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A C-linked peptidocalix[4]arene bearing four dansyl groups: a highly selective fluorescence chemosensor for fluoride ions

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Abstract—A new C-linked peptidocalix[4]arene functionalized with four L-alanine and dansyl units at the upper rim has been prepared, which exhibited highly selective recognition towards F^- along with weaker complexation to AcO^- and $H_2PO_4^-$ and no complexation to Cl^-, Br^-, I^-, and HSO_4^- by fluorescence spectroscopy and ^1H NMR method.

On account of the important roles of anion in biology, catalysis, and chemical processes, the selective and efficient recognition of anion is an increasingly topical field in supramolecular chemistry.[1] In particular, the studies of new receptors toward F^- anion are quite intriguing because of its beneficial effects in human physiology.[2] Synthetic anion receptors contain either positively charged amidinium, guanidinium, or ammonium or neutral H-bonding donor group such as (thio)ureas, pyrroles, activated amides to accomplish anion binding by the interaction of favorable electrostatics and hydrogen bounds.[3] In recent years, anion coordination studies of amide functions employing the hydrogen bonding have been explored extensively.[4] Due to high sensitivity and simplicity of fluorescence among many signal types available, the design and synthesis of fluorescent devices for recognition is currently of importance in chemical trace detection. However, there are few examples of fluoroionphores based on calixarenes developed for anion.

Calixarenes substituted with amino acids at the upper rim have been reported for the complexation of amino acid, anion, and dimerization.[5] Although peptides possess the required structural elements, little attention has been paid to them as neutral anion receptors. Up to now, only a few examples were reported where natural amino acids are used as binding units in biomimetic receptors for anion recognition.[5a] In this paper, we report a selective fluorescent anion chemosensor based on a C-linked peptidocalix[4]-arene, which showed high selective recognition of F^- over other anions examined such as Cl^-, Br^-, I^-, HSO_4^-, AcO^-, and $H_2PO_4^-$.

As shown in Scheme 1, a simple route was chosen for the synthesis of new fluorescent molecule **4** starting from **1**.[6] Isobutyl chloroformate together with Et_3N converted *N*-Boc-L-alanine to the anhydride, and the subsequent addition of 5,11,17,23-tetraamino-25,26,27,28-tetra(2-ethoxyethoxy)calix[4]arene **1** afforded the *N*-Boc-L-alanylaminocalix[4]arene **2**. Treatment of crude **2** with HCl/AcOEt at room temperature removed the Boc protecting group to generate the L-alanylamino amide hydrochloride, which was converted with aqueous NaOH into the free base L-alanylamino amide **3** in 75% yield. Due to its alleged instability, compound **3** was used directly in next step without further purification. The addition of 4.8 equiv of dansyl chloride to **3** in CH_2Cl_2 gave the fluorescent molecule **4** in 60% yield after the column chromatography. The structure of **4** in cone conformation was confirmed by ^1H and ^{13}C NMR, MALDI-TOF MS, 2D ^1H–^1H COSY spectroscopy and elemental analysis.[7]

The complex properties of the new host **4** towards anion (*n*-Bu_4N^+ salts) were evaluated in CH_3CN. Fluorescence

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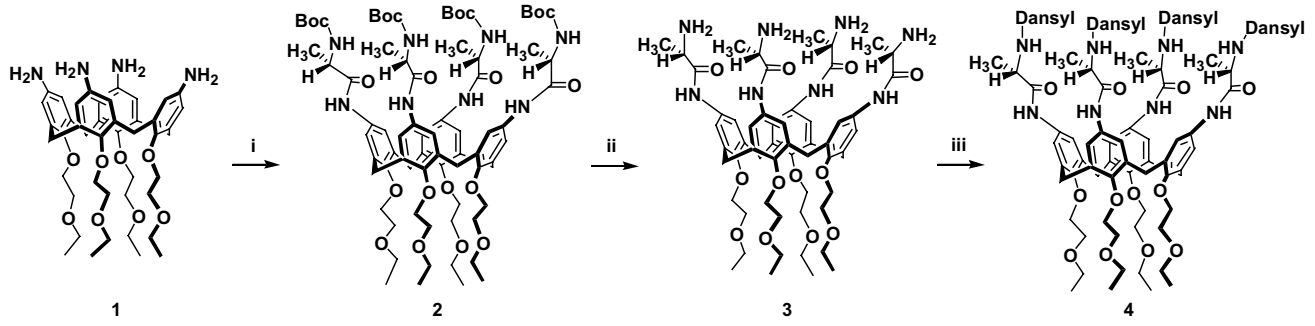

Scheme 1. Reagents and conditions: (i) ClCOOBu-*i*, Et_3N, *N*-Boc-L-Ala, rt, 6 h, 65%; (ii) 2 M HCl/AcOEt, rt, 16 h, 75%; (iii) dansyl chloride, rt, 8 h, 60%.

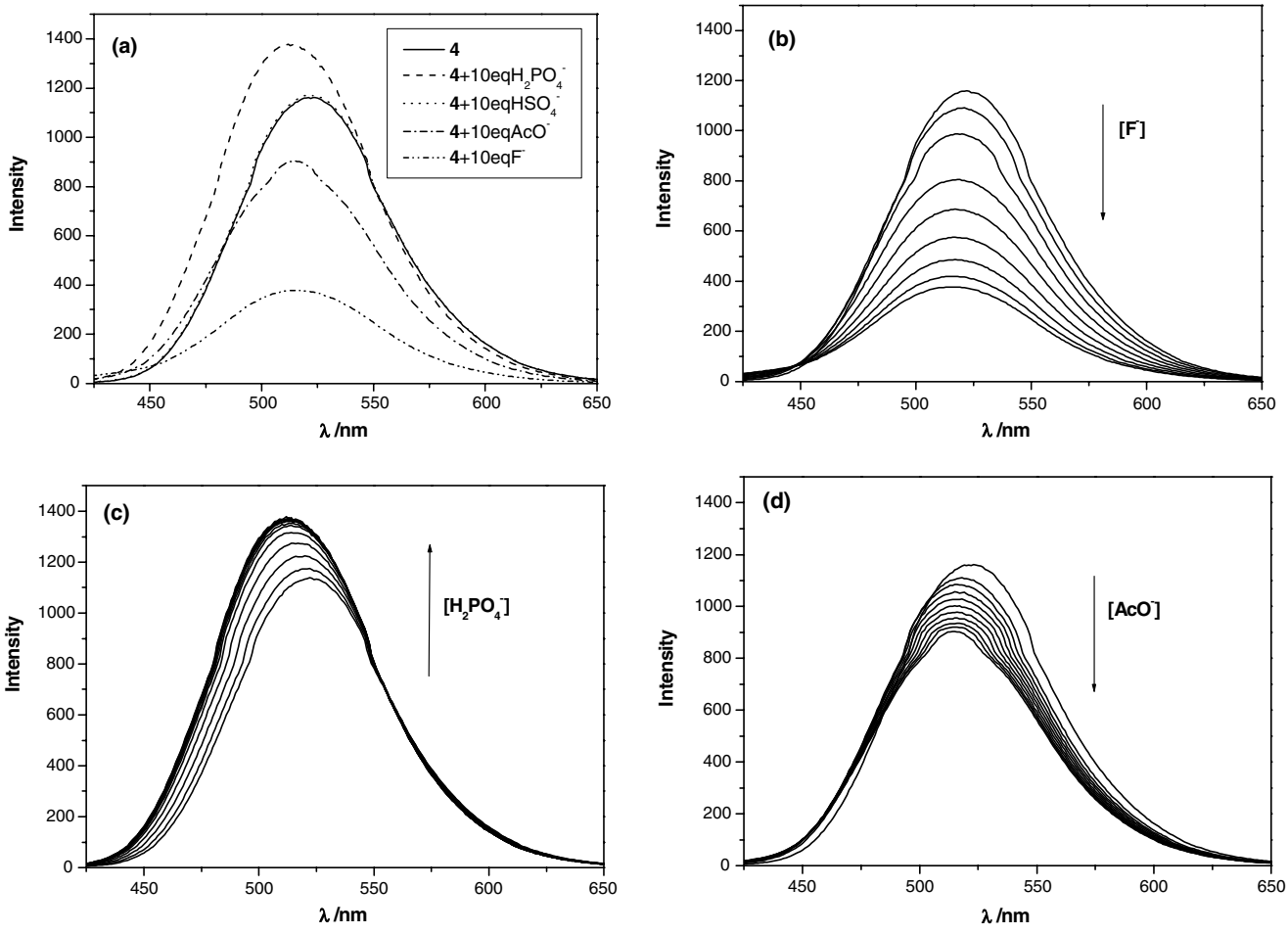

Figure 1. Fluorescence emission spectra of **4** (1×10^{-5} M) in the presence of (a) 10 equiv of each of F^-, $H_2PO_4^-$, AcO^- and HSO_4^-; (b) F^-; (c) $H_2PO_4^-$; (d) AcO^- in CH_3CN. The concentration of F^- : 0, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0×10^{-5} M; The concentration of $H_2PO_4^-$: 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0×10^{-5} M; The concentration of AcO^-: 0, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 9.0, 10.0×10^{-5} M; $\lambda_{ex} = 340$ nm. Anions used were in the form of their *n*-Bu_4N^+ salts.

titration experiments were recorded on excitation at 340 nm and emission at 521 nm, respectively. As shown in Figure 1, a decrease in the fluorescence intensity of **4** upon the addition of F^- was observed. When the concentration of F^- increased to 10 equiv, the intensity was changed to 30% of initial one. Further addition of F^- produced only a nominal decrease in fluorescence intensity. In the case of AcO^-, the spectral changes of **4** were similar to but smaller than those of F^-. On the contrary, the intensity increase was particularly evident until 3 equiv of $H_2PO_4^-$ were added. As similar behavior,[8] a 6 nm blue shift was observed due to the deprotonation of sulfonamide group upon anion binding, which was explained by an increase of the electronic density on aromatic rings caused by the deprotonation process. When 10 equiv of each Cl^-, Br^-, I^-, and HSO_4^-

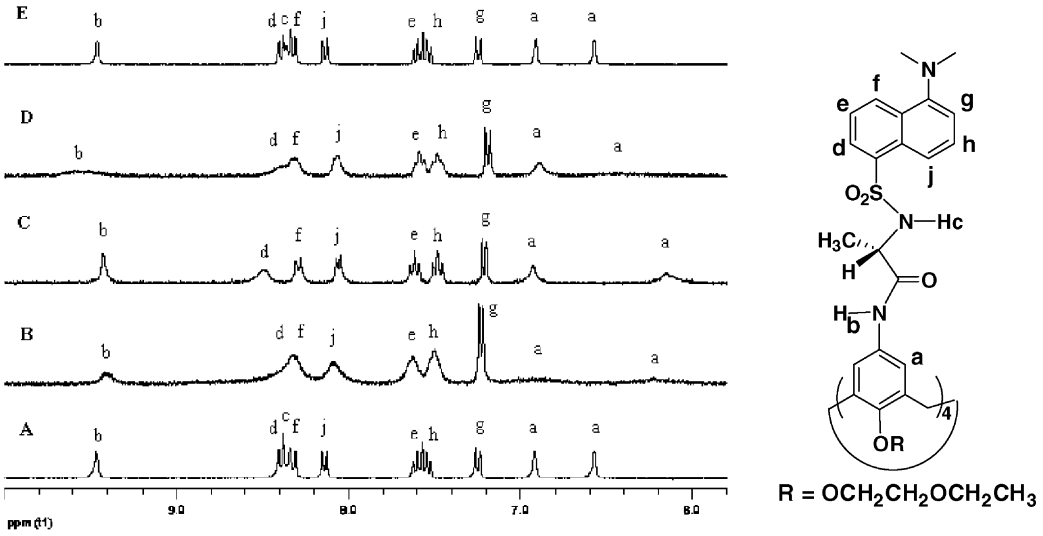

Figure 2. Partial ^{1}H NMR (300 MHz) spectra of host **4** in DMSO-d_6. (A) host **4**; (B) **4**+2 equiv of F^-; (C) **4**+2 equiv of AcO^-; (D) **4**+2 equiv of $H_2PO_4^-$; (E) **4**+2 equiv of Cl^-. Anions used were in the form of their n-Bu_4N^+ salts.

were added to a solution of **4**, only a marginal fluorescence quenching of the sensor was observed. Host **4** formed 1:1 stoichiometric solution complexes with anion according to the Stern–Volmer plot.[9] From the fluorescence titration experiments, the association constants for F^-, AcO^-, and $H_2PO_4^-$ were estimated to be 29,500, 2600, and 5300 M^{-1}, respectively. The fluorescence quantum yield was determined by using 9,10-diphenylanthracene in cyclohexane as a standard ($\Phi_f = 1.0$). The value of Φ_f of **4** on addition of 10 equiv of F^- ($\Phi_f = 0.10$) and 3 equiv of AcO^- ($\Phi_f = 0.24$) was lower than that of free **4** ($\Phi_f = 0.38$), respectively. With $H_2PO_4^-$, there was an enhancement in quantum yield ($\Phi_f = 0.45$). This result was in agreement with that of fluorescence spectroscopy.

In order to study the nature of anion coordination, NMR experiments were carried out. The ^{1}H NMR spectrum of **4** in DMSO-d_6 showed dramatic changes upon the addition of 2 equiv of F^-, AcO^-, and $H_2PO_4^-$ while no spectral changes were observed upon the addition of Cl^-, Br^-, I^-, and HSO_4^- in the same conditions (Fig. 2). When F^-, AcO^-, and $H_2PO_4^-$ were added, the signal of H_c disappeared and signals of other protons were broadened and shifted due to the formation of strong hydrogen bonds between the SO_2NH and anion. This was certified by 2DCOSY. When 2 equiv of F^-, AcO^- or $H_2PO_4^-$ were added, the correlation of SO_2NH and CH of L-Ala disappeared. Furthermore, when 2 equiv of $H_2PO_4^-$ were added, the signal of H_b ($\Delta\delta H_b = 0.12$) was shifted downfield owing to the formation of hydrogen bond to the tetrahedral oxoanion.

In conclusion, we have presented a new fluorescent anion chemosensor based on a C-linked peptidocalix[4]arene containing four L-alanine and dansyl units, which showed high selective recognition of F^- over other anions examined as Cl^-, Br^-, I^-, HSO_4^-, AcO^-, and $H_2PO_4^-$ and may be considered as a potential fluorescent chemosensor for F^-.

Acknowledgements

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7. Analytic and spectroscopic data for compounds **2**–**4**.
   5,11,17,23-Tetrakis(*N*-Boc-L-alanylamino)-25,26,27,28-tetra(2-ethoxyethoxy)calix[4]arene (**2**). To a cold solution (−15 °C) of *N*-Boc-L-alanine acid (0.080 g, 0.42 mmol) and Et_3N (0.06 mL, 0.42 mmol) in dry CH_2Cl_2 (2 mL), isobutyl chloroformate (0.059 g, 0.42 mmol) was added. After the mixture was stirred for 1 h, **1** (0.04 g, 0.052 mmol) was added. Then the mixture was allowed to slowly warm to rt and stirred for 6 h. After removal of the solvent, the residue was dissolved with EtOAc and the organic phase was washed with 10% Na_2CO_3, 0.1 M HCl, and brine and dried over Na_2SO_4. The solvent was removed to leave the residue, which was chromatographed (CH_2Cl_2/acetone, 3:1, v/v) to give a white solid in 65% yield. Mp: 238–239 °C; $[\alpha]_D^{25}$ −11.2 (*c* 0.5, DMSO); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 9.61$ (s, 4H, N*H*), 7.05 (s, 4H, Ar*H*), 6.75–6.85 (m, 8H, N*H*, Ar*H*), 4.43 (d, $J = 12.6$ Hz, 4H, H_{ax} of ArCH_2Ar), 3.99–4.05 (m, 12H, C*H*CH$_3$, OCH_2CH$_2$O), 3.78–3.82 (m, 8H, OCH$_2$CH_2O), 3.48 (q, $J = 6.96$ Hz, 8H, CH_2CH$_3$), 3.06 (d, $J = 12.8$ Hz, 4H, H_{eq} of ArCH_2Ar), 1.35 (s, 36H, C(CH_3)$_3$), 1.16 (d, $J = 6.21$ Hz 12H, CHCH_3), 1.13 (t, $J = 6.99$ Hz, 12H, CH$_2$CH_3); ^{13}C NMR (75 MHz, DMSO-d_6): $\delta = 171.2$, 155.2, 152.2, 134.6, 133.4, 120.0, 78.3, 73.5, 69.3, 65.8, 50.2, 31.1, 28.5, 18.6, 15.4; MALDI-TOF MS: $m/z = 1480$ (M^++Na); 1496 (M^++K); Anal. Calcd for $C_{76}H_{112}O_{20}N_8$: C, 62.62; H, 7.74; N, 7.69; Found: C, 62.28; H, 7.79; N, 7.54.
   5,11,17,23-Tetrakis(L-alanylamino)-25,26,27,28-tetra(2-ethoxyethoxy)calix[4]arene (**3**). To a stirred solution (−15 °C) of **2** (0.070 g, 0.048 mmol) in EtOAc (2 mL) was added HCl in EtOAc (ca. 1 M, 2 mL). The mixture was stirred at rt until the disappearance of the starting material (16 h). Then the mixture was treated with 1 M aq NaOH and extracted with EtOAc. The organic phase was washed with brine and dried over Na_2SO_4. Evaporation of the solvent in vacuo gave the crude product **3** in 75% yield, which was used for the subsequent reaction without further purification. Mp: 162–163 °C; $[\alpha]_D^{25}$ −29 (*c* 0.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.99$ (s, 4H, N*H*), 7.09 and 6.79 (2s, 8H, Ar*H*), 4.51 (d, $J = 12.9$ Hz, 4H, H_{ax} of ArCH_2Ar), 4.10 (t, $J = 7.83$ Hz, 8H, OCH_2CH$_2$O), 3.80–3.84 (m, 12H, C*H*CH$_3$, OCH$_2$CH_2O), 3.53 (q, 8H, $J = 6.54$ Hz, CH_2CH$_3$), 3.14 (d, $J = 12.8$ Hz, 4H, H_{eq} of ArCH_2Ar), 1.37 (d, $J = 6.9$ Hz, 12H, CHCH_3), 1.22 (t, $J = 6.9$ Hz, 12H, CH$_2$CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 173.6$, 153.0, 135.1, 132.0, 120.5, 73.3, 69.5, 66.4, 51.1, 31.1, 21.7, 15.3; HRMS calcd for $C_{56}H_{81}O_{12}N_8$ [M+H$^+$] 1057.5974, found 1057.5983.
   5,11,17,23-Tetrakis(dansyl-L-alanylamino)-25,26,27,28-tetra(2-ethoxyethoxy)calix[4]arene (**4**). To a solution of **3** (0.136 g, 0.129 mmol) and Et_3N (0.087 mL, 0.618 mmol) in dry CH_2Cl_2 (8 mL) was added dansyl chloride (0.167 g, 0.618 mmol) in dry CH_2Cl_2 (8 mL). The mixture was stirred at rt for 8 h. After evaporation of the solvent in vacuo, the residue was chromatographed (CH_2Cl_2/acetone, 4:1, v/v) to give a bright yellow product in 60% yield. Mp: 156–157 °C; $[\alpha]_D^{25}$ −25.6 (*c* 0.5, acetone); ^{1}H NMR (300 MHz, DMSO-d_6): $\delta = 9.46$ (s, 4H, N*H*), 8.39 (d, $J = 8.62$ Hz, 4H, Ar*H*), 8.36 (s, 4H, SO_2N*H*), 8.33 (d, $J = 8.50$ Hz, 4H, Ar*H*), 8.14 (d, $J = 6.47$ Hz, 4H, Ar*H*), 7.60 (t, $J = 7.85$ Hz, 4H, Ar*H*), 7.55 (t, $J = 8.32$ Hz, 4H, Ar*H*), 7.25 (d, $J = 7.54$ Hz, 4H, Ar*H*), 6.92 and 6.58 (2s, 4H each, Ar*H*), 4.38 (d, $J = 13.43$ Hz, 4H, H_{ax} of ArCH_2Ar), 4.01 (t, $J = 5.1$ Hz, 8H, OCH_2CH$_2$O), 3.80–3.85 (m, 12H, C*H*CH$_3$, OCH$_2$CH_2O), 3.50 (q, $J = 7.14$ Hz, 8H, CH_2CH$_3$), 2.98 (d, $J = 13.27$ Hz, 4H, H_{eq} of ArCH_2Ar), 2.79 (s, 24H, N(CH_3)$_2$), 1.15 (t, $J = 6.93$ Hz, 12H, CH$_2$CH_3), 1.00 (d, $J = 6.91$ Hz, 12H, CHCH_3); ^{13}C NMR (75 MHz, acetone-d_6): $\delta = 169.5$, 152.5, 151.9, 135.7, 134.6, 132.4, 130.2, 129.7, 129.5, 129.2, 128.3, 123.3, 119.9, 119.2, 115.2, 73.5, 69.4, 65.9, 53.0, 44.7, 30.8, 18.5, 14.9; MALDI-TOF MS: $m/z = 2012$ (M^++Na); 2028.9 (M^++K); Anal. Calcd for $C_{104}H_{124}O_{20}$ $N_{12}S_4 2H_2O$: C, 61.64; H, 6.37; N, 8.29; S, 6.33; Found: C, 61.53; H, 6.34; N, 8.19; S, 6.28.
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