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Accepted Article

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To be cited as: *Chem. Asian J.* 10.1002/asia.201800856

Link to VoR: http://dx.doi.org/10.1002/asia.201800856

A Journal of
ACES
Asian Chemical Editorial Society

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Calix[5]phyrin for Fluoride Ion Sensing with Visible and Near Infrared Optical Responses

Tomohiro Higashino,*[a] Atsushi Kumagai,[a] Hiroshi Imahori*[a,b]

Abstract: Fluoride (F⁻) ion sensing is an important topic due to its roles in health, medical, and environmental sciences. In this regard, colorimetric sensors with a near infrared (NIR) optical response are useful in biological systems because they can avoid interference from endogenous chromophores. Although calix[*n*]phyrins are highly attractive as sensors with the NIR optical response, studies on calix[*n*]phyrins are still limited owing to their intrinsic instability against ambient light and air. In this study, we report the synthesis and characterization of a new calix[5]phyrin bearing one sp^3-hybridized carbon atom as a π-expanded calix[*n*]phyrin. Upon addition of tetrabutylammonium fluoride, the calix[5]phyrin exhibited distinct NIR absorptions at 908 and 1064 nm as well as a visible color change. Importantly, it revealed an excellent selectivity for F⁻ ion. These results demonstrate that calix[5]phyrins are promising colorimetric and NIR sensors of F⁻ ion.

Anion sensing has attracted considerable attention in supramolecular chemistry owing to the widespread importance in chemical and biological processes.[1] Among anions, fluoride (F⁻) ion is an important target due to its roles in health, medical, and environmental sciences.[2] In this regard, colorimetric sensors that can recognize anions through color changes are highly desirable because of facile detection by the naked eye.[3,4] In particular, sensors with a near infrared (NIR) optical response are fascinating in biological systems because they can avoid interference from endogenous chromophores.[5]

Pyrrole-containing macrocycles have been developed as promising molecules for colorimetric anion sensing (Figure 1).[6] In particular, they are promising candidate for F⁻ ion sensing molecules because F⁻ ion tends to form the hydrogen bond with polar NH groups and deprotonate NH protons of the various hosts. Among them, calix[4]pyrroles, tetrapyrrolic macrocycles with four sp^3-hybridized *meso* carbon atoms, are the most studied receptors.[6c,7] Since typically calix[4]pyrroles possess little absorption in visible region, anions can be easily detected by the naked eye with coloring. However, it is still difficult to create their sensors with a NIR optical response because of their intrinsic non-conjugated macrocyclic structures. Meanwhile, calix[*n*]phyrins, which are hybrids of porphyrins and calixpyrroles, have also drawn significant attention as anion receptors.[6b,c,8] Since calix[*n*]phyrins possess absorption in visible region as the result of their π-conjugated nature, they are an excellent candidate for sensors with the NIR optical response. For instance, calix[4]phyrin **1**, possessing absorption up to 700 nm, displayed a new band at around 800 nm in the presence of F⁻ ion.[8c] However, compared to calixpyrroles, studies on calix[*n*]phyrins are still limited owing to their intrinsic instability against ambient light and air.[9] Therefore, we thought that a new calix[*n*]phyrin with π-expanded structure would be a potential platform as colorimetric sensors for F⁻ ion with the NIR optical response.

In this study, we focused on calix[5]phyrins bearing one sp^3-hybridized carbon atom as π-expanded calix[*n*]phyrins. So far two calix[5]phyrins **2** and **3** have been synthesized, but their anion-sensing abilities have not been examined.[10] Recently, we found expanded porphyrins with a dithieno[3,4-*b*:3',4'-*d*]thiophene (β-DTT) unit stable even without electron-deficient *meso*-aryl substituents (i.e., pentafluorophenyl).[11] Bearing in mind the improved stability by incorporation of the β-DTT unit, we designed a calix[5]phyrin with the β-DTT unit **4**. In addition, the peripheral thiophene-fused structure would provide a π-extended structure, which could be suitable for visible and NIR detection of anions.

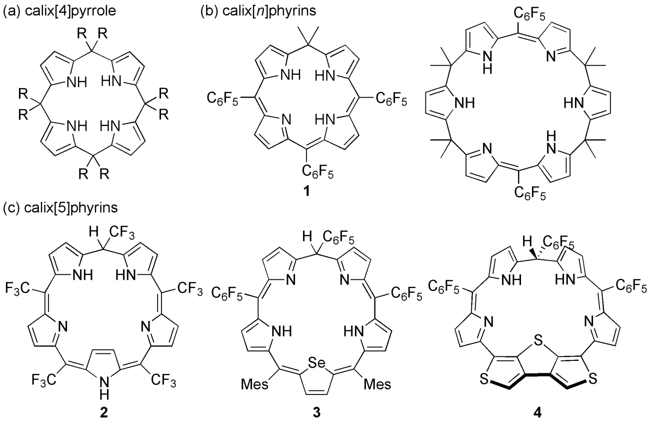

Figure 1. Structures of pyrrole-containing macrocycles.

Herein, we synthesized a new calix[5]phyrin with the β-DTT unit **4** and examined its anion-sensing ability. The calix[5]phyrin **4** exhibited F⁻ ion sensing ability with an excellent selectivity. It is noteworthy that **4** is the rare example of F⁻ ion sensing molecules with a distinct absorption in NIR region more than 1100 nm in the presence of F⁻ ion.[8f]

The calix[5]phyrin **4** was synthesized by the route illustrated in Scheme 1. 3,5-Di(pyrrolyl)dithienothiophene **5**[11] and

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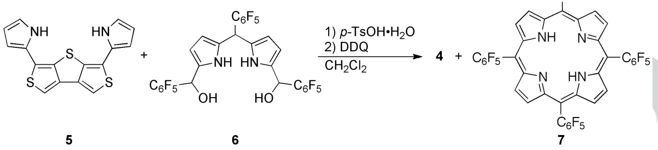
10.1002/asia.201800856

dipyrromethane dicarbinol **6**[12] were synthesized according to the literatures. The acid-catalyzed condensation of **5** and **6** followed by oxidation with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) afforded a mixture of calix[5]phyrin **4** and 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin **7**. However, due to a high affinity of **4** with **7**, we could not separate two products by typical silica-gel column chromatography. Fortunately, we found that the adsorption behavior of **4** to silica-gel was enhanced by the treatment with Na_2CO_3 aqueous solution. Consequently, we obtained pure **4** after the treatment of the mixture of **4** and **7** with saturated Na_2CO_3 aqueous solution and subsequent silica-gel column chromatography using a 1:1 mixture of CH_2Cl_2 and hexane with acetic acid (1% v/v). Although the role of Na_2CO_3 is unclear at this stage, deprotonation of **4** might be effective to adsorption of **4** to silica-gel. The isolated yield of **4** was 3.6%. The high-resolution mass spectrometry (HR-MS) of **4** (Figure S1) shows the ion peak at *m*/*z* = 991.0106 (calcd for $C_{45}H_{14}N_4F_{15}S_3$, $[M+H]^+$: 991.0136), which is consistent with its calix[5]phyrin structure. The ^{1}H NMR spectrum of **4** displays a signal arising from the *meso*-proton at 5.65 ppm (Figure S2). The four signals from β-protons at δ = 6.92–6.41 ppm and the signal from NH protons at δ = 12.80 ppm indicate the nonaromatic character of **4**. It should be noted that **4** can be stored at –20 °C for several months and is stable against ambient light and air even in solution for more than one week. Then, we attempted reduction and oxidation of **4**. When $NaBH_4$ was added to a solution of **4**, we found a new species, probably phlorin-type compound, by TLC analysis. However, it was not possible to isolate and characterize it because of its instability under ambient conditions. On the other hand, oxidation of **4** with MnO_2, DDQ, or tris(4-bromophenyl)aminium hexachloroantimonate resulted in decomposition.



Scheme 1. Synthesis of thiophene-fused calix[5]phyrin **4**.

In the next step, we carried out single crystal X-ray diffraction analysis. We could not obtain the suitable crystals of **4**, but obtained the co-crystals of **4** and porphyrin **7** by vapor diffusion of *n*-octane into the mixture in toluene. The structure of **4** was unambiguously revealed with an sp^3-hybridized *meso*-carbon at 15-position (Figure 2a,b).[13] All the pyrrole rings point inward to the center of the macrocycle. The sp^3-carbon of **4** possesses an equatorial hydrogen atom, which coincides with those of known calix[5]phyrins **2** and **3**.[10] The pyrrole rings A/B and C/D display dipyrrin-like planar structures. The pyrroles A and D are tilted by 26.4° with respect to the β-DTT plane, which suggests the effective π-conjugation through the β-DTT unit. Notably, the unique packing structure reveals that one porphyrin molecule of **7** was sandwiched between two calix[5]phyrin molecules of **4** through the two pentafluorophenyl rings of **4** (Figure 2c). The distances between these two rings are about 3.3 Å, showing involvement of the π-π interactions. Moreover, the CH–π interactions between the β-protons and the β-DTT unit are evident. The high affinity of **4** with **7** is probably attributed to these π-π and CH–π interactions.

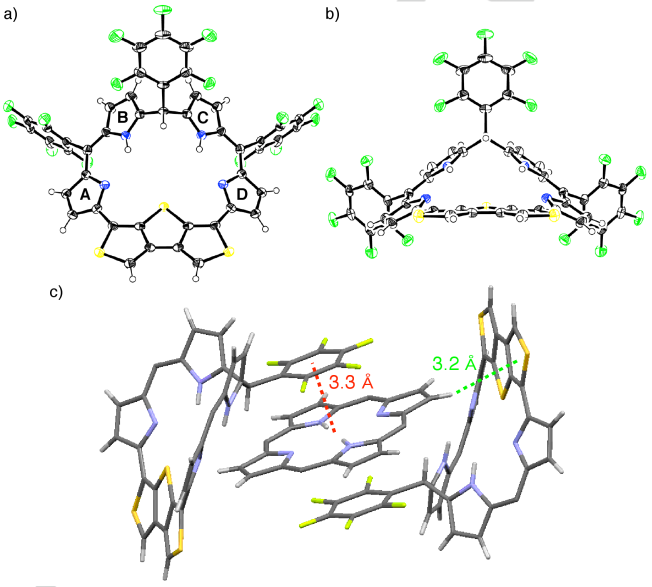


Figure 2. X-Ray crystal structure of cocrystal of **4** and **7**: a) perspective view and b) side view (right) of **4**. Thermal ellipsoids represent 50% probability. One of the two independent molecules in the unsymmetric unit cell is shown. Solvent molecules are omitted for clarity. c) The packing structure in which one porphyrin molecule of **7** is sandwiched with two calix[5]phyrin molecules of **4**. The non-interacting pentafluorophenyl groups are omitted for clarity. The π-π interactions between the pentafluorophenyl ring and the porphyrin macrocycle (red) and CH–π interaction between the β-protons of **7** and the β-DTT unit (green) are also indicated.

The UV/Vis absorption spectrum of **4** in CH_2Cl_2 is shown in Figure 3. The spectrum displays an intense Soret-like band at 474 nm, which is comparable to those of other calix[5]phyrins (466 nm for **2** and 490 nm for **3**).[10] In contrast, **4** exhibits no Q-like band, while calix[5]phyrins **2** and **3** exhibit weak Q-like bands at 663 and 691 nm, respectively.[10] Absence of the Q-band of **4** can be rationalized by the cross-conjugated nature of the β-DTT unit.[11] It is striking that the absorption spectrum of **4** is completely different from that of *meso*-pentafluorophenyldipyrrin.[14] Thus, in **4** dipyrrin-like character does not appear, but calix[5]phyrin-like character does as a consequence of the π-system through the β-DTT unit. The steady-state fluorescence spectrum of **4** was also measured in CH_2Cl_2 (Figure 3). The weak fluorescence is observable at 647 nm. The fluorescence quantum yield (Φ_F) was determined to be 0.004 using 5,10,15,20-tetraphenylporphyrin (TPP) as a standard (Φ_F = 0.11) (Figure S3).[15]

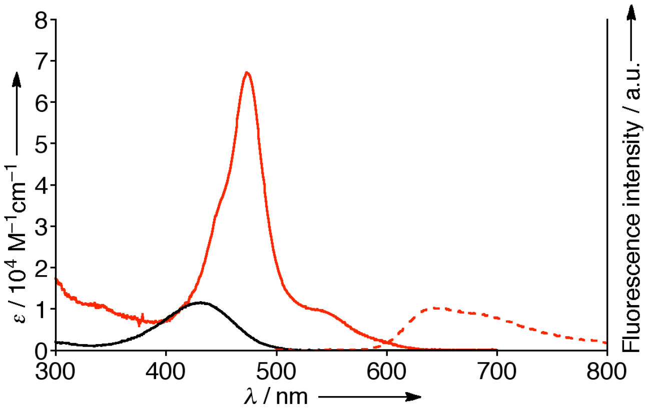


Figure 3. UV/Vis absorption (red solid line) and fluorescence (red dashed line) spectra of **4** and UV/Vis absorption spectrum of *meso*-pentafluorophenyldipyrrin (black solid line) in CH_2Cl_2. For fluorescence spectrum, the sample was excited at 474 nm. The fluorescence intensity was normalized to the absorption at 543 nm.

The electrochemical properties of **4** were studied by cyclic voltammetry (CV) and differential pulse voltammetry (DPV) in CH_2Cl_2 versus ferrocene/ferrocenium ion (Fc/Fc^+) with tetrabutylammonium hexafluorophosphate (Figure S4). The calix[5]phyrin **4** shows two reversible reduction peaks at –1.39 and –1.57 V. On the other hand, no significant oxidation peaks are detectable.

We examined anion-sensing ability of **4** in THF. Upon addition of tetrabutylammonium fluoride (TBAF), the color was changed from orange to violet. Then, we performed the titration experiments, as shown in Figure 4. A two-step spectral change is visible. Namely, at the first step (0–2 equivalent of TBAF), the absorbance at 474 nm is dramatically decreased, whereas those at 381 and 527 nm are significantly increased. This remarkable change of the absorption in visible region enables to detect color change by the naked eye. It is noteworthy that the broad peaks emerge in NIR region (908 and 1064 nm) together with the weak absorption at around 1700 nm. At the second step, the absorption in visible region shows little change. Whereas the peak at 1064 nm is decreased, the peak at 908 nm is still increased. These results corroborate that the calix[5]phyrin **4** can detect F^- ion with the NIR optical response. It is noteworthy that **4** is the rare example of F^- sensors with a distinct absorption at wavelength more than 1100 nm.[8f] The two-step spectral change suggests the formation of 1:1 and 1:2 complexes of **4** with F^- ion. From the binding isotherms (Figure S5), the binding constants K_1 and K_2 are determined to be 2.1×10^4 and 2.9×10^5 M^{-1}, respectively.[16] The interaction parameter α is calculated from the following equation: $\alpha = 4K_2/K_1$. Because $\alpha > 1$ indicates positive cooperativity, the formation of 1:2 complex is favorable over the formation of 1:1 complex.[16] In contrast to the distinct spectral change of **4** upon the addition of TBAF, tetrabutylammonium chloride (TBACl), tetrabutylammonium bromide (TBABr), and tetrabutylammonium iodide (TBAI) does not yield such spectral change (Figure S6). Thus, the calix[5]phyrin **4** demonstrates the excellent selectivity for F^- ion.

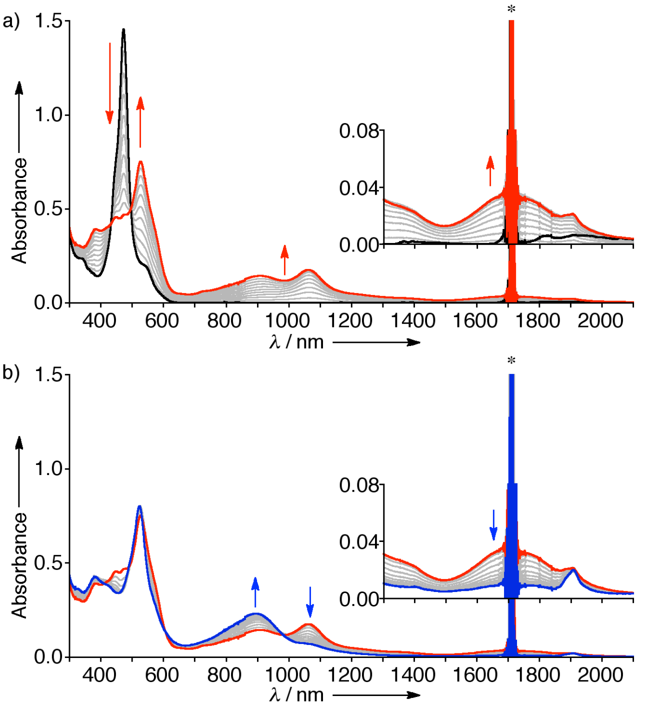


Figure 4. Changes in the UV/Vis/NIR absorption spectra of **4** upon titration with TBAF in THF: a) from 0 (black) to 2 (red), and b) from 2 (red) to 4 (blue) equivalents of TBAF. The total concentration of **4** was maintained at 20 μM. The background absorbance marked with * may arise from the overtones of C-H vibration of the solvent.

To examine the mechanism of F^- ion sensing of **4**, we also performed spectroscopic analysis upon the tetrabutylammonium hydroxide (TBAOH). Upon addition of TBAOH, the color is also changed from orange to violet (Figure S7). However, the addition of TBAOH provides a one-step spectral change. After addition of TBAOH, the spectrum exhibits an intense peak at 550 nm and broad absorption at around 1000 nm. Nevertheless, it is completely different from that of **4** upon addition of F^- ion. Thus, deprotonation mechanism should be ruled out.

The ^1H and ^{19}F NMR spectra of **4** in THF-d_8 were also recorded in the presence of TBAF (Figures S8 and S9). The addition of 2 equivalents of TBAF induces the broadening of the NH peak, which indicates the interaction between the NH and F^- ion. In addition, ^{19}F NMR exhibits a new broad signal at –154 ppm, suggesting bound F^- ion.[8c] Further addition of TBAF displays the disappearance of initial peaks. The new broad peaks imply conformational changes derived from the flexible structure of **4**. Importantly, the signals of HF_2^- at ~16.0 ppm in ^1H NMR and –216 ppm in ^{19}F NMR are not detectable even after the addition of 4 equivalents of TBAF.[17] These NMR experiments also suggests F^- ion binding rather than deprotonation.[4]

To obtain the insight into the F^- ion binding complexes of **4**, we performed DFT calculations at the B3LYP/6-31G(d,p) level. The optimized structures exhibit the interaction of F^- ion with the hydrogen atom at 15-position as well as NH (Figure S10). Furthermore, we carried out time-dependent DFT (TD-DFT) calculations to evaluate the colorimetric response of **4**. The lowest excitation energies of 1:1 and 1:2 complexes (885 and 631 nm) are smaller than that of **4** (575 nm), which is in agreement with the new absorption in NIR region upon addition of TBAF (Figure S11).

In summary, we synthesized a new calix[5]phyrin with the β-DTT unit **4** as a π-expanded calix[*n*]phyrin. The structure of **4** was unambiguously determined by X-ray diffraction analysis. Upon addition of TBAF, **4** exhibited distinct NIR absorptions at 908 and 1064 nm as well as a visible color change. Importantly, **4** revealed an excellent selectivity for F^- ion. These results demonstrate that **4** is a promising colorimetric and NIR sensor of F^- ion. We believe that calix[*n*]phyrins with the β-DTT unit could be potential candidates as NIR sensors of various ions.

Acknowledgements

This work was supported by the JSPS (KAKENHI Grant Numbers 18K14198 (T.H.) and 18H03898 (H.I.)).

Keywords: fluorine • porphyrinoids • anion sensing • calix[5]phyrin • sensors

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[13] Crystallographic data for **4**: $C_{45}H_{13}F_{15}N_4S_3 \cdot 0.5(C_{44}H_{10}F_{20}N_4) \cdot 3$(toluene), M_r = 1750.42, orthorhombic, *Pbcm* (No.57), a =10.9653(2), b = 39.2684(7), c = 33.5155(6) Å, V = 14431.4(4) Å^3, ρ_{calcd} = 1.611 g cm^{-3}, Z = 8, 122440 reflections measured, 19801 unique (R_{int} = 0.1165), R_1 = 0.0907 [$I > 2\sigma(I)$], wR_2 = 0.2759 (all data), GOF = 1.084. CCDC 1846275 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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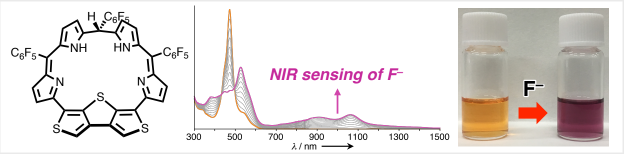

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