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A Novel *N*-linked Peptidocalix[4]arene Receptor for Anions

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A novel *N*-linked fluorescent peptidocalix[4]arene functionalized with two *L*-phenylalanine and dansyl ethylenediamine units at the upper rim has been prepared. The fluorescence and ^{1}H NMR spectra were used to investigate its properties of molecular recognition for some important anions. This compound shows selective fluorescent response towards F^- different from AcO^-, $H_2PO_4^-$, Cl^-, Br^-, NO_3^-, I^- and HSO_4^-.

Keywords: Calixarene; Fluorescent chemosensor; Anion recognition; Hydrogen bonding

INTRODUCTION

Enzymes have the amazing ability of separating a special substrate from other compounds with their highly organized cavities or channels. One of the hot fields in supramolecular chemistry is to reach an efficient complementarity of molecular recognition as in nature. Compared with cations and small neutral molecules, anions have been little researched but they have recently attracted more interest because of their important roles in biomedical and chemical processes [1]. Recognition of the anions by neutral receptors which contain activated amides or (thio)ureas can be challenging [2–17]. On the other hand, calixarenes have been commonly used as scaffolds for synthetic receptors advantageously due to their unique cavity shape [18–20]. Peptides and amino acids possess the required structural elements and the introduction of them into the upper rim of the calixarene could lead to the receptors interacting with anions by hydrogen bonding. Moreover, the chiral receptors of anions may serve as good candidates in future studies of bio-mimics. In recent years, some examples were reported where natural amino acids were used as binding units in biomimetric receptors for anion recognition [21–27]. Among them there are a few examples of fluoroionophores based on peptidocalixarenes developed for anion recognition. Previously, we reported two *cone* calix[4]arene conformers which exhibited good recognition to F^- and AcO^-, respectively [28,29]. In this paper, we report another anion chemosensor based on a *N*-linked peptidocalix[4]arene which showed selective fluorescent behavior of F^- over other anions examined such as Cl^-, Br^-, I^-, HSO_4^-, NO_3^-, AcO^- and $H_2PO_4^-$.

RESULTS AND DISCUSSION

A simple route was chosen to synthesize the new fluorescent molecule **4** starting from **1** (Scheme 1) [30]. The calix[4]arene bisacid **1** was converted to calix[4]arene biscarbonyl chloride using $SOCl_2$ and then was condensed with *L*-phenylalanine methyl ester to afford the difunctionalized macrocycle **2** in 70% yield. Hydrolysis of compound **2** was carried out by a simple treatment with LiOH in THF/H_2O to form acid **3** in 95% yield. Finally, compound **3** condensing with dansyl ethylenediamine in the presence of DCC and HOBT in CH_2Cl_2 afforded the desired fluorescent molecule **4** in 60% yield after column chromatography. The structure of **4** in *cone* conformation was confirmed by ^{1}H and ^{13}C NMR, 2D ^{1}H—^{1}H COSY, MALDI-TOF MS spectroscopy and elemental analysis.

The complex properties of the new host **4** towards anions (*n*-Bu_4N^+ salts) were evaluated in CH_3CN. Fluorescence titration experiments were recorded on excitation at 340 nm and emission at 521 nm, respectively. As shown in Fig. 1, a decrease in the fluorescence intensity of **4** upon the addition of F^-

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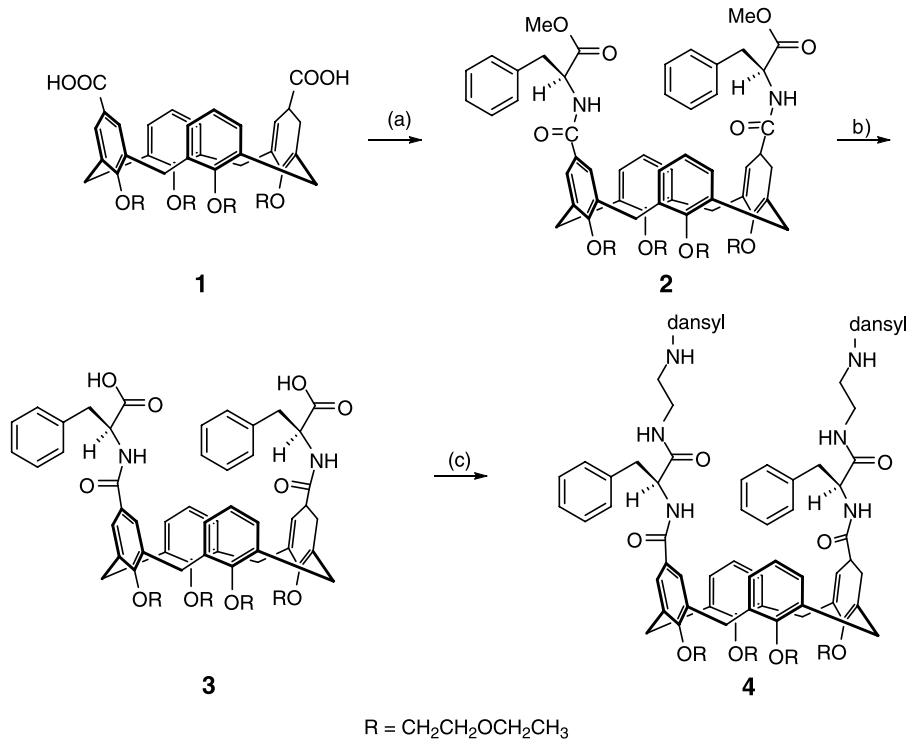


SCHEME 1 Reagents and conditions: (a) SOC12, L-phenylalanine-OMe, Et3N, 70%; (b) LiOH, HF/H2O, rt, 6h, 95%; (c) NH2CH2CH2NH-dansyl, DCC/HOBT, Et3N, rt, 60%.

was observed, accompanied with the blue shift of the emission peak. When the concentration of F^- increased to 20 equivalents, the intensity was changed to 70% from the initial one. Further addition of F^- produced only a nominal decrease in fluorescence intensity. However the fluorescence intensity of **4** was gradually increased with the addition of AcO^-. When the concentration of AcO^- increased to 20 equivalents, the intensity remained almost stable. In the case of $H_2PO_4^-$, the fluorescence intensity of **4** was not changed except a slight blue shift. R. Métivier *et al.* have reported that there was a big blue shift of the fluorescence spectra of dansyl group upon cation binding, which was due to an increase of the electronic density on aromatic rings caused by the deprotonation process [31]. Similarly, in our system, the blue shift observed on binding of F^-, AcO^- and $H_2PO_4^-$ could be attributed to the deprotonation of sulfonamide group or the formation of strong hydrogen bonds too. When other anions such as NO_3^-, Cl^-, Br^-, I^- and HSO_4^- were added to the solution of **4** on the same condition, only a marginal fluorescence quenching of the sensor was observed. From the Stern–Volmer plot (the fluorescence quenching followed the Stern–Volmer equation) [32,33], the association constant between host **4** and F^- was estimated to be 1800 M^{-1} from the fluorescence titration experiments. Due to the tiny change of the fluorescence spectral of **4** in addition of $H_2PO_4^-$ and AcO^-, the association constant of **4**

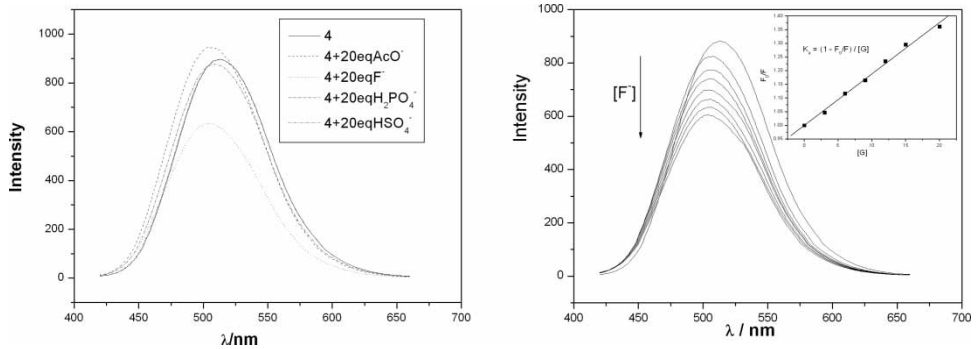


FIGURE 1 Fluorescence emission spectra of **4** (1×10^{-5} M) in the presence of (a) 20 equiv of each of F^-, $H_2PO_4^-$, AcO^- and HSO_4^-; (b) F^- in CH_3CN. The concentration of F^-: 0, 3.0, 6.0, 9.0, 12.0, 15.0, 20.0, 25.0 $\times 10^{-5}$ M; $\lambda_{ex} = 340$ nm. Anions used were in the form of their n-Bu_4N^+ salts.

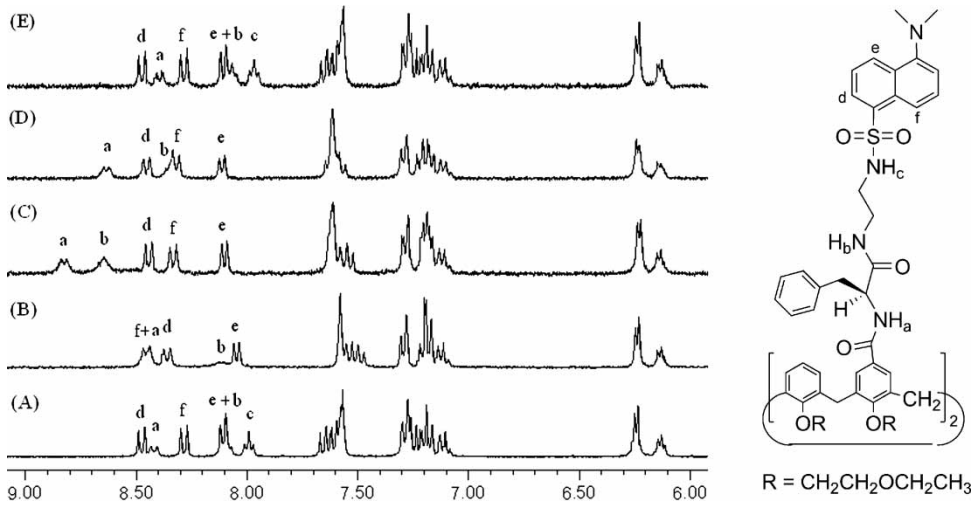
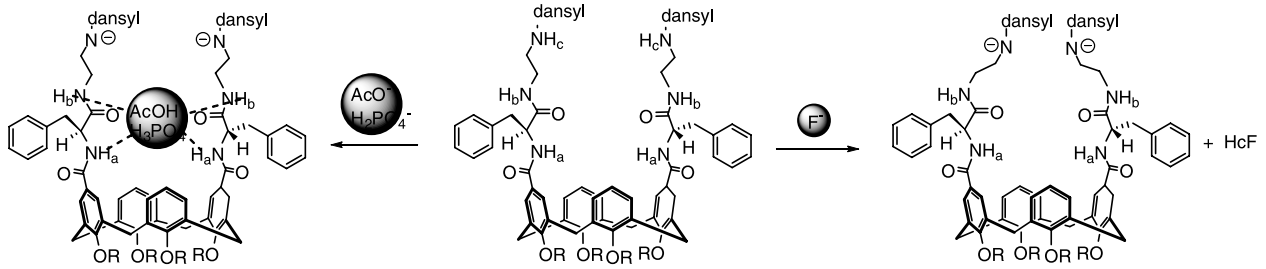


FIGURE 2 Partial ^{1}H NMR (300 MHz) spectra of host **4** in DMSO-d_6. (A) host **4**; (B) **4** + 2 equivs of F^-; (C) **4** + 2 equivs of AcO^-; (D) **4** + 2 equivs of $H_2PO_4^-$; (E) **4** + 2 equivs of NO_3^-. Anions used were in the form of their *n*-Bu_4N^+ salts.

toward $H_2PO_4^-$ or AcO^- could not be estimated. So host **4** was a selective fluorescent chemosensor for F^-.

^{1}H NMR spectroscopy has been widely used to investigate receptor–substrate interaction and it can provide details of the interaction between the host and the guest. Further indications of anion complexation were obtained from ^{1}H NMR titrations. The ^{1}H NMR spectrum of **4** in DMSO-d_6 showed dramatic changes upon the addition of two equivalents of F^-, AcO^- and $H_2PO_4^-$ while no spectral change was observed upon the addition of Cl^-, Br^-, I^- and HSO_4^- under the same conditions (Fig. 2). The H_c of SO_2NH group became invisible on addition of two equivalents of F^-, AcO^- and $H_2PO_4^-$, which are presumably the required equivalents of anion to remove both H_c protons [34]. The disappearance of H_c of the SO_2NH group in ^{1}H NMR spectra is coincidental with the blue shift of their fluorescence spectra due to deprotonation. However, compared with F^-, a large chemical shift change of H_a and H_b in the presence of AcO^- or $H_2PO_4^-$ were observed ($\Delta\delta$ H_a = 0.41 and H_b = 0.57 for AcO^-, $\Delta\delta$ H_a = 0.21 and H_b = 0.26 for $H_2PO_4^-$, and $\Delta\delta$ H_a = 0.03 and H_b = 0.02 for F^-) but other dansyl proton signals showed almost no change. It could be explained as the HF formed does not interact with the complex very much at all, allowing the dansyl moieties to interact more strongly, partly quenching the fluorescence. On the other hand, due to multi binding sites, the protonated AcO^- and $H_2PO_4^-$ remain bound by the other hydrogen bonds, which could be confirmed by the large chemical shift change of H_a and H_b. This kind of conformation change may inhibit the reduction in fluorescence. The experiment results indicated that host **4** could recognize F^-, AcO^- or $H_2PO_4^-$ due to deprotonation H_c of SO_2NH by anions and the formation of hydrogen bonds between H_a and H_b of two CONH with protonated AcO^- or $H_2PO_4^-$. A probable structure for complex with **4** was shown in Scheme 2.

In conclusion, we have presented a new fluorescent anion chemosensor based on a *N*-linked peptidocalix[4]arene with two *L*-phenylalanine and dansyl ethylenediamine units, which showed selective recognition of F^- over other anions examined as Cl^-, Br^-, I^-, HSO_4^-, AcO^- and $H_2PO_4^-$ from fluorescence spectroscopy. In addition, the recognition of AcO^- and $H_2PO_4^-$ was observed according to the ^{1}H NMR method.



SCHEME 2 Probable structure for complex with **4**.

MATERIALS AND METHODS

General Methods

Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded using a AV300 instrument. Tetramethylsilane (TMS) was used as an internal standard, with chemical shifts expressed in parts per million (ppm) downfield from the standard. Mass spectra were determined by MALDI-TOF technique. Elementary Analysis was performed in the Analytic Laboratory of this Institute. Flash column chromatography was carried out with silica gel (160–200 mesh). Thin-layer chromatographies (TLC) were performed with fluorescent silica gel GF254 precoated on glasses. The solvents were purified and dried before used.

Preparation of Compound 2

The mixture of **1** (1.20 g, 1.5 mmol) and 2 ml of $SOCl_2$ in 3 ml of CH_2Cl_2 was refluxed for 4 h. The excess $SOCl_2$ and solvent were removed under reduced pressure and the product was used for the next step without purification. In a solution of *L*-phenylalanine methyl ester hydrochloride (0.968 g, 4.5 mmol) and triethylamine (0.66 ml, 9 mmol) in 10 ml of dry CH_2Cl_2, carbonyl chloride (1.254 g, 0.84 mmol) in 10 ml dry CH_2Cl_2 was added dropwise. This mixture was stirred at room temperature for 8 h, and then water was added. The organic layer was separated, washed by water, dried over Na_2SO_4. After removal of the solvent, the crude product was purified by column chromatography (CH_2Cl_2/acetone, 2:1 v/v). Yield: 70%. Mp: 62–63°C; $[\alpha]_D^{25}$ −32.8° (c 0.5, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.27$–7.42 (m, 10H, ArH), 7.18 (d, $J = 7.2$ Hz, 4H, ArH), 6.53 (d, $J = 7.4$ Hz, 2H, NH), 6.24–6.36 (m, 6H, ArH), 5.08–5.12 (m, 2H, C**H**CH_2), 4.53 (d, $J = 13.4$ Hz, 4H, Hax of $ArCH_2Ar$), 4.29 (t, $J = 5.6$ Hz, 4H, OCH_2CH_2O), 3.99 (t, $J = 5.6$ Hz, 4H, OCH_2CH_2O), 3.86 (t, $J = 5.6$ Hz, 4H, OCH_2CH_2O), 3.76–3.80 (m, 10H, OCH_2CH_2O, OCH_3), 3.56 (q, $J = 7.0$ Hz, 4H, C**H**$_2$$CH_3$), 3.51 (q, $J = 7.0$ Hz, 4H, C**H**$_2$$CH_3$), 3.28 (t, $J = 5.6$ Hz, 4H, CHC**H**$_2$), 3.20 (d, $J = 13.4$ Hz, 4H, Heq of $ArCH_2Ar$), 1.24 (t, $J = 7.0$ Hz, 6H, CH_2C**H**$_3$), 1.16 (t, $J = 7.0$ Hz, 6H, CH_2C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.7$, 165.3, 159.4, 153.3, 135.0, 134.4, 131.4, 127.8, 127.0, 126.5, 126.3, 126.0, 125.5, 121.0, 72.2, 71.4, 68.3, 68.0, 64.9, 64.6, 51.9, 50.7, 36.3, 29.3, 13.7; MALDI-TOF MS: $m/z = 1145.1$ $(M + Na)^+$; 1161.0 $(M + K)^+$; Anal calcd for $C_{66}H_{78}O_{14}N_2$: C, 70.57; H, 7.00; N, 2.49; Found: C, 70.07; H, 6.96; N, 2.43.

Preparation of Compound 3

To a solution of **2** (0.85 g, 0.76 mmol) in 8 ml of THF and 2 ml of H_2O, LiOH (0.091 g, 3.79 mmol) was added. This mixture was stirred for 6 h. After removal of the solvent under reduced pressure, 15 ml of water was added. The mixture was neutralized with 2N HCl, extracted with CH_2Cl_2. The organic layer was dried over Na_2SO_4. After removal of the solvent, the product was obtained as white solid. Yield: 95%. Mp: 100–101°C; $[\alpha]_D^{25}$ −39.2° (c 0.5, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.18$–7.32 (m, 10H, ArH), 6.87–6.89 (m, 2H, NH), 6.58–6.74 (m, 10H, ArH), 4.80–4.84 (m, 2H, C**H**CH_2), 4.51 (d, $J = 13.1$ Hz, 4H, Hax of $ArCH_2Ar$), 4.15–4.18 (m, 4H, OCH_2CH_2O), 4.02–4.07 (m, 4H, OCH_2CH_2O), 3.78–3.85 (m, 8H, OCH_2CH_2O), 3.48–3.54 (m, 8H, OC**H**$_2$$CH_3$), 3.10–3.24 (m, 8H, Heq of $ArCH_2Ar$, CHC**H**$_2$), 1.20 (m, 12H, CH_2C**H**$_3$); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.9$, 168.6, 159.7, 156.0, 136.2, 135.5, 134.4, 129.6, 128.6, 127.7, 127.5, 127.3, 127.1, 122.9, 73.6, 73.1, 69.7, 69.6, 66.4, 54.2, 37.0, 30.9, 15.3; MALDI-TOF MS: $m/z = 1117.5$ $(M + Na)^+$; 1133.5 $(M + K)^+$; Anal calcd for $C_{64}H_{74}O_{14}N_2$: C, 70.18; H, 6.80; N, 2.56; Found: C, 69.75; H, 6.94; N, 2.51.

Preparation of Compound 4

In a solution of compound **3**, DCC (0.35 g, 1.70 mmol) and HOBT (0.23 g, 1.7 mmol) in 8 ml of dry CH_2Cl_2, dansyl ethylenediamine (0.49 g, 1.67 mmol) in 8 ml of dry CH_2Cl_2 was added dropwise. The mixture was stirred at room temperature for 8 h. After removal of the solvent under vacuum, the yellow product was purified with column chromatography (CH_2Cl_2/acetone, 2:1 v/v). Yield: 60%. Mp: 145–146°C; $[\alpha]_D^{25}$ −16° (c 0.5, DMSO-d_6); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 8.48$ (d, $J = 8.6$ Hz, 2H, ArH), 8.42 (d, $J = 8.2$ Hz, 1H, CONH), 8.28 (d, $J = 8.6$ Hz, 2H, ArH), 8.06–8.10 (m, 4H, ArH, CONH), 7.99 (t, $J = 5.8$ Hz, 2H, SO_2NH), 7.56–7.67 (m, 8H, ArH), 7.08–7.30 (m, 12H, ArH), 6.24 (d, $J = 4.6$ Hz, 4H, ArH), 6.13 (t, $J = 4.6$ Hz, 2H, ArH), 4.48–4.55 (m, 2H, C**H**CH_2), 4.44 (d, $J = 13.2$ Hz, 4H, Hax of $ArCH_2Ar$), 4.27 (t, $J = 5.6$ Hz, 4H, OCH_2CH_2O), 3.76–3.89 (m, 8H, OCH_2CH_2O, OCH_2CH_2O), 3.74 (t, $J = 5.0$ Hz, 4H, OCH_2CH_2O), 3.52 (q, $J = 7.0$ Hz, 4H, C**H**$_2$$CH_3$), 3.44 (q, $J = 7.0$ Hz, 4H, C**H**$_2$$CH_3$), 3.01–3.24 (m, 12H, Heq of $ArCH_2Ar$, $NHCH_2$, CHC**H**$_2$), 2.82 (s, 12H, $N(CH_3)_2$), 2.72–2.78 (m, 4H, CH_2NH), 1.17 (t, $J = 7.0$ Hz, 6H, C**H**$_2$$CH_3$), 1.07 (t, $J = 7.0$ Hz, 6H, CH_2C**H**$_3$); ^{13}C NMR (75 MHz, acetone-d_6): $\delta = 171.6$, 166.7, 160.3, 155.2, 151.6, 137.7, 135.8, 135.7, 133.3, 133.2, 129.6, 129.4, 129.1, 128.6, 128.0, 127.9, 127.8, 127.6, 127.4, 126.1, 123.1, 122.0, 119.2, 115.0, 73.6, 73.1, 69.6, 69.3, 65.7, 65.6, 54.9, 44.5, 42.0, 39.0, 37.3, 30.3, 14.6, 14.5; MALDI-TOF MS: $m/z = 1666.9$ $(M + Na)^+$; 1682.8 $(M + K)^+$; Anal calcd for $C_{92}H_{108}O_{16}N_8S_2$: C, 67.13; H, 6.61; N, 6.81; S, 3.90; Found: C, 66.93; H, 6.93; N, 7.04; S, 4.02.

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