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Fluoride sensing with a PCT-based calix[4]arene

Suh Hyun Lee,[a] Hyun Jung Kim,[a] Yeon Ok Lee,[a]
Jacques Vicens[b] and Jong Seung Kim[a,*]

[a]*Department of Chemistry, Institute of Nanosensor and Biotechnology, Dankook University, Seoul 140-714, Republic of Korea*
[b]*Laboratoire de conception moléculaire, associé au CNRS, LC4, ECPM-ULP, Strasbourg, France*

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Abstract—Novel calix[4]arene-based anion sensor **1** with two coumarin units attached via amido functions acting also as binding sites is presented. Complexation of F^- by PCT-based **1** causes selectively red-shift in UV–vis absorption and in fluorescence emission due to H-bonding followed by deprotonation of NH-amide groups.

With the concepts provided by supramolecular chemistry, anion sensing has recently arisen as a place of choice in the research field devoted to the detection of given species.[1] This rapid growth is coming from the realization of the diverse roles played by anions in biological and chemical systems.[2] High sensitive and simple tools are demanded for detection of anions. Fluorescent chemosensors are effectively used to analyze and measure their presence in living systems and intensive research has been devoted regarding anion selective receptors using the fluorescent change as a means of detection.[3] Among the biologically functional anions, peculiar interest is given to fluoride (F^-) as one with a specific importance because of its role in dental care and treatment of osteoporosis.[4]

Artificial anion receptors are generally composed of binding sites and of covalently linked signaling units. Anion binding sites include not only positively charged moieties such as guanidinium or ammonium based on electrostatic interactions,[2] but also neutral groups such as (thio)ureas, calix[4]pyrroles, porphyrins or amides acting by the formation of hydrogen bonds.[5,6] Particularly, amide NH function is known to form a strong H-bonding interaction with anions.[2] Calixarenes have been found to achieve high selectivity and binding efficiency for both cations and anions.[7] As a signaling mechanism, most anion chemosensors developed to date utilize internal charge transfer in the ground state for colorimetric chemosensors and PET (photoinduced electron transfer),[8] PCT (photoinduced charge transfer)[9] and excimer/exciplex formation[10] for fluorescent chemosensors.

Although the PCT has been widely exploited for cation sensing, there are few examples of such chemosensors based on calix[4]arene for anions. With respect to F^- detection, we recently reported a calixarene with two fluorogenic pyrene units acting as a fluoride-selective PCT chemosensor based on formation of a static pyrene excimer.[7d] We now report on a novel PCT-based chemosensor **1**. Compound **1** consists of a calix[4]arene with two coumarin units[11] and showed a unique feature in the absorption and emission spectra in the presence of F^-. Its anion complexation behavior was compared to **2**.

As shown in Scheme 1, **1** was prepared in 54% yield by reacting calix[4]arene with 2 equiv of coumarin derivative **3**[12] in the presence of K_2CO_3 as a base and a catalytic amount of NaI in refluxing CH_3CN.[12] The cone conformation of **1** was deduced from the characteristic AB pattern for the $ArCH_2Ar$ in its ^1H NMR spectrum in $CDCl_3$. A peak at 31.8 ppm was found in the ^{13}C NMR for the $ArCH_2Ar$. Reference molecule **2** was synthesized by a similar procedure but using Cs_2CO_3.[12] The 1,3-alternate conformation of **2** was deduced from its ^1H NMR spectrum exhibiting an AB system appearing partially at 3.81 ppm ($J = 8.0$ Hz) for the $ArCH_2Ar$ and from ^{13}C NMR showing a peak at 37.85 ppm for the related carbon.

Calixarenes **1** and **2** bearing two coumarin signaling units and two amido groups as the binding sites were

* Corresponding author. Tel.: +82 2 799 1351; fax: +82 797 3277; e-mail: jongskim@dankook.ac.kr

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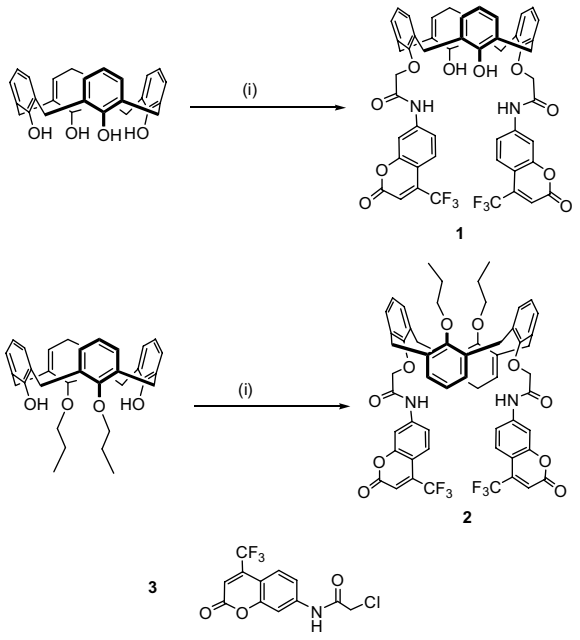

Scheme 1. Synthetic routes for **1** and **2**. (i) **3**, K_2CO_3, NaI, CH_3CN, N_2.

anticipated to act as a PCT-based chemosensor. Figure 1 shows the changes of the absorption spectrum of **1** (20 μM in CH_3CN) upon addition of F^-, Cl^-, Br^-, I^-, $CH_3CO_2^-$, HSO_4^-, and $H_2PO_4^-$ (60 mM as their tetrabutylammonium salts). Only F^- and $CH_3CO_2^-$ showed changes over the anions. Free ligand **1** displayed a strong absorption band at 335 nm corresponding to the coumarins. Titration of **1** as a function of [F^-] (shown in Fig. 2) gave a decreasing intensity with the formation of red-shifted band at 349 nm. Another new band at 408 nm appeared. Both new bands were attributed to H-bonding between amide N–H and F^- followed by deprotonation.

The study of the luminescence of **1** evidenced a similar F-selectivity over the other anions. As shown in Figure 3, **1** showed a unique emission band at 420 nm with excitation at $\lambda_{ex} = 335$ nm which declined upon addition of F^- eventually quenched to give a small band

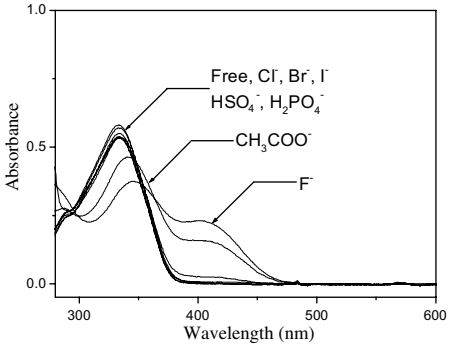

Figure 1. Uv-vis spectra of **1** (20 μM) upon addition of tetrabutylammonium salts of F^-, Cl^-, Br^-, I^-, $CH_3CO_2^-$, HSO_4^-, and $H_2PO_4^-$ (60 mM) in CH_3CN.

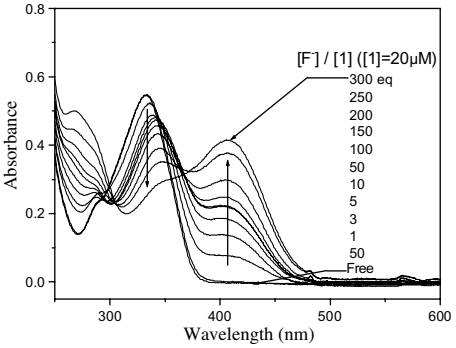

Figure 2. Changes in UV–vis spectra for **1** (20 μM) in CH_3CN upon addition of tetrabutylammonium fluoride.

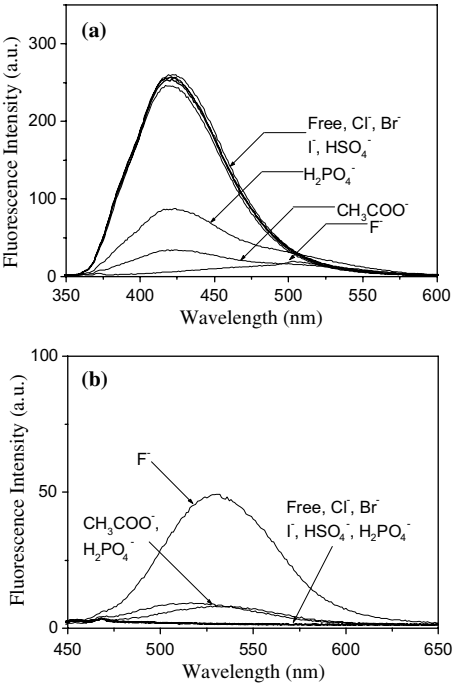

Figure 3. Fluorescence spectra of **1** (6 μM): (a) $\lambda_{ex} = 335$ nm; (b) $\lambda_{ex} = 408$ nm upon addition of tetrabutylammonium salts of F^-, Cl^-, Br^-, I^-, $CH_3CO_2^-$, HSO_4^-, and $H_2PO_4^-$ (6.0 mM) in CH_3CN.

at 508 nm. This was ascribed to a PET effect from the F^- to coumarin.[7d] When excited at $\lambda_{ex} = 408$ nm, a red-shifted absorption band upon addition of F^-, the fluorescence intensity of **1** was enhanced compared to those of other anions.

The titration of **1** (6.0 μM in MeCN) by F^- with an excitation at $\lambda_{ex} = 335$ nm exhibited a decrease of its emission intensity with a red-shift to 508 nm which is induced by H-bonding followed by deprotonation (Fig. 4). From this titration, we determined association constants (K_a)[13] of **1** for F^- (1.08×10^4) and for $CH_3CO_2^-$ (3.77×10^2) due to their basicity and to a recognition complementarity.

^1H NMR was used to look into the nature of the peaks formed during luminescent F^- titration. Figure 5 shows the chemical shift changes of the ^1H NMR spectrum of **1**

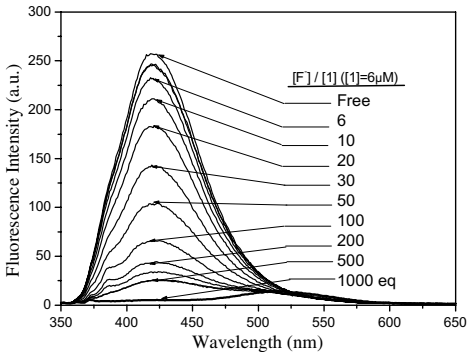

Figure 4. Fluorescence titration spectra of **1** (6.0 μM) with tetrabutylammonium fluoride in CH_3CN, $\lambda_{ex} = 335$ nm.

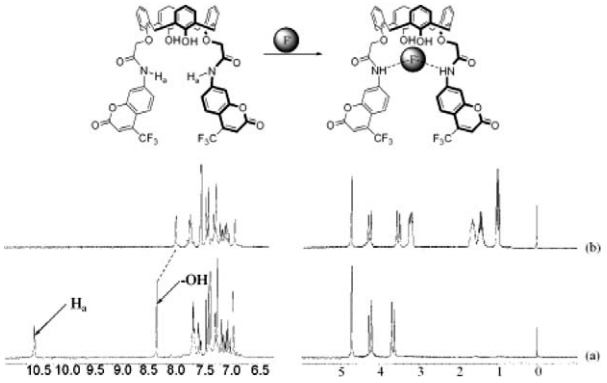

Figure 5. Partial ^1H NMR (200 MHz) of **1** (0.03 mM) in $CDCl_3$: (a) **1** only; (b) **1** + 1.0 equiv of tetrabutylammonium fluoride. *x*-axis is for ppm.

upon addition of 1.0 equiv of F^- in $CDCl_3$. The amide H_a proton disappeared with no particular changes in the aromatic proton signals. As a result, we estimated that the amide N–H of **1** participates in the H-bonding with F^-. Similarly, OH protons are high-field shifted with probable H-bonding with F^-.

The interaction of amide hydrogen atoms with F^- promotes the delocalization of π-electrons from the anionic nitrogen atoms to the coumarin units provoking a change of the π–π transition of the chromophore to green, as shown in Figure 6.

Compound **2** fully O-substituted was investigated to compare with **1**. As shown in Figure 7, the fluorescence

Figure 6. Visual changes for **1** upon addition of (a) no anion, (b) F^-, (c) Cl^-, (d) Br^-, (e) I^-, (f) CH_3COO^-, (g) HSO_4^-, and (h) $H_2PO_4^-$. Irradiation at $\lambda_{ex} = 335$ nm using UV lamp.

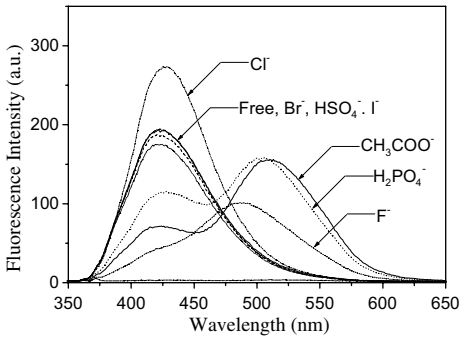

Figure 7. Fluorescence spectra of **2** (6 μM) $\lambda_{ex} = 335$ nm upon addition of tetrabutylammonium salts of F^-, Cl^-, Br^-, I^-, $CH_3CO_2^-$, HSO_4^-, and $H_2PO_4^-$ (6.0 mM) in CH_3CN.

changes of **2** upon addition of F^- is more significant than that of **1**, in which there is a meaningful red-shifted emission band for **1**·F^-. Concerning the luminescence mechanism, it is reasonable to postulate that when **1** coordinates F^-, both PETs of (i) fluoride to coumarin and of (ii) phenolate anion to coumarin are applied leading to a remarkable quenching of the fluorescence intensity. For **2** only PET[7d] (i) might be applied. We also noticed that **2** was selective not only for F^- but also for $CH_3CO_2^-$ and $H_2PO_4^-$. Presumably **2** presents a larger distance between the amide functions (due to the 1,3-alternate conformation) so that anions with larger size such as $CH_3CO_2^-$ and $H_2PO_4^-$ can be maintained within them.

In summary, we have presented a new anion PCT-chemosensor based on calix[4]arene bearing two coumarin units selective for F^- over other anions examined as Cl^-, Br^-, I^-, HSO_4^-, $CH_3CO_2^-$, and $H_2PO_4^-$ and may be considered as a potential fluorescent chemosensor for F^-.[7]

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11. 4-Trifluoromethyl-7-coumarin possesses an excited state where the negative charge is transferred from the nitrogen atom to the coumarin ring see: Choi, K.; Hamilton, A. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 3912, and references therein.
12. General: Uncorrected melting points (mps), Buchi 500. ^{1}H NMR and ^{13}C NMR, Varian (δ in ppm frpm TMS, J in hertz) FAB MS mass spectra, JEOL-JMS-HX 110A/110A High Resolution Tendem Mass Spectrometry in Korean Basic Science Institute (Korea). All reactions were run under a nitrogen atmosphere. All reagents and solvents were commercial and used without further purification. UV–vis spectra were recorded with a S-3100 UV–vis spectrophotometer. Fluorescence spectra were recorded with a RF-5301PC spectrofluorophotometer. Experimental conditions are given in the main text. Preparation of **1**: Calix[4]arene (0.32 g; 0.79 mmol), **3** (0.44 g; 1.44 mmol), K_2CO_3 (0.11 g, 0.79 mmol), NaI (catalytic amount), and CH_3CN (100 mL) were refluxed for 24 h. After removal of the solvents in vacuo, the resulting solid was dissolved in CH_2Cl_2 (100 mL) and aqueous $NaHCO_3$ solution (100 mL). The organic phase was washed with water (2×50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and the solvents were evaporated to give a solid which was recrystallized from Et_2O to give pure **1** (0.36 g; 54% yield) as a white solid. Mp: 230–232 °C. IR (KBr pellet, cm^{-1}): 3322, 1780. ^{1}H NMR (200 MHz, $CDCl_3$): 10.45 (s, 2H, CON*H*coumarin), 8.17 (s, 2H, ArO*H*), 7.49–6.75 (m, 8H, Ar*H*, coumarin; 8H, ArH_m; 4H, ArH_p), 4.71 (s, 4H, ArOCH_2CO), 4.22 (d, 4H, ArCH_2Ar, $J = 13.9$ Hz), 3.65 (d, 4H, ArCH_2Ar, $J = 13.9$ Hz). ^{13}C NMR ($CDCl_3$): 165.7, 158.7, 154.9, 151.3, 149.7, 141.4, 132.4, 130.1, 129.4, 127.5, 121.1, 117.3, 109.8, 106.5, **31.8**. FAB MS m/z (M^+): Calcd, 962.84. Found: 962.82. Anal. Calcd for $C_{52}H_{36}F_6N_2O_{10}$: C, 64.87; H, 3.77. Found: C, 64.86; H, 3.79. Preparation of **2**: The procedure is the same as for **1** using Cs_2CO_3. White solid (59% yield). Mp: 280–284 °C. IR (KBr pellet, cm^{-1}): 3322, 1780. ^{1}H NMR (200 MHz; $CDCl_3$): 8.77 (s, 2H, CON*H*coumarin), 7.66–6.55 (m, 8H, Ar*H*, coumarin; 8H, ArH_m; 4H, ArH_p), 3.87 (s, 4H, ArOCH_2CO), 3.81 (d, 4H, ArCH_2Ar, $J = 8.0$ Hz), 3.53–3.43 (m, 4H, ArCH_2Ar; 4H, ArOCH_2CH$_2$), 1.47 (sextet, 4H, $J = 4.0$ Hz, $CH_2CH_2CH_3$), 0.83 (t, 6H, $J = 4.0$ Hz, $CH_2CH_2CH_3$). ^{13}C NMR ($CDCl_3$): 168.43, 159.07, 157.70, 155.01, 154.53, 141.77, 135.08, 133.05, 131.42, 129.96, 125.87, 123.38, 123.14, 116.75, 109.71, 108.11, 73.04, 71.43, **37.85**, 22.67, 9.97. FAB MS m/z (M^+): Calcd,1047.0. Found: 1047.2. Anal. Calcd for $C_{58}H_{48}F_6N_2O_{10}$: C, 66.53; H, 4.62. Found: C, 66.68; H, 5.40. Preparation of **3**: 7-Amino-4-(trifluoromethyl)coumarin (0.30 g; 1.29 mmol), $ClCH_2COCl$ (0.15 g; 1.29 mmol), NEt_3 (0.40 g; 3.90 mmol), and THF (100 mL) were refluxed for 24 h. After removal of the solvents to the resulting solid was dissolved in CH_2Cl_2 (100 mL) and aqueous $NaHCO_3$ (100 mL). The organic layer was washed with water (2×50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvents were evaporated to give a solid which was recrystallized from Et_2O to give pure **3** (0.27 g; 68% yield) as a yellow solid. Mp: 182–185 °C. IR (KBr pellet, cm^{-1}): 3322, 1780. FAB MS m/z (M^+): Calcd, 305.64. Found, 305.62. Anal. Calcd for $C_{12}H_7ClF_3NO_3$: C, 47.16; H, 2.31. Found: C, 47.17; H, 2.32. ^{1}H NMR (200 MHz; $CDCl_3$): δ 8.47 (s, 1H, CON*H*), 7.88 (s, 1H, Ar*H*), 7.71 (d, 1H, $J = 16.0$ Hz, Ar*H*), 7.45 (d, 1H, Ar*H*, $J = 16.0$ Hz.), 6.74 (s, 4H, COC*H*CCF$_3$), 4.24 (s, 2H, COCH_2Cl).
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