pyrene pendants of **1** would form a static dimer in the ground state, influenced by H-bonding between F^- and the amide protons. To gain an insight into the static excimer formation by the F^- complexation, we looked into the excitation spectrum of **1** as a function of F^- concentration ($[F^-]$) at 460 nm. The red-shifted band does not match with the band emerging from excitation at 385 nm. This clearly indicates that the formation of new 460 nm excimer band of **1** is due to the *static* excimer

formation by the F^- complexation (Figure S4, Supporting Information).



We also observed the selective color changes of **1** and **2** upon the addition of various anions (Figure 4). The color change of **1** or **2** began with addition of 1 equiv of F^- ion to a solution of the ligand. To prove that the added F^- binds two hydroxyl protons ($-\text{OH}$ s) of **2**, we synthesized **3** and compared the absorption spectra of **2** and **3**. The complexation of anions with **3** provides red-shifted absorption bands corresponding to hydroquinone–hydrazone, which shows the same spectral pattern as that of **2** (Figure S7, Supporting Information). It can thus be concluded from the complexation studies of anions with **1–3** that the anions prefer to bind to the more acidic part: they bind to amide protons ($-\text{NH}$ s) of **1**, while they bind to hydroxyl protons ($-\text{OH}$ s) of **2**.

Ab initio calculations were also employed to investigate the structural changes of **1** and **2** upon their complexation with F^- . Density functional theory calculations employing the B3LYP exchange correlation functionals using the 3-21G basis set revealed that a fluoride anion binds the amide protons of **1**, while it binds the hydroxy protons of **2**, which is consistent with our experimental analysis. The binding energies of **1** and **2** in the complexation with a fluoride anion are 173.1 and 154.0 kcal/mol, respectively. In the complex of **1** and F^- ($\mathbf{1}\cdot\text{F}^-$), the interatomic distances between F^- and H atoms are 1.865 and 2.177 Å, and those between F^- and N atoms are 2.856 and 3.107 Å. Thus, a fluoride anion forms typical H-bondings with **1**. On the other hand, in $\mathbf{2}\cdot\text{F}^-$, the interatomic distances between F^- and H atoms are 1.228 and 1.232 Å, and those between F^- and O atoms are 2.367 and 3.68 Å. This is apparently due to space constraints induced by the hydroxy groups of **2**. As a matter of fact, the bond angles $\text{H}\cdots\text{F}\cdots\text{H}$ for **2** are more bent (114°) than **1** (155°) as can be seen in the optimized geometries (Figure 5). The experimentally observed spectroscopic data can be qualitatively explained from the calculated structures and electronic properties. In previous studies, it was shown that molecule **1** could form an excimer upon the excitation because the two pyrene moieties are facing each other with a slightly tilt. In contrast, compound **2** may not have an excimer upon the excitation because the two pyrene moieties are completely orthogonal as can be seen in the optimized structures. The highest occupied molecular orbitals (HOMOs) of **1**, **2**, $\mathbf{1}\cdot\text{F}^-$, and $\mathbf{2}\cdot\text{F}^-$ explain the difference of UV spectra changes of **1** and **2** upon the addition of F^- . For **1**, **2**, and $\mathbf{1}\cdot\text{F}^-$, the HOMOs

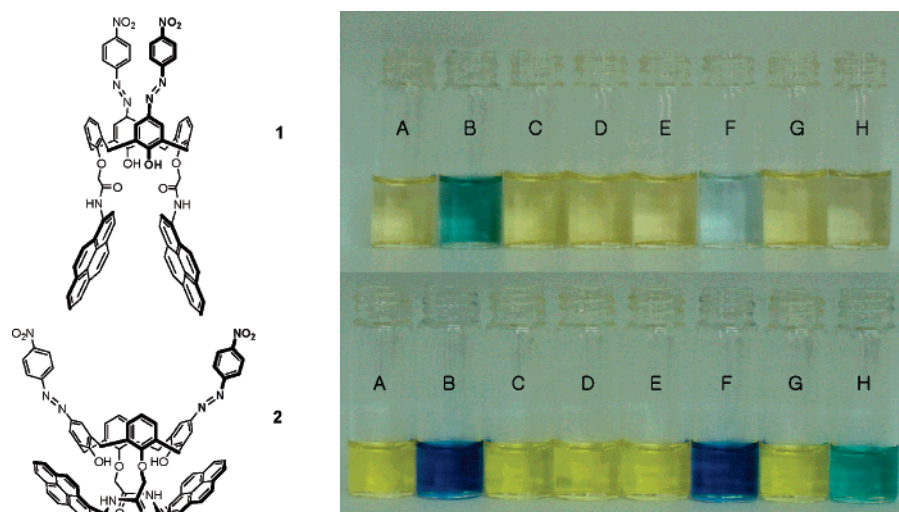


FIGURE 4. Color change of **1** and **2** (20.0 μM) with 100 equiv of anion (A = Free receptor, B = F^- , C = Cl^- , D = Br^- , E = I^- , F = CH_3CO_2^- , G = HSO_4^- , H = H_2PO_4^-).

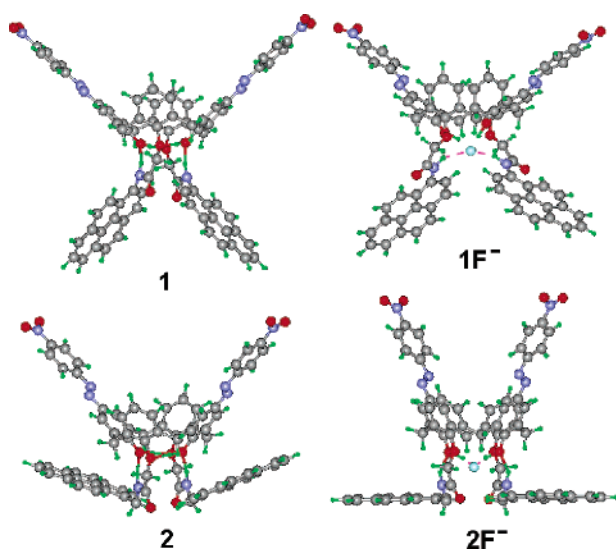


FIGURE 5. B3LYP/3-21G-optimized structures of **1**, **1**· F^- , **2**, and **2**· F^- .

are localized in the pyrene moieties, whereas for **2**, the HOMO is localized in the 4-nitrophenylazo moieties. This results are consistent with the experimental observation that the UV spectra of **1**, **2**, and **1**· F^- are similar but the UV spectrum of **2**· F^- shows another peak at ~ 600 nm resulting in the color change. The reason of having similar UV spectra in **1** and **1**· F^- is due to the methylene spacer between $-\text{NH}$ and pyrene which does not allow the resonance when the amide proton is deprotonated by the added F^- . On the other hand, **2** and **2**· F^- reveal the significantly different UV spectra due to resonance effects. A direct connection between 4-nitrophenylazo and hydroxy groups becomes feasible when the hydroxy protons are partly deprotonated by the added F^- . An intramolecular H-bonding interaction between $-\text{NH}$ of **1** and F^- anion was previously reported in a similar compound.⁵

In summary, bifunctional (fluorescence and visible light absorption) fluoride sensors **1** and **2** were successfully synthesized. The binding site of **1** and **2** for anions could be differentiated based on the acidity of the compounds and the H-bonding patterns. The fluoride anion is bound to the amide

groups ($-\text{NH}$ s) of **1** and to the hydroxyl protons ($-\text{OH}$ s) of **2**. The addition of F^- to the solution of **1** changes the characteristic excimer emission peak at 480 nm and forms a new emission peak at 460 nm. Contrary to **1**, the addition of F^- to the solution of **2** changes the characteristic absorption spectrum. Theoretical calculations support this regioselective binding of the F^- anion, which is responsible for the different sensing characteristics displayed by **1** and **2**.

Experimental Section

Synthesis. Compounds **2**–**5** were prepared following the literature procedures.^{6,7}

5,17-Bis[(4-nitrophenylazo)phenyl]-25,27-bis[*N*-(1-pyrenyl)aminocarbonylmethoxy]calix[4]arene, Cone (1**).** A solution of **4** (0.30 g, 0.335 mmol), 1-aminopyrene (0.14 g, 0.91 mmol), and triethylamine (1.5 mL, 2.07 mmol) in dry THF (20 mL) was refluxed with stirring for 2 days and then evaporated in vacuo. The resulting solid was dissolved in CH_2Cl_2 (100 mL), and the organic layer was washed three times with water, dried over MgSO_4 , and evaporated in vacuo. The crude product was chromatographed on silica gel with EtOAc as eluent to give 0.25 g (54%) of **1** as a brownish solid. Mp: 315–320 $^\circ\text{C}$. IR (KBr pellet): 3400, 1690 cm^{-1} . FAB MS m/z (M^+): calcd 1236.3, found 1236.5. Anal. Calcd for $\text{C}_{76}\text{H}_{52}\text{N}_8\text{O}_{10}$: C, 73.78; H, 4.24. Found: C, 73.80; H, 4.25.

General Procedures for Fluorescence Studies. Stock solutions (0.1 mM) of the metal tetrabutylammonium salts were prepared in MeCN. Stock solutions of **1** and **2** (0.06 mM) were prepared in MeCN. For all measurements, excitation was at 343 nm with excitation and emission slit widths at 3 nm. Fluorescence titration experiments were performed using 6 μM solutions of **1** and **2** in MeCN and various concentrations of metal tetrabutylammonium salts in MeCN.

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Supporting Information Available: Additional UV/vis, fluorescence spectra, and calculation data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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