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Strapped-calix[4]pyrroles Bearing Acridine Moiety

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Calix[4]pyrrole bearing 5-aryl acridine-derived straps on one side of the tetrapyrrolic core have been synthesized and characterized. The solution state binding studies of the synthesized hosts were investigated by proton NMR spectroscopy and Isothermal Titration Calorimetry (ITC) in acetonitrile. The system displayed enhanced affinities for chloride and bromide anion with high selectivity and the inner aryl *C—H* of the strap served as a C—*H* hydrogen bond donor site. The fluorescence measurement indicated that the incorporated acridine moiety has minimal interaction with the anion binding event.

Keywords: Strapped-calix[4]pyrrole; Anion binding; Acridine; Fluorophore

INTRODUCTION

The synthesis of anion receptors possessing high affinity and adequate selectivity for various targeted substrates is an ongoing challenge in the area of supramolecular chemistry due to their important roles in biological systems [1–3]. A few inherent properties of anions, such as low charge density and variety in geometry, make the proper design and synthesis of anion receptors even more challenging. Among the various neutral anion receptors reported, calix[4]pyrroles possess several attributes that make them attractive. They are, for instance, easily synthesized in a single step from acid catalyzed condensation of pyrrole and acetone and have been demonstrated to bind with various anions including halides, acetate and phosphate anion in organic media. Various modification of either β-pyrrolic or *meso*-positions have been performed in order to achieve improved binding properties of calix[4] pyrroles [4–10]. More recently, the systems bearing a diametrical strap on one side of the calix[4]pyrrole have been synthesized and the solution state binding studies showed larger enhancement in affinity and selectivity compare to the normal calix[4]pyrroles [11–14]. Unlike simple calix[4]pyrrole, the strapped systems did not show any counter cation effect due to strong affinity between host and anion [15–18]. The observed affinities were superior to the previous modified calix[4]pyrrole systems, such as deep cavity or β-pyrrolic functionalization of calix[4]pyrroles even in polar DMSO solvent. These results indicate that the desired affinity could be achieved by pre-organizing the binding domain of calix[4] pyrroles. Thus, introduction of built-in chromogenic reporter groups in the calix[4]pyrrole associated with pre-organization would be ideal for selective sensing and detection of anions. Such systems would allow the detection of analytes via direct colorimetric or fluorometric means with higher affinity. Since the fluorescence sensors are useful detection methods for biomolecules, development of fluorescence anion sensors based on calixpyrroles would be worthwhile. Based on these considerations, we have now reported strapped calix[4]pyrrole systems bearing fluorogenic reporter groups such as acridine. Here, we report the synthesis of anion receptors based on the strapped calix[4]pyrrole bearing acridine as fluorogenic moiety.

RESULTS AND DISCUSSIONS

Unlike the other calixpyrrole-based systems reported, the current systems consist of fluorogenic sites for sensing application. Also reported are some preliminary results of the solution phase anion binding characteristics of the synthesized system.

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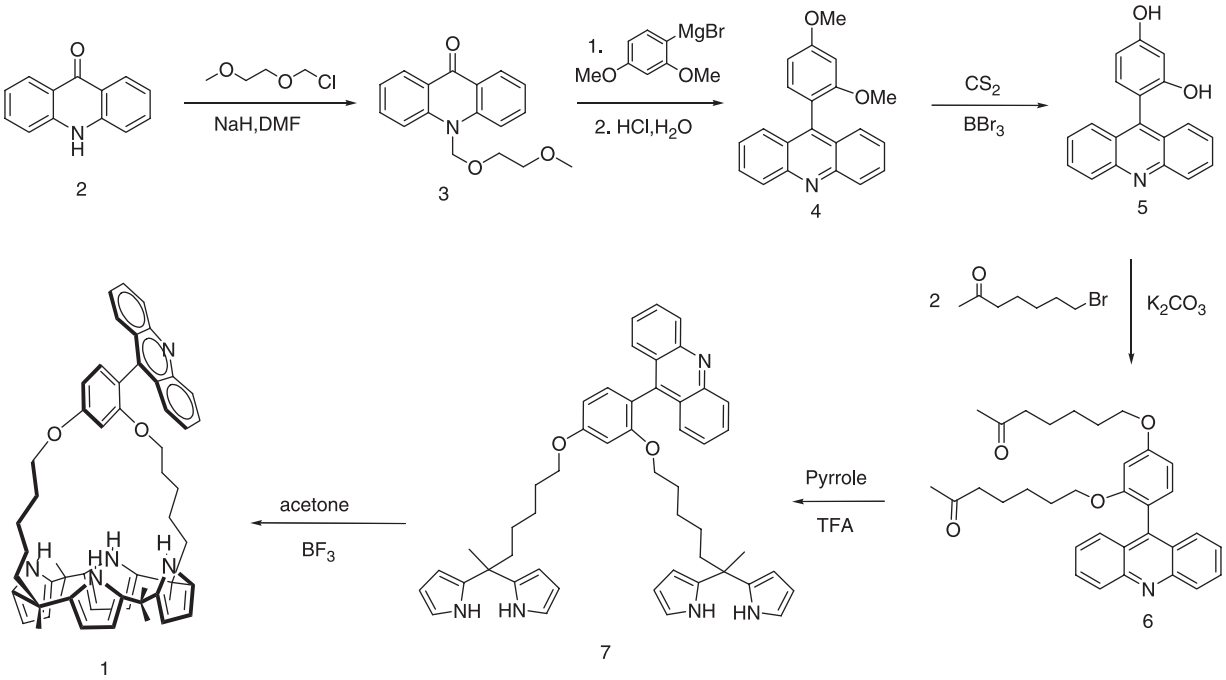
The key part in the design of new receptors is introduction of a flexible strap bearing fluorogenic group to the normal calix[4]pyrrole base. The diametrically placed strap on one side of the calix[4]pyrrole-base possesses the reporter group directly connected to the central aromatic which is interacting with the bound anion [12–14]. Since modulation of binding affinity is closely related with manipulation of binding domain, the system designed here, could provide the fundamental insights into the interplay between chromophore and anion binding event leading eventually to the sensing applications. Since the fluorescence probes are widely used in biological assay [19], combination of anion binding events with fluorescence changes would be interesting motifs for sensing applications. The acridine-attached system **1** was synthesized as described in Scheme 1. 9-Acridone **2** was protected with MEM-chloride to afford **3** and then reaction with 2,4-dimethoxyphenyl magnesium bromide followed by acidic workup afforded new acridine derivative **4** in 44% yield [20]. Cleavage of phenolic ether gave compound **5**, which is then reacted with two equivalents of 7-bromo-2-heptanone to give **6** [21]. Acid catalyzed condensation of **6** with pyrrole afforded bis-dipyrromethane derivative **7** in high yield. Finally, **7** was condensed and cyclized in neat acetone to give the desired receptor **1** in 12% yield. The structure of **1** was characterized by ^{1}H NMR, ^{13}C NMR and high resolution mass spectrometry. Compound **1** showed absorption at $\lambda_{max} = 358$ nm and emission at 462 nm (Scheme 1).

Preliminary anion binding properties of systems **1** was carried out in chloroform-*d* using proton NMR spectroscopy. The results indicated high affinity and slow complexation/decomplexation kinetics and thus quantitative anion affinities could not be made by proton NMR spectroscopy. However, the studies provided good qualitative evidence for halide anion binding. For example, as shown in Fig. 1, titration of receptor **1** with chloride anion studied in the form of its tetrabutylammonium salt gave rise to a new set of signals by adding one equivalent of chloride anion indicating 1/1 binding stoichiometry. The typical changes of the signals during the titration include the following: The pyrrole N—H protons appeared originally at 6.92 ppm and 7.04 ppm in the absence of chloride anion were shifted to 11.51 ppm in the presence of chloride anion. The central single aromatic C—H proton shown at 6.71 ppm was shifted to 7.91 ppm. The β-pyrrolic proton on the other hand, originally appearing at 5.90–6.00 ppm, was found to be shifted to 5.52–5.60 ppm as expected. The fact that the acridine protons remained almost unchanged throughout the titration, indicates the minimal interaction between acridine moiety and central phenyl group. Quantitative analyses of the solution phase anion binding properties were made using isothermal titration calorimetery (ITC).

The association constant obtained from ITC measurement in CH_3CN (dry) at 30°C for the formation of [**1**·Cl^-] complex was $2.41 \times 10^7\,M^{-1}$ and for the formation of [**1**·Br^-] was $6.81 \times 10^4\,M^{-1}$ as shown in Fig. 2.



SCHEME 1

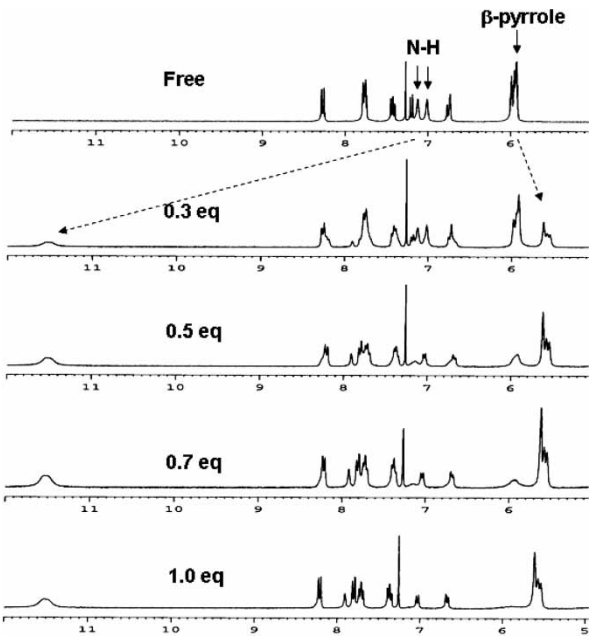


FIGURE 1 ^{1}H NMR spectral changes upon the addition of Cl^- (as its tetrabutylammonium salt) to the $CDCl_3$ solutions of **1** (1.2×10^{-3} M).

Thus, the receptor **1** showed a selectivity factor of ~350 for chloride/bromide anion. Attempted measurements in the change of the fluorescence emission associated with anion binding were not successful due to inconsistent small changes of spectral intensity during titration. Presumably this is due to either the weak interactions between attached fluorophore and the binding event or intermolecular energy quenching by $\tilde{\pi}-\tilde{\pi}$ stacking interaction. The orthogonal conformation between acridine and phenyl moiety may be part of the reason.

In summary, we have shown that the strapped calix[4]pyrrole, bearing an acridine functional group, show high affinity for the chloride anion. The current system did show appreciable selectivity for chloride over bromide anion. Also attractive is the use of modified strapped systems to create clefts that might allow for the specific targeting of non-spherical anions such as, e.g., oxalate or pyrophosphate, that have obvious biological importance. Work along these lines is currently in progress.

EXPERIMENTAL

Proton NMR spectra (400 MHz, Bruker DPX-400) were recorded using TMS as the internal standard. High and low resolution FAB mass spectra were obtained on an AUTO SPEC M-363 high-resolution mass spectrometer. Column chromatography was performed over silica gel (Merck, 230–400 mesh). Pyrrole was distilled at atmospheric pressure from CaH_2. All other reagents were obtained from Aldrich and used as received unless noted otherwise. Compounds (**2**), (**3**) and (**4**) were synthesized according to the literature procedure [20]. Isothermal titration calorimetery (ITC) measurements were performed as follows: Solutions of the chosen receptor in rigorously dry acetonitrile were made up so as to provide a receptor concentration range of ~1.0 mM. These solutions were then individually titrated with the appropriate alkylammonium salts at 30 ± 0.01°C. The original heat pulses were normalized using reference titrations carried out using the same salt solution but pure solvent, as opposed to a solution containing the receptor.

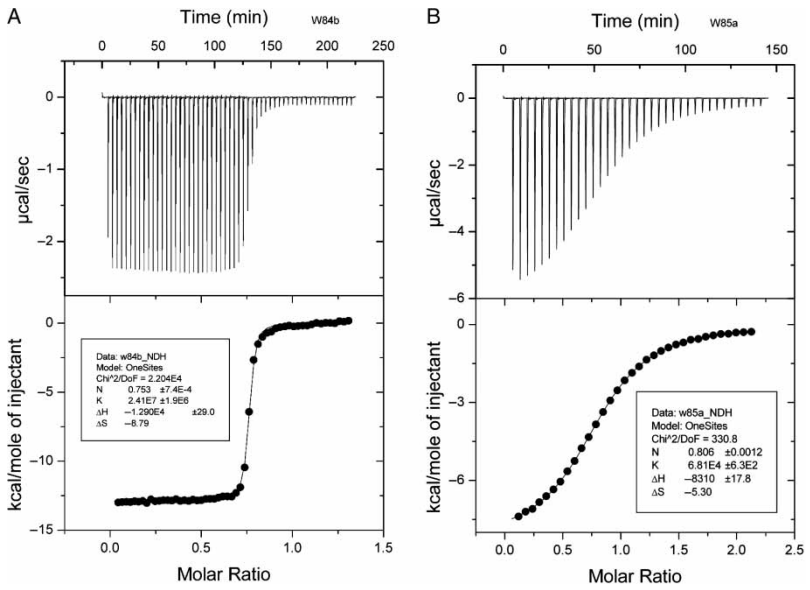


FIGURE 2 ITC traces of the titration of **1** (1.3 mM) with chloride anion (a) and bromide anion (b) (as their TBA salt) in dry acetonitrile at 293 K.

4-Acridin-9-yl-benzene-1,3-diol (5)

9-(2,4-Dimethoxy-phenyl)-acridine (**4**) (0.49 g, 1.55 mmol) was dissolved in dry CH_2Cl_2 (100 mL) with stirring. The mixture was cooled to 0°C, then BBr_3 (1 M solution in CH_2Cl_2, 6.8 mL) was added dropwise. The whole mixture was stirred for 24 hr at room temperature. The mixture was washed with water, organic layer was dried (Na_2SO_4) and solvent was removed *in vacuo*. The remaining solid was pure enough to carry out the next step without further purification. ^{1}H NMR (methanol-d_4) δ 6.63–6.67 (m, 2H, Ar-H), 7.14–7.16 (m, 1H, Ar-H), 7.39–7.42 (m, 2H, Ar-H), 7.67–7.69 (m, 2H, Ar-H), 7.73–7.77 (m, 2H, Ar-H), 8.25–8.27 (m, 2H, Ar-H); ^{13}C NMR (methanol-d_4) δ 163.09, 162.57, 157.90, 141.35, 138.92, 133.89, 130.95, 129.18, 127.84, 120.96, 112.83, 109.15, 104.46; EI-MS Calcd for $C_{19}H_{13}NO_2$ 287.09, Found 287.10.

6-[4-Acridin-9-yl-3-(5-oxo-hexyloxy)-phenoxy]-hexan-2-one (6)

4-Acridin-9-yl-benzene-1,3-diol (**5**) (0.2 g, 0.71 mmol) was dissolved in DMF (20 mL) and K_2CO_3 (0.98 g, 7.1 mmol) was added with stirring. The mixture was stirred for 15 min at 60°C. Then, 6-bromohexan-2-one (0.51 g, 2.84 mmol) was added and the whole mixture was stirred for 24 hr at 60°C. The mixture was then combined with water (50 mL) and extracted with CH_2Cl_2. The organic layer was washed with water, dried (anhyd. Na_2SO_4) and solvent was removed *in vacuo*. The resulting solid was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc = 7/3). Yield 200 mg (58%); ^{1}H NMR ($CDCl_3$) δ 1.04–1.07 (m, 2H, CH_2), 1.24–1.29 (m, 2H, CH_2), 1.73 (s, 3H, CH_3), 1.82–1.88 (m, 6H, CH_2), 2.20 (s, 3H, CH_3), 2.57–2.61 (t, $J = 6.75$ Hz, 2H, CH_2), 3.80–3.84 (m, 2H, CH_2), 4.09–4.15 (m. 2H, CH_2), 6.67–6.70 (m, 2H, Ar-H), 7.13–7.17 (m, 1H, Ar-H), 7.39–7.43 (m, 2H, Ar-H), 7.69–7.71 (m, 2H, Ar-H), 7.73–7.77 (m, 2H, Ar-H), 8.24–8.27 (m, 2H, Ar-H); ^{13}C NMR ($CDCi_3$) δ 213.17, 208.75, 160.88, 157.76, 132.36, 130.01, 129.34, 127.18, 125.93, 125.29, 105.37, 100.16, 68.15, 67.82, 43.27, 42.77, 30.01, 29.40, 28.78, 28.01, 20.49, 20.25.; FAB-MS Calcd for $C_{31}H_{33}NO_4$ 483.24, Found 484.28.

Compound (7)

6-[4-Acridin-9-yl-3-(5-oxo-hexyloxy)-phenoxy]-hexan-2-one (**6**) (156 mg, 0.323 mmol) was dissolved in pyrrole (2 mL, 28.83 mmol) and trifluoroacetic acid (25 μL, 0.33 mmol) was added. The mixture was stirred for 26 hr at 60°C. The mixture then was combined with aqueous NaOH (30 mL, 0.1 N) and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and the solvent was removed *in vacuo*. The resulting solid was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc = 8/2) to afford a viscous solid. Yield 95 mg (41%); ^{1}H NMR ($CDCl_3$) δ 0.72–0.74 (m, 2H, CH_2), 1.17 (s, 3H, CH_3), 1.18–1.22 (m, 2H, CH_2), 1.44–1.48 (m, 2H, CH_2), 1.54–1.58 (m, 2H, CH_2), 1.65 (s, 3H, CH_3), 1.82–1.86 (m, 2H, CH_2), 2.08–2.12 (m. 2H, CH_2), 3.76 (t, 2H, CH_2), 4.04 (t, 2H, CH_2), 5.81–5.82 (m, 2H, pyrrole-H), 6.02–6.04 (m, 2H, pyrrole- H), 6.12–6.16 (m, 4H, pyrrole-H), 6.51–6.53 (m, 2H, pyrrole-H), 6.62–6.65 (m, 2H, Ar-H), 6.65–6.66 (m, 2H, pyrrole-H), 7.10–7.13 (m, 1H, Ar-H), 7.36–7.40 (m, 2H, Ar-H), 7.53 (br s, 2H, pyrrole-NH), 7.67–7.69 (m, 2H, Ar-H), 7.72–7.76 (m, 2H, Ar-H), 7.81 (br s, 2H, pyrrole-NH), 8.24–8.26 (m, 2H, Ar-H). ^{13}C NMR ($CDCl_3$) δ 160.84, 157.80, 148.79, 145.13, 137.95, 137.78, 132.41, 129.83, 129.47, 128.90, 127.23, 126.02, 125.92, 125.16, 117.09, 117.04, 116.77, 107.79, 107.60, 105.34, 104.59, 104.36, 100.21, 68.24, 67.98, 41.00, 40.67, 39.14, 38.74, 29.69, 29.17, 26.35, 25.80, 21.22, 20.68. FAB-MS Calcd for $C_{47}H_{49}N_5O_2$ 715.39, Found 716.0.

Compound (1)

9-{2,4-Bis-[5,5-bis-(1H-pyrrol-2-yl)hexyloxy]phenyl} acridine (**7**) (77 mg, 0.11 mmol) was dissolved in acetone (25 mL) and $BF_3{\cdot}OEt_2$ (14 μL, 0.11 mmol) was added. The mixture was stirred for 6 hr at room temperature followed by addition of aqueous NaOH (0.1 N). The mixture was extracted with CH_2Cl_2 and the organic layer was dried (Na_2SO_4) and solvent was removed *in vacuo*. Resulting solid was purified by column chromatography on silica (CH_2Cl_2/EtOAc = 9/1) to afford pale yellow solid. Yield 10 mg (12%); ^{1}H NMR ($CDCl_3$) δ 1.15–1.19 (m, 2H, CH_2), 1.33–1.40 (m, 2H, CH_2), 1.42 (s, 3H, CH_3), 1.47–1.54 (m, 17H, CH_2 and CH_3), 1.77–1.86 (m, 4H, CH_2), 2.00–2.04 (m, 2H, CH_2), 3.72 (t. 2H, CH_2), 4.19 (t, 2H, CH_2), 5.90–5.95 (m, 6H, pyrrole-H), 5.97–6.00 (m, 2H, pyrrole-H), 6.70–6.71 (m, 1H, Ar-H), 6.72–6.76 (m, 1H, Ar-H), 6.91 (br s, 2H, pyrrole-NH), 7.04 (br s, 2H, pyrrole-NH), 7.18–7.20 (m, 1H, Ar-H), 7.39–7.43 (m, 2H, Ar-H), 7.62–7.77 (m, 4H, Ar-H), 8.25–8.27 (m, 2H, Ar-H). ^{13}C NMR δ 160.90, 158.34, 149.26, 138.59, 138.42, 136.59, 136.49, 133.32, 130.25, 129.94, 127.50, 126.32, 125.67, 118.16, 105.78, 104.87, 103.54, 103.51, 102.67, 68.29, 67.93, 41.26, 40.98, 39.88, 39.51, 35.92, 31.11, 29.98, 29.07, 28.97, 28.13, 28.04, 22.70, 21.26; FAB-MS Calcd for, $C_{53}H_{57}N_5O_2$ 795.45., Found 796.50.

CONCLUSIONS

We have synthesized a strapped calix[4]pyrrole bearing fluorogenic moiety. The system did show appreciable affinity for halide anions and show high selectivity for the chloride anion over bromide anion in organic solvent. The fluorometric changes associ-

ated with anion binding were minimal due to the diagonal arrangement of fluorophore and the interacting aromatic. Proper conjugation may be necessary to exhibit correlation between fluorescence changes and the anion binding event.

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