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Pyrrole-Strapped Calix[4]pyrroles Bearing Pyrene Moiety: Synthesis and Anion Binding Property

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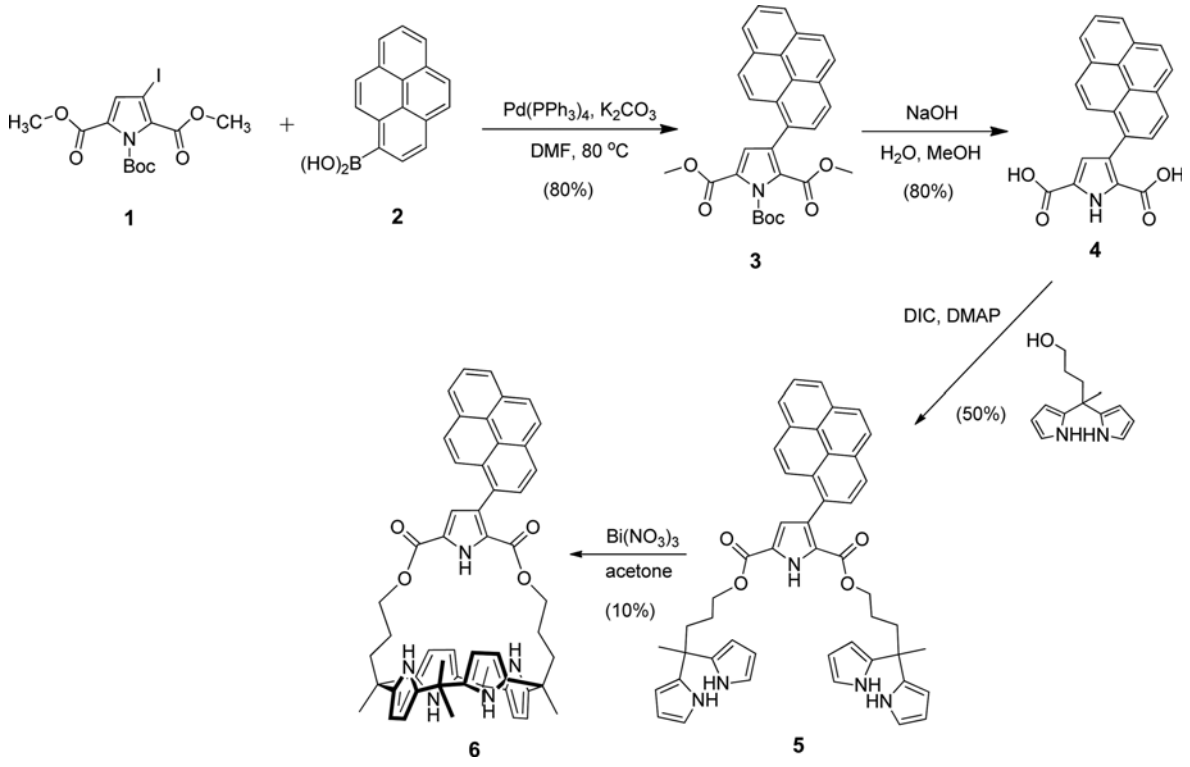
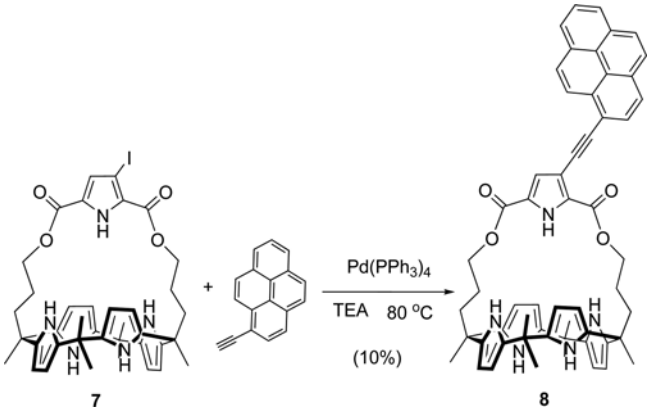
The design and synthesis of neutral anion receptors with high affinity and selectivity for a variety of analyte anions have been a big challenge in supramolecular chemistry. The use of hydrogen bonding interactions as recognition motifs for specific anions has been studied extensively because of the key role of anions in biology as well as in environmental concern.[1] Application of anion receptors in various fileds including ion selective electrodes, fluorescent chemosensors and electrochemical signaling devices, has been received particular interest in recent years.[2-5] Although hydrogen bonding is weak, non-covalent interactions that are strongly affected by both pH and solvent, they are commonly used as the driving force in anion recognition. However, the effective design of anion receptors is still challenging compared with those of cation receptors. Among the various neutral anion receptors, calix[4]pyrroles have proved as versatile hosts for anions especially for halide anions. We have reported strapped calix[4]pyrroles as new homologues for anion-binding and ion-pair recognition motifs.[6,7] The calix[4]-pyrroles bearing diametrically crossing strap showed enhanced affinity and selectivity compred with those of unstrapped compounds.

As part of our ongoing efforts to develop versatile receptors based on the strapped calix[4]pyrroles, we herein report the first example of a new class of calix[4]pyrroles, **6** and **8**, bearing fluorescence probe on the strapping element. Since the pyrrole N-H on the strap participates in the anion recognition, it is expected that the fluorescence of the pyrene moiety changes upon guest binding. The system that bearing directly attached fluorophore **6** is expected to display different fluorescence property from the system **8** bearing tripple bond between recognition site and probe site.

Compound **3** was synthesized in high yield by coupling reaction of compound **1** and **2** as shown in Scheme 1. Base-



Scheme 1. Synthesis of fluorophore-attached, strapped calix[4]pyrrole **6**.



Scheme 2. Synthesis of compound **8**.

catalyzed hydrolysis of ester **3** afforded compound **4** which is followed by esterification with *meso*-(3'-hydroxyprophyl-methyl)dipyrromethane afforded desired bis-dipyrromethane **5** in 50% yield.[8] Lewis acid catalyzed condensation of compound **5** with acetone gave the desired receptor **6** in 10% yield. The acid catalyzed condensation of bis-ketone **4** with pyrrole afforded bis-dipyrromethane **5** in 52% yield. The triple bond separated model **8** was synthsized by Sono-gashira coupling of β-iodopyrrole with pyrenyl acetylene in 10% yield as shwon in Scheme 2.[9]

It was also anticipated that the more acidic pyrrole N-H on the strap participate in the recognition event. So, the ability to bind anion was tested in CD_2Cl_2 by proton NMR spectro-scopy as shown in Figure 1. Inspection of these figures reveals that the complexation is slow exchanging system. The both of the two sets of the pyrrole N-Hs shifted to down field indicating typical anion binding to the cavity. The calix[4]pyrrole N-Hs were shifted from 7.25 ppm to 11.13 ppm and 9.85 ppm to 13.18 ppm respectively upon addition of ~1.0 equiv of TBACl.

Concomittently, the β-pyrrolic protons were shifted to up-field. These observation are similar to the results obtained previously with simple diester-strapped system.[10] The results also indicate that the binding stoichiometry is 1/1 and the chloride anion bind to the cavity generated by calix[4]-pyrrole and the strapping element.

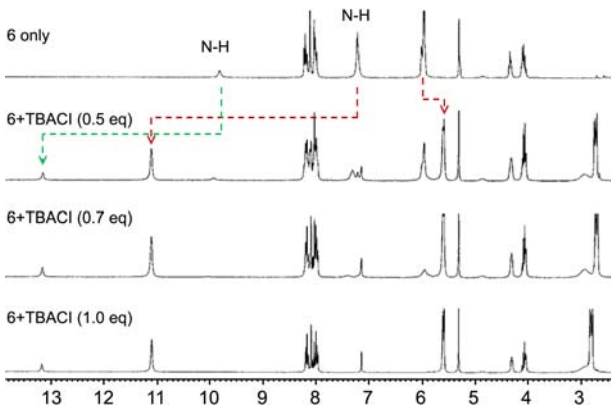


Figure 1. ^{1}H NMR titration of receptor **6** with Cl^- (as its tetrabutyl ammonium salt) in CD_2Cl_2.

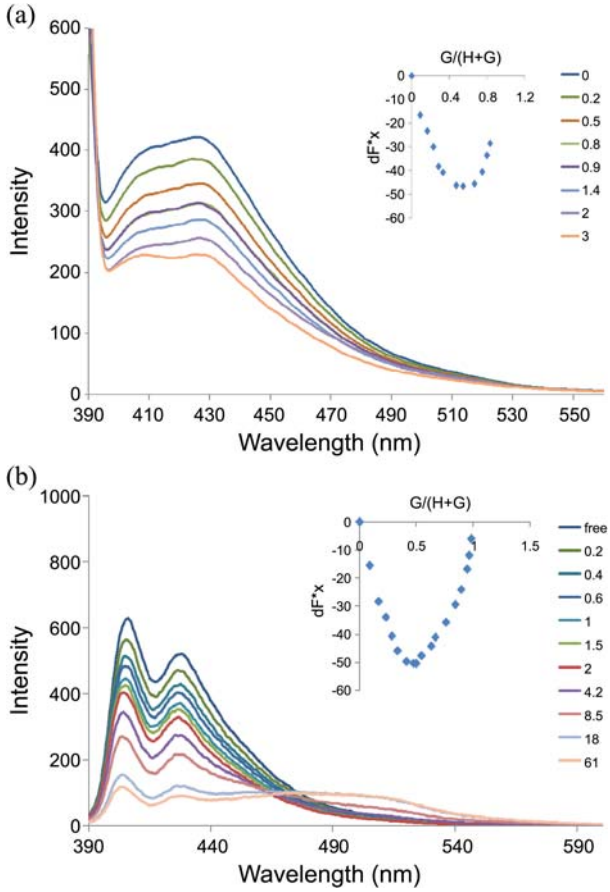


Figure 2. Fluorescence spectral changes of receptor **6** (a) and receptor **8** (b) upon titration with F^- (as its tetrabutyl ammonium salt) in 5% acetonitrile in toluene (λ_{ex} = 350 nm). [**6**] = [**8**] = 2.30 × 10^{-6} M.

Since the proton NMR analysis indicates the binding of anion to the cavity, we tested the fluorescence changes of pyrenyl moiety upon anion binding. The N-H-anion hydro-gen bonding eventually would modulate the fluorescence of pyrene. Figure 2 shows the fluorescence titration of receptor **6** and **8** with fluoride anion in 5% acetonitrile in toluene.

The fluorescence spectra of both receptor **6** and **8** display a typical monomeric emission and show anion-dependent quenching of the fluorescence. The quenching must be as-sociated with increased electron density in the pyrrole and related with weak PET process. As expected, the calculated binding constants from the titration shown in Figure 2, were

Table 1. Association constants for various anions obtained from the fluorescence titration

Anion	Receptor **6**	Receptor **8**
	K (M^{-1})	K (M^{-1})
F^-	3.0 × 10^6	2.7 × 10^6
Cl^-	4.9 × 10^6	4.6 × 10^6
AcO^-	2.8 × 10^6	NA
$H_2PO_4^-$	3.4 × 10^5	NA

found to be 2.7×10^6 M^{-1} for **6** and 3.0×10^6 M^{-1} for **8**, respectively. Repeated titration with Cl^- also shows similar but slightly larger affinity (4.9×10^6 M^{-1} for **6** and 4.9×10^6 M^{-1} for **8** as shown in Table 1. Other anions such as AcO^- and $H_2PO_4^-$ also show slow complexation/decomplexation kinetics with relatively higher affinity (2.8×10^6 M^{-1} and 3.4×10^5 M^{-1} respectively measured with the receptor **6** but less than those of chloride anion. Both of the receptors either bearing directly attached signalling unit or the dimensionally separated system show similar fluorescence property.

In summary, we have successfully synthesized a new strapped calix[4]pyrrole derivatives bearing fluorophore at the strapping element. The synthesized receptors strongly bind with halide anion and the binding event can be monitored by fluorescence changes of the fluorophore. Current receptor systems shows the rational approach for the designer receptors that combined with fluorogenic signaling unit. The approach detailed here could provide a useful complementary tool for modulation of detection methods.

Experimental

^{1}H NMR, ^{13}C NMR spectra (300 or 400 MHz) were recorded using TMS as the internal standard. Fluorescence titration studies were carried out at 298 K. Toluene solutions of the receptor or substrate were titrated by adding known quantities of a concentrated solution of the corresponding substrate or receptor. The data were fitted to a 1:1 receptor-to-substrate binding profile according to the method of Oster[11] using changes in the emission. Job plots were obtained using emission spectra that spectra were recorded on a Perkin Elmer LS-55B at 298 K. All reagents were obtained from Aldrich or TCI used as received unless noted otherwise. The precursor of the compound **1** was synthesized by reported procedure[10] and compound **2** was purchased from Aldrich.

1-Tert-butyl 2,5-Dimethyl 3-Iodo-1*H*-pyrrole-1,2,5-tricarboxylate 1. Iodine (0.47 g, 1.84 mmol) and bis(trifluoacetoxy)iodobenzene (0.79 g, 1.84 mmol) was added to a solution of compound **9** (1 g, 3.53 mmol) in dichloromethane (11 mL). The mixture was stirred for 24 h at 25 ºC. Then saturated $Na_2S_2O_3$ (10 mL) was added, and the reaction mixture was then diluted with diethyl ether (30 mL). The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica column chromatography (dichloromethane) to obtain 0.92 g of **1** (65%), ^{1}H NMR ($CDCl_3$) δ 7.04 (s, 1H, pyrrole β-H), 3.91 (s, 3H, OCH_3), 3.86 (s, 3H, OCH_3), 1.64 (s, 9H, CH_3).

Compound 3. $Pd(PPh_3)_4$ (0.29 g, 0.25 mmol) and K_2CO_3 (1.26 g, 9,13 mmol) was added to a solution of compound **1** (2.08 g, 5.07 mmol) in dimethylformamide (100 mL) at 80 °C under nitrogen. Then compound **2** (1.0 g, 4.06 mmol) was added, and the whole mixture was stirred for 24 h at 80 °C under nitrogen. The mixture was then poured into water, the phases were separated and the aqueous phase was extracted with dichloromethane. The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica column chromatography (dichloromethane) to obtain 2.0 g of **3** (81%), ^{1}H NMR ($CDCl_3$) δ 7.99 (m, 9H, pyrene-H), 6.97 (s, 1H, pyrrole β-H), 3.87 (s, 3H, OCH_3), 3.32 (s, 3H, OCH_3), 1.66 (s, 9H, CH_3). ^{13}C NMR ($CDCl_3$) δ 160.77, 149.31, 131.75, 124.49, 119.70, 86.94, 52.58, 27.82.

Compound 4. NaOH (0.89 g, 20.0 mmol) was added to a solution of compound **3** (2.0 g, 4.1 mmol) in H_2O/MeOH (50 mL/10 mL). The mixture was then slowly heated to boiling (80 °C), refluxed for 20 h, and then cooled to room temperature. The basic solution was acified with 3 *N* HCl (until pH = 1). Upon cooling, the product was precipitated and filtered to yield compound **4** of 1.14 g (80%). ^{1}H NMR (DMSO-d_6) δ 12.63 (br s, 2H, COOH), 12.4 (br. s, 1H, NH), 8.13(m, 9H, pyrene-H), 6.92 (s, 1H, pyrrole β-H).

Compound 5. *N,N'*-Diisopropyl carbodiimide (0.67 g, 5.32 mmol) and 4-dimethylaminopyridine (65 mg, 0.53 mmol) was added to a solution of compound **4** (0.47 g, 1.33 mmol) in dichloromethane (50 mL). Then, the compound **10** (1.16 g, 5.32 mmol) was added, and the reaction mixture was stirred for 8 h at room temperature. The mixture was then poured into water, the phases were separated and the aqueous phase was extracted with dichloromethane. The organic layer was dried over anhyd. Na_2SO_4, filtered and evaporated. The residue was purified by silica column chromatography (EtOAc/hexane = 1/1.5) to obtain 0.50 g of **5** (50%). ^{1}H NMR ($CDCl_3$) δ 10.26 (br s, 1H, NH), 8.05 (m, 9H, pyrene-H), 7.61 (br. s, 2H, NH), 7.23 (br s, 1H, NH), 7.21 (s, 1H, pyrrole β-H), 7.02 (br s, 1H, NH) 6.49 (s, 2H, pyrrole α-H), 6.21 (s, 1H, pyrrole β-H), 6.07 (s, 4H, pyrrole β-H), 5.95 (s, 1H, pyrrole β-H), 5.83 (d, 2H, pyrrole β-H), 4.26 (t, 2H, OCH_2), 3.79 (t, 2H, OCH_2), 2.03 (m, 2H, CH_2), 1.63 (m, 2H, CH_2), 1.53 (s, 3H, CH_3), 1.10 (br s, 2H, CH_2), 0.88 (s, 3H, CH_3), 0.68 (br s, 2H, CH_2); MALDI-TOF Calcd for $C_{48}H_{45}N_5O_4$755.902, Found 755.35 (M), 756.35 (M+1), 757.35 (M+2).

Compound 6. To a solution of compound **5** (0.38 g, 0.50 mmol) in acetone (100 mL) was added $Bi(NO_3)_3$ (97 mg, 0.20 mmol). The resulting mixture was stirred for 2 h at r.t. and then TEA (1.2 mL) added and the solvent was removed under reduced pressure. The residue was purified by silica column chromatography (dichloromethane), yielding 41 mg of **6** (10%), ^{1}H NMR (CD_2Cl_2) δ 9.91 (br s, 1H, NH), 8.13 (m, 9H, pyrene-H), 7.32 (br s, 4H, NH), 7.21 (s, 1H, pyrrolic β-H), 6.02 (s, 2H, pyrrolic β-H), 5.91 (s, 6H, pyrrolic β-H), 4.26 (t, 2H, OCH_2), 4.07 (t, 2H, OCH_2), 2.00 (m, 4H, CH_2), 1.83-1.58 (m, 4H, CH_2), 1.53-1.22 (s, 18H, CH_3) ^{13}C NMR ($CDCl_3$) β 160.90, 137.88, 131.71-124.76, 119.03, 117.69, 108.18, 105.23, 65.83, 53.89, 39.20-37.13, 26.62-23.61.

Compound 8. $Pd(PPh_3)_4$ (16 mg, 0.014 mmol) and TEA (18 mg, 0.18 mmol) was added to a solution of compound **7** (70 mg, 0.09 mmol) in dimethylformamide (10 mL) at 80 °C under nitrogen. 1-Ethynyl Pyrene (17 mg, 0.07 mmol) was added, and the reaction mixture was stirred for 24 h at 80 °C under nitrogen. The mixture was poured into water, the phases were separated and the aqueous phase was extracted with dichloromethane. The organic layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by silica column chromatography (dichloromethane) to

obtain 9 mg of **8** (11%), ^{1}H NMR ($CDCl_3$) δ 9.51 (br. s, 1H, NH), 8.11 (m, 9H, pyrene-H), 7.35 (s, 1H, pyrrole β-H), 7.23 (br. s, 4H, NH), 5.96 (s, 8H, pyrrole β-H), 4.39 (t, 2H, OCH_2), 4.31 (t, 2H, OCH_2), 2.04-1.51 (m, 8H, CH_2), 1.51-1.22 (s, 18H, CH_3).

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