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A Calix[4]pyrrole Bearing a Quaternary Ammonium Group: A Fluoride-Selective Anion Receptor

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Abstract A calix[4]pyrrole (**1**) bearing a quaternary ammonium pendant *via* its meso phenoxy linker has been synthesized as the bromide salt form. It was revealed by ^{1}H NMR spectroscopic analyses performed in DMSO-d_6 that receptor **1** binds F^- with high affinity and selectivity over other halide anions. The binding of receptor **1**•Br^- with F^- and Cl^- takes place by anion metathesis with the anions including F^- and Cl^-.

Keywords Anion receptor, Fluoride, Selectivity, Anion metathesis, Calix[4]pyrrole

Introduction

With appreciation of critical roles played by the fluoride anion (F^-) in various environmental, biological, and chemical processes and its involvement in public health as well as in medicine, the fluoride anion has become a special target anion for selective recognition.[1-7] For instance, the fluoride anion has been employed in many countries as an additive to toothpaste and water supplies owing to its beneficial effects on dental health.[1,2] The fluoride anion was also reported to have potential use in the treatment of osteoporosis.[3-5] By contrast, high level of the fluoride anion existing in the environment and in drinking water have been suspected of causing several types of human pathologies including kidney failure, dental and skeletal fluorosis, neurological and metabolic dysfunctions, and osteoporosis.[6,7] Therefore, numerous efforts have been made to develop receptors capable of recognizing and detecting the fluoride anion with high affinity and selectivity.[8-13] However, the design of such a fluoride-selective receptor is challenging because of the small size, high charge density, and Lewis basicity of the fluoride anion as well as its strong tendency to form ion pairs with cations. To attain high affinity and selectivity for such a specific anion, the size matching between the receptor and the targeted anion and the preorganization and directions of its binding motifs are of critical importance. In addition, the structural rigidity and geometry of the receptor are crucial in attaining better anion selectivity.[14,15] The tendency of an anion to form a strong ion pair with a certain cation could be utilized for the construction of receptors selective for highly basic anions such as the fluoride anion. In this vein, a calix[4]pyrrole bearing a cationic functional group would be a strong candidate for a fluoride-selective anion receptor.[16,17] The calix[4]pyrrole unit with well-defined three dimensional geometry can act as a preorganized hydrogen bonding donor for anions while the appended cationic group could provide an additional motif for anion binding *via* electrostatic attraction between the unlike charges. Taking these

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into account, we designed and prepared calix[4]pyrrole **1** functionalized with a quaternary ammonium group at its meso-phenoxy group for selective recognition of the fluoride anion. Herein, we report the synthesis and detailed binding properties of the cationic calix[4]pyrrole (**1**) for halide anions (as their respective tetrabutyl-ammonium (TBA^+) salt forms) in DMSO-d_6.

Experimental Methods

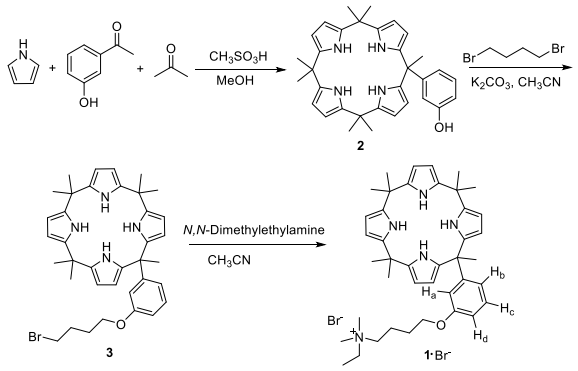
Solvents and reagents used for the synthetic work were purchased from Aldrich, TCI, or Alfa Aesar and used without further purification. Compounds **2** and **3** were prepared as reported previously.[18] NMR spectra were recorded on a Bruker Advance-300 MHz instrument. The NMR spectra were referenced to residual solvent peaks and the spectroscopic solvents were purchased from either Cambridge Isotope Laboratories or Aldrich. Fast atom bombardment (FAB) mass spectra (MS) were recorded on a JMS-700 (JEOL) spectrometer. TLC analyses were carried out using Sorbent Technologies silica gel (200 mm) sheets. Column chromatography was performed on Sorbent silica gel 60 (40–63 mm).

Synthesis of receptor 1•Br$^-$. A mixture of compound **3** (1.00 g, 1.56 mmol) and *N*,*N*-dimethylethylamine (2.28 g, 31.2 mmol) in acetonitrile was heated at reflux overnight and allowed to cool to room temperature. The resulting precipitate was collected by filtration to give receptor **1**•Br$^-$ in quantitative yield as a white solid: ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.53 (s, 2H, pyrrolic NH), 9.38 (s, 2H, pyrrolic NH), 7.17 (t, 1H, *J* = 7.9 Hz), 6.77 (d, 1H, *J* = 8.3 Hz), 6.40 (d, 1H, *J* = 8.3 Hz), 6.36 (s, 1H), 5.79–5.69 (m, 8H), 3.87 (t, 2H, *J* = 5.6 Hz), 3.27 (t, 2H, *J* = 5.6 Hz), 2.95 (s, 6H), 1.77-1.63 (m, 5H), 1.56 (s, 6H), 1.49 (s, 3H), 1.45-1.42 (m, 11H), 1.20 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR (75 MHz, DMSO) δ 140.7, 139.3, 114.0, 66.9, 62.5, 59.1, 49.9, 44.7, 35.1, 31.1, 26.2, 19.3, 8.3 ppm. HRMS (FAB) *m/z* 634.4479 $[M]^+$ calcd for $C_{41}H_{56}N_5O_1$, found 634.4502.

Results and Discussion

The Synthetic procedure for anion receptor **1** is shown in Scheme 1. Briefly, the condensation reaction of pyrrole with acetone and 3-hydroxyaceophenone in the presence of methanesulfonic acid as a catalyst produced calix[4]pyrrole **2** having a phenol group at one of its meso-carbons.[18] Subsequently, the phenol hydroxy group of compound **2** was subject to the reaction with 1,4-dibromobutane using K_2CO_3 as a base to afford compound **3** bearing the 4-bromobutyl group.[18] Finally, the desired anion receptor (**1**) was synthesized as the bromide salt form in quantitative yield by refluxing the acetonitrile solution containing compound **3** with an excessive amount of *N*,*N*-dimethylethylamine. Receptor **1**•Br$^-$ was completely characterized by standard spectroscopic analysis including ^{1}H and ^{13}C NMR spectroscopy and high-resolution mass spectrometry (HRMS).

Scheme 1. Synthesis of receptor **1**•Br$^-$



The capability of receptor **1** to bind halide anions was evaluated by ^{1}H NMR spectroscopic analysis performed in DMSO-d_6. With no anions added, the pyrrolic NH proton signals of receptor **1** appear as two singlets at 9.33 ppm and 9.58 ppm, respectively, in DMSO-d_6 (Figure 1a). These chemical shifts are negligibly different from those of compound **3** having the neutral bromobutyl group instead of the quaternary ammonium bromide salt of receptor **1** (Figure 1b). This finding was taken as evidence that the bromide anion of receptor **1** is present outside its calix[4]pyrrole cavity (Figure 1). Upon treatment of receptor **1**•Br$^-$ with an excess quantity (>10 equiv) of halide anions such as F^-, Cl^-, Br^-, and I^- (as their

respective TBA^+ salt forms), only fluoride and chloride gave rise to appreciable ^1H NMR spectral changes consistent with anion binding (Figures 2). This finding proposed that receptor **1** is able to bind fluoride and chloride selectively among halide anions in DMSO.

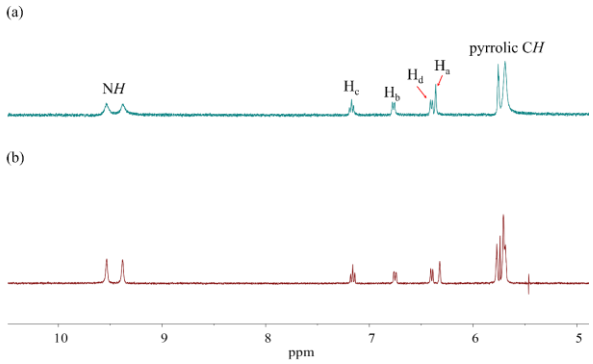


Figure 1. Partial ^1H NMR spectra of (a) receptor **1**•Br^- and (b) compound **3** recorded in DMSO-d_6.

To quantify the binding affinity of receptor **1** for fluoride and chloride, we carried out ^1H NMR spectroscopic titrations with the fluoride and chloride anions in DMSO-d_6 (Figures 3 and 4). Specifically, when receptor **1**•Br^- was titrated with the fluoride anion (as the TBA^+ salt) in DMSO-d_6, two sets of distinguishable resonances were seen for all observable proton signals in ^1H NMR spectra before saturation was achieved by the addition of 2.27 equiv of F^- (Figure 3). These peaks are ascribable to the original bromide salt form of receptor **1** and its fluoride complex formed *via* anion metathesis, respectively, suggesting that the binding/release equilibrium between receptor **1** and the fluoride anion is slow on the ^1H NMR time scale. This finding mirrors a strong binding interaction between the receptor and the fluoride anion. It was further supported by large chemical shift changes of the *β*-pyrrolic proton signals and, in particular, the NH proton resonances. Specifically, the two singlet peaks corresponding to the pyrrolic NH protons of receptor **1** undergo a significant downfield shift by $\Delta\delta \approx 3.0$ ppm upon its exposure to the fluoride anion (Figure 3). These large chemical shift changes are attributable to the hydrogen bonding interactions

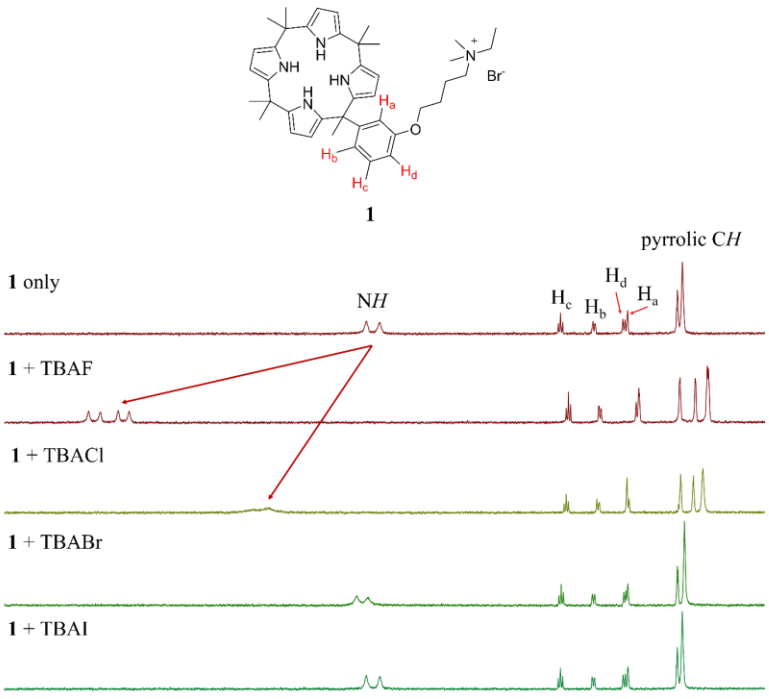


Figure 2. Partial ^1H NMR spectra of receptor **1**•Br^- (3 mM) recorded in DMSO-d_6 after adding ~10 equiv of the indicated anions as their TBA^+ (tetrabutylammonium) salts.

between the calix[4]pyrrole NHs of receptor **1** and the fluoride anion, which stands in sharp contrast to what was seen with the initial bromide salt form of receptor **1**. In addition, the singlets of the NH proton signals become split into two doublets (J = 41.1 Hz) because of strong coupling between the bound fluoride anion and the NH protons.[19] By contrast, the signals of the β-pyrrolic CH protons of receptor **1**•Br^- undergo upfield shift, a finding consistent with increased electron density of the pyrrole rings resulting from the formed hydrogen bonds between the calix[4]pyrrole NHs and the fluoride anion (Figure 3). The association constant (K_a) of receptor **1**•Br^- for F^- was estimated to be 1,987 M^{-1} from the ^{1}H NMR spectral titration (Figure 3 and Table 1).[19] Relatively small chemical shift changes took place when receptor **1**•Br^- was subjected to the titration with the chloride anion (as the TBA^+ salt) in DMSO-d_6. For instance, the proton signals corresponding to both the β-pyrrolic CHs and the meso-phenoxy CHs were gradually upfield-shifted in ^{1}H NMR spectra recorded during the titration of receptor **1**•Br^- with the chloride anion before saturation was reached upon the addition of ca. 5.00 equiv of the chloride anion. By contrast, the proton signals of the calix[4]pyrrole NHs experienced a downfield shift by $\Delta\delta \approx 1.2$ ppm suggesting that the chloride anion is also bound to the calix[4]pyrrole moiety *via* hydrogen bonds similarly as in the case of the fluoride anion (Figures 3 and 4). Compared with the fluoride anion, the chloride anion gave rise to relatively small chemical shift changes in receptor **1**•Br^- and more quantity of this anion was required to achieve saturation. These findings led us to conclude that receptor **1** binds the fluoride anion with high affinity and selectivity over the chloride anion. The association constant of receptor **1** for the chloride anion was approximated to K_a = 270 M^{-1} in DMSO from the ^{1}H NMR spectral changes shown in Figure 4 (Table 1).[20] By contrast, no appreciable chemical

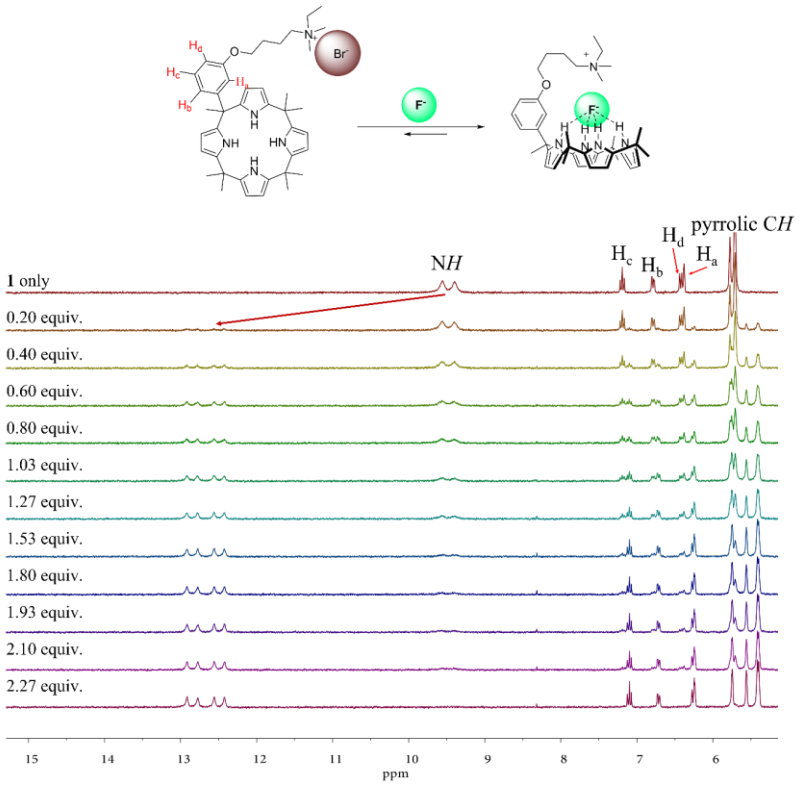


Figure 3. Bottom: Partial ^{1}H NMR spectra recorded during the titration of **1**•Br^- (3 mM) with F^- (as the TBA^+ salt form) in DMSO-d_6. Top: Putative binding mode of receptor **1**•Br^- for F^-.

shift changes were observed during the titrations of receptor **1**•Br^- with the bromide or iodide anions in DMSO. This finding suggested that receptor **1**•Br^- has little or no interactions with the bromide or iodide anion in DMSO.

In conclusion, a calix[4]pyrrole (**1**) with a quaternary ammonium arm has been synthesized as the bromide salt form. ^{1}H NMR spectroscopic analyses carried out in DMSO-d_6 revealed that receptor **1** is able to bind the fluoride anion with high affinity and selectivity in DMSO over other halide anions including Cl^-, Br^-, and I^-. In sharp contrast to what was seen with the bromide anion of the original salt form of receptor **1**, the fluoride and chloride anions proved to form hydrogen bonds with the calix[4]pyrrole NHs of receptor **1**.

Table 1. Association constants (K_a, M^{-1}) of receptors **1**•Br^- for halide anions estimated by ^{1}H NMR spectroscopic titrations in DMSO-d_6 at room temperature.

Anions[a]	Association constants (M^{-1})
F^-	1987 M^{-1}
Cl^-	270 M^{-1}
Br^-	-[b]
I-	-[b]

[a]All anions were used in the form of their respective tetrabutylammonium (TBA^+) salts. The K_a value was not determined due to too weak receptor-anion interactions.

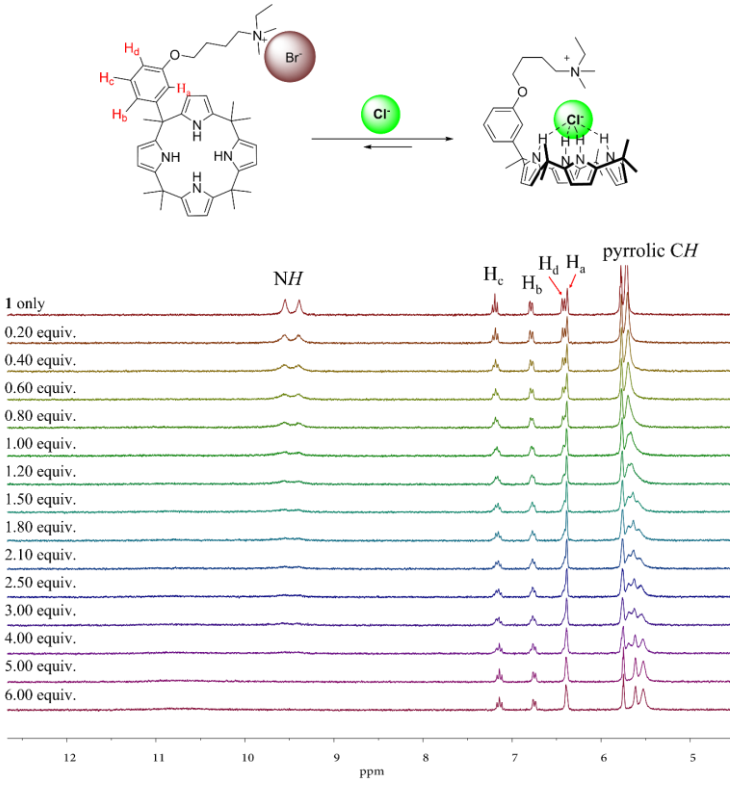


Figure 4. Bottom: Partial ^{1}H NMR spectra recorded during the titration of **1**•Br^- (3 mM) with Cl^- (as the TBA^+ salt form) in DMSO-d_6. Top: Putative binding mode of receptor **1**•Br^- for Cl^-.

Acknowledgements

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