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Fluorescent calix[4]triazole for selective fluoride anion sensing†

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Fluoride ions (F^-) play an important role in preventing cavities and treating osteoporosis, but excessive exposure can lead to serious health problems such as fluorosis and kidney damage. These dual characteristics highlight the need for selective and sensitive methods to detect fluoride ions for health monitoring. Accordingly, in this study, we investigated the anion-binding ability of **Py-CT4**, a fluorescent chemosensor in which pyrene is linked to calix[4]triazole *via* an ester linker. Notably, **Py-CT4** exhibited significant fluorescence quenching for F^- compared to other anions, and its fluorescence intensity gradually decreased with increasing F^- concentration. This phenomenon is driven by electron transfer from calix[4]triazole to pyrene, initiated by hydrogen bonding with F^- and followed by F^- -induced deprotonation of calix[4]triazole. The selectivity of **Py-CT4** for F^- appears to stem from its relatively flexible structure and low acidity compared to the previously reported **Py-CT4+**. **Py-CT4** thus represents the first macrocyclic receptor based on charge-neutral 1,2,3-triazole that selectively recognizes F^- through fluorescence quenching. Compared to traditional detection methods, **Py-CT4** utilizes the advantages of fluorescent detection, such as higher sensitivity, faster response times, and ease of use, for fluoride ion detection. **Py-CT4** also demonstrates excellent selectivity for F^- even in the presence of competing anions. These features make **Py-CT4** a promising tool for monitoring fluoride ions in biological and environmental systems, providing valuable insights into public health and safety.

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Introduction

The fluoride ion (F^-) is the smallest anion, with a high charge density that confers unique chemical properties such as high electronegativity and strong basicity. Fluoride is a trace element essential for human health, and the body is highly sensitive to its concentration. Adequate fluoride intake has beneficial effects on dental health and osteoporosis treatment.¹ However, excessive fluoride exposure can lead to serious health issues, including fluorosis, urolithiasis, and cancer.² Therefore, monitoring fluoride is critical for health reasons. Among the various reported methods for detecting fluoride ions,³ fluorescence detection is a simple, cost-effective technique that enables rapid and highly sensitive monitoring. Accordingly, numerous fluorescent sensors for fluoride have been developed,⁴ most of which rely on intermolecular interactions such as hydrogen bonding and typically involve structures containing N–H and/or O–H hydrogen bond donors.⁵

Sufficiently polar C–H bonds can also act as hydrogen bond donors for anions.⁶ The 1,2,3-triazole moiety, with its high dipole moment, forms a polar C–H bond capable of binding

anions *via* hydrogen bonding.⁷ As such, 1,2,3-triazole has become an important structural motif in the field of anion recognition.⁸ However, only one fluorescent chemosensor based on 1,2,3-triazole for fluoride detection has been reported to date, and its structure is limited to acyclic systems.⁹

The photoinduced electron transfer (PET) mechanism relies on fluorescence on/off switching and is widely used in anion fluorescent chemosensors.¹⁰ A typical PET-based fluorescent sensor follows a “receptor–spacer–fluorophore” design,¹¹ wherein analyte binding either inhibits or activates PET, producing or quenching fluorescence. Recently, various PET-based anion fluorescent chemosensors have been developed, in which receptors containing neutral hydrogen bond donors (*e.g.*, amide, urea, or thiourea) are linked to fluorophores *via* spacers.¹² Most of these sensors exhibit fluorescence quenching upon anion addition, including fluoride.¹³ This is due to hydrogen bonding or deprotonation of the hydrogen bond donor by the anion, which increases the electron density of the donor and promotes electron transfer to the fluorophore. To the best of our knowledge, no PET-based fluorescent sensor using 1,2,3-triazole as a hydrogen bond donor has been reported that quenches fluorescence upon fluoride addition.

Our group previously developed macrocyclic calixtriazoles as a novel host platform, incorporating 1,2,3-triazole rings in place of the phenol moieties of calixarenes.¹⁴ Although some time has passed since the initial development of calix[*n*]triazole, its

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applicability has not been thoroughly explored. By contrast, the usefulness of its *N*-alkylated derivative, calix[*n*]triazolium, has been a main subject in our studies.

Several anion recognition studies using calix[*n*]triazolium have been conducted by our group. For instance, we successfully achieved selective sensing of adenosine monophosphate (AMP)¹⁵ and developed a crown ether-appended calixtriazolium system for recognizing H_2PO_4^- .¹⁶ Additionally, we recently developed a PET fluorescent chemosensor functionalized with pyrene (**Py-CT4+**; Fig. 1A) and investigated its anion recognition ability.¹⁷ This chemosensor exhibited fluorescence quenching due to PET, caused by electron transfer from pyrene to electron-deficient calix[4]triazolium in the unbound state. When **Py-CT4+** bound to HSO_4^- , its fluorescence intensity increased due to the inhibition of PET.

In light of the several physicochemical differences between triazolium and triazole, we recently comprehended that the precursor for **Py-CT4+**, **Py-CT4** (Fig. 1B), might also exhibit interesting and unique molecular sensing properties. The expected differences between **Py-CT4+** and **Py-CT4** were as follows: (1) the triazole C5-Hs of calix[4]triazole are less acidic than the triazolium C5-Hs of calix[4]triazolium.¹⁸ This suggests that calix[4]triazole can form a stable interaction with an anion that is more basic than the anion that binds to calix[4]triazolium. (2) In the ^1H NMR spectrum, calix[4]triazole in **Py-CT4** appears as a single peak,^{14a} whereas calix[4]triazolium in **Py-CT4+** shows a major single peak along with an additional minor peak (Fig. S1†).^{15b} This is presumably because calix[4]triazole has a more flexible structure that allows dynamic conformational changes. This flexibility may provide structural adaptation to other specific anions. (3) Neutral calixtriazoles have a higher electron density than positively charged calixtriazoles.¹⁹

Accordingly, when the calix[4]triazolium in **Py-CT4+** is changed to calix[4]triazole, a change in the electron flow in the PET pathway is expected.

Based on these considerations, we describe here a study focused on identifying the anion-recognition ability of **Py-CT4** (Fig. 1B). Specifically, this research explores the selective binding mechanism of **Py-CT4**, where the hydrogen bond-mediated interaction between calix[4]triazole of **Py-CT4** and F^- activates PET, resulting in fluorescence quenching. This mechanism is due to the unique physicochemical properties of **Py-CT4**, which enable its selective recognition of F^- and the resulting “turn-off” fluorescence response. To the best of our knowledge, this is the first report of a PET-based macrocyclic “turn-off” fluorescent chemosensor that selectively recognizes anions through hydrogen bonding with 1,2,3-triazole.

Results and discussion

A fluorescence study was conducted to gain insight into the fluorescence properties of **Py-CT4** for different anions (Fig. 2A and B). **Py-CT4** exhibited turn-on fluorescence at 400 nm in its unbound state (Fig. 2A; see blank). Unlike **Py-CT4+**, in **Py-CT4**,

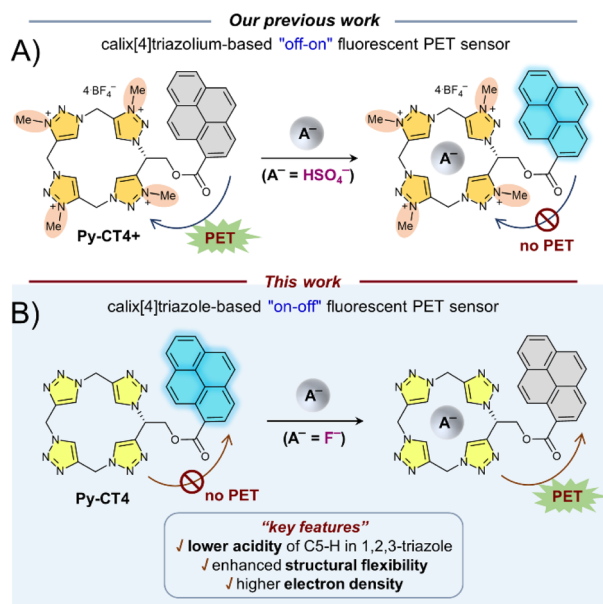


Fig. 1 Our previous work and this work. (A) Previous work: calix[4]triazolium-based "off-on" fluorescent PET sensor. (B) This work: calix[4]triazole-based "on-off" fluorescent PET sensor.

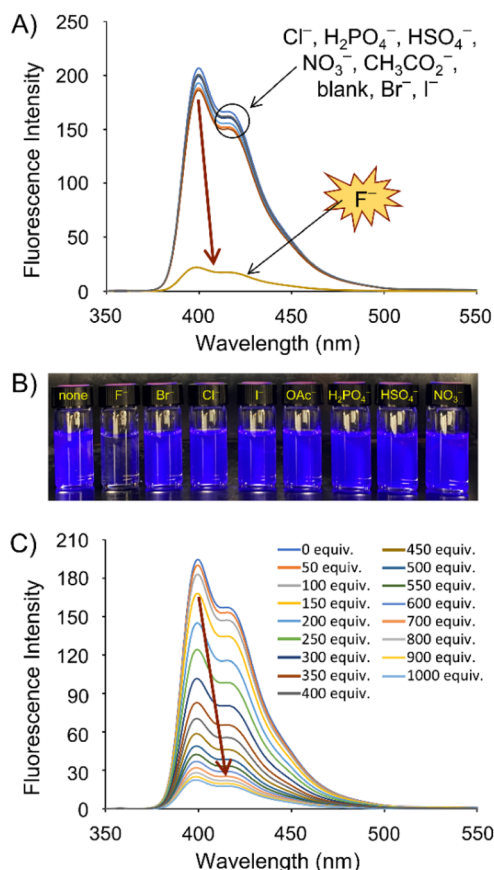


Fig. 2 (A) Fluorescence spectra of **Py-CT4** (10 μM , λ_{ex} = 355 nm) in the presence of 100 equiv. of various anions in a DMSO solution. (B) Corresponding fluorescence responses of **Py-CT4** (10 μM) to different anions in a DMSO solution. (C) Fluorescence spectra of **Py-CT4** (10 μM) upon titration with F^- (0–1000 equiv.) in a DMSO solution.

the electron density of the calix[4]triazole is sufficiently high, making its energy level similar to that of pyrene. As a result, PET from calix[4]triazole to pyrene was thought to be suppressed, thereby maintaining the fluorescence of **Py-CT4**.²⁰ The binding ability of **Py-CT4** to anions was investigated by analyzing the relative emission intensity changes of **Py-CT4** after the addition of various anions (such as tetrabutylammonium salts, F^- , Cl^- , Br^- , I^- , $H_2PO_4^-$, NO_3^- , HSO_4^- , or $CH_3CO_2^-$) to **Py-CT4**. Most of the added anions had negligible effects on the fluorescence emission intensity of **Py-CT4**. In contrast, when the same concentration of fluoride anions was added to **Py-CT4**, quenched fluorescence was observed. This is because **Py-CT4** has high flexibility, making it difficult to lock into the specific conformation required for binding with complex anions such as $H_2PO_4^-$ and HSO_4^- . As a result, **Py-CT4** may exhibit low binding stability with such complex anions.²¹ By comparison, anions with simple structures, which require minimal conformational changes for binding, allow **Py-CT4** to achieve greater stability, resulting in a tendency to prefer such anions.²² In addition, because **Py-CT4** has very weak acidity, it prefers anions with high basicity for stable binding. Accordingly, **Py-CT4** selectively recognizes F^- , which has a simple structure and high basicity.²³ In the case of fluorescence quenching of **Py-CT4** by F^- , it appears to result from increased electron density of calix[4]triazole due to interaction with F^- , which promotes PET from calix[4]triazole to pyrene.²⁴ These results clearly demonstrate that physicochemical properties of **Py-CT4** influence its anion recognition and fluorescence response, leading to outcomes different from those of **Py-CT4+**.

The sensing properties of **Py-CT4** for F^- were further studied through fluorescence titration experiments (Fig. 2C). With the gradual addition of F^- to **Py-CT4**, the fluorescence intensity of **Py-CT4** gradually decreased, indicating a close interaction between **Py-CT4** and F^- . These titration results were applied to Bindfit²⁵ to determine the stoichiometry and association constants between **Py-CT4** and F^- . Among BindFit's three binding models (1 : 1, 1 : 2, and 2 : 1), the 1 : 1 binding model with the least errors and uncertainties was the most appropriate, and the association constant between **Py-CT4** and F^- was calculated as $74.30 \pm 12 \text{ M}^{-1}$ (Fig. S2–S4 and Table S1†). Additionally, Job's plot shows a maximum at the 0.5 M fraction, supporting a 1 : 1 stoichiometric ratio of **Py-CT4** and F^- (Fig. S5†).

Anion competition experiments were also performed to demonstrate the selectivity of **Py-CT4** for F^- . For this purpose, the change in the fluorescence intensity after the addition of F^- to a **Py-CT4** solution containing interfering anions was recorded. As shown in Fig. 3, when equal amounts of F^- and competing anions (such as tetrabutylammonium salts, Cl^- , Br^- , I^- , $H_2PO_4^-$, NO_3^- , HSO_4^- , or $CH_3CO_2^-$) were added to **Py-CT4**, the fluorescence intensity of **Py-CT4** reduced by F^- was not significantly affected by the competing anions. Importantly, oxygen-containing anions, which are known to interfere with fluoride anion recognition, did not alter the emission intensity of **Py-CT4** diminished by F^- .²⁶ This indicates that **Py-CT4** can be used as a selective fluorescent chemosensor for F^- in the presence of other competing anions.

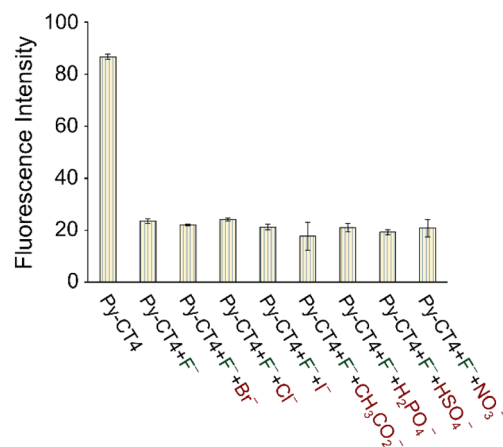


Fig. 3 Fluorescence response at 403 nm of **Py-CT4** (10 μM) containing 100 equiv. of F^- and selected anions (100 equiv.) in a DMSO solution (excitation at 355 nm).

To further investigate the binding interaction properties of **Py-CT4** and F^- , ^1H NMR titration experiments were performed (Fig. 4). Gradual addition of F^- to **Py-CT4** caused the peak of the triazole proton (H_a) to become broader, decrease, and shift slightly downfield. When F^- was added in excess, the H_a signal eventually disappeared while a broad triplet peak was observed at 16.1 ppm, attributed to the proton of the hydrogen difluoride anion $[HF_2]^-$.^{20a} These results indicate that **Py-CT4** forms $C-H \cdots F^-$ hydrogen bonds at low concentrations of F^- , whereas deprotonation of the triazole proton occurs at higher concentrations of F^- . This indirectly demonstrates that hydrogen bond donation by triazole to F^- plays an essential role in the selective

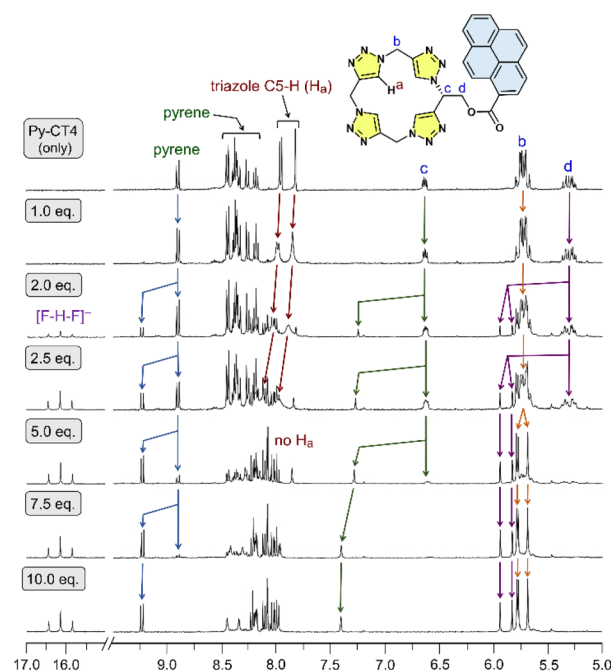


Fig. 4 Partial ^1H NMR titration spectra of **Py-CT4** (1.5 mM) in $\text{DMSO}-d_6$ with increasing concentrations of F^- anion.



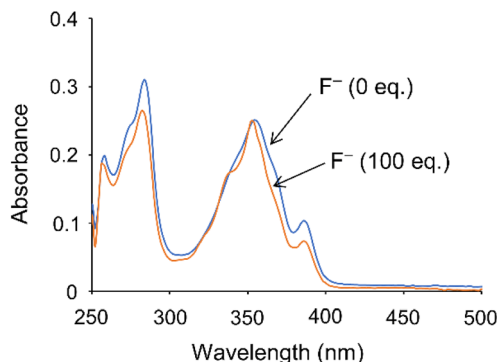


Fig. 5 UV-Vis spectra of **Py-CT4** (10 μ M) in the presence of 0 or 100 equiv. of F^- in a DMSO solution.

recognition of F^- by **Py-CT4**. Along with the change in the triazole signal (H_a), most protons, except for the triazole proton, also showed a downfield shift. In particular, the protons located on the bridge between the triazole rings (H_b and H_c) showed a change from multiplet to singlet peaks along with a downfield shift, which indicates a structural change in the calix[4]triazole receptor framework.^{14,27} This conformational change is presumably triggered by changes in the intramolecular hydrogen bonding environment of the calix[4]triazole receptor due to deprotonation of the triazole proton by F^- .²⁸

Most ideal PET sensors have a spacer between the fluorophore and receptor, which prevents ground-state $n-\pi$ or $\pi-\pi$ interactions.²⁹ Accordingly, recognition of the analyte by the receptor is accompanied by no or only very small changes in the absorption spectrum of the fluorophore.³⁰ As shown in Fig. 5, the UV-Vis spectrum of **Py-CT4** appears in the 250–400 nm range, and no noticeable change in absorption is observed upon the addition of F^- (100 equiv.). This result suggests that the ester spacer prevents interactions between calix[4]triazole and pyrene, indicating that there are no significant ground-state interactions between these two moieties. This provides indirect support that **Py-CT4** is an ideal PET sensor.

Conclusions

This study explores the anion recognition properties of calix[4]triazole-based **Py-CT4**. In a previous study, **Py-CT4+**, a calix[4]triazolium-based fluorescent sensor, exhibited selective fluorescence turn-on due to PET inhibition when combined with the complex anion HSO_4^- . In this study, we showed that calix[4]triazole-based **Py-CT4** exhibits selective fluorescence quenching when combined with F^- . The selectivity of **Py-CT4** for F^- is believed to result from the combination of the high flexibility and low acidity of calix[4]triazole. Meanwhile, the fluorescence quenching of **Py-CT4** toward F^- is expected to be caused by the facile PET from calix[4]triazole, whose electron density is increased by F^- , to pyrene. These results indicate that **Py-CT4** is a new neutral anion-sensing platform that exhibits anion selectivity and a fluorescence response different from that of charged **Py-CT4+**, through a combination of its unique physicochemical properties.

This study utilizes the different physicochemical properties of calix[4]triazole and calix[4]triazolium. Through this, we assess the potential of triazole and triazolium in the development of novel anion receptors. Additionally, F^- recognition by fluorescence changes of **Py-CT4** presents a simple and cost-effective alternative to traditional analytical methods. Notably, the selectivity of **Py-CT4** for F^- in the presence of competing anions suggests that **Py-CT4** has the potential to lead to practical applications such as F^- detection in drinking water or biological samples. Future research will focus on optimizing the structure of calix[n]triazole to enhance its anion selectivity and sensitivity and utilize it for various applications such as biological diagnostics and environmental monitoring. Accordingly, these studies will provide new insights into anion recognition and become a useful technology for advancing medicine and the environment.

Data availability

The data used for this research is provided in the main article and its accompanying ESI.†

Author contributions

J. Cho performed all experiments and wrote the manuscript and ESI.† S. Kim supervised this study and revised the manuscript.

Conflicts of interest

There are no conflicts of interest to declare.

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