ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 2958–2960

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A non-symmetric pillar[5]arene-based selective anion receptor for fluoride†

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Received 7th January 2012, Accepted 30th January 2012
DOI: 10.1039/c2cc00125j

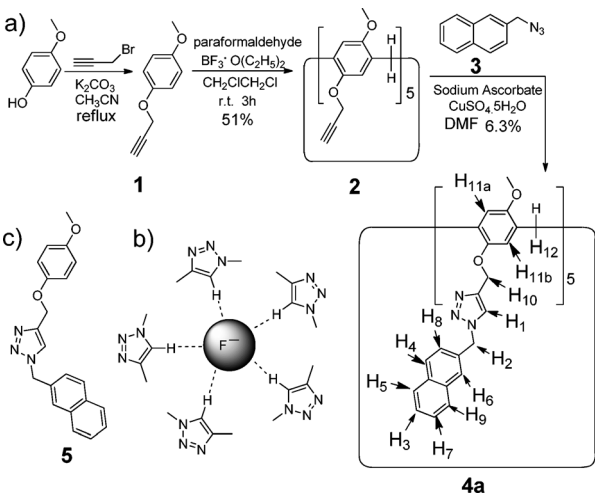
A novel non-symmetric pillar[5]arene-based anion receptor containing multiple triazole anion-binding sites was designed and synthesized. It has high affinity and selectivity for the fluoride anion.

Anions are associated with many biological, environmental, chemical, and pathological processes.[1] In recent years, a great number of artificial compounds that are able to bind anions with high affinity and/or selectivity have been reported.[2] These receptors are often constructed from a combination of strong hydrogen-bonding donors,[3] positively charged moieties,[4a] and Lewis acid metal ions.[4b] Among anions, the fluoride anion (F^-) is of particular interest owing to its important role in dental care and clinical treatment of osteoporosis.[5] Excess F^- in the body can result in gastric and kidney disorders, dental and skeletal fluorosis, urolithiasis, or even death.[6] Fluoride is the smallest anion with a high charge density and a hard Lewis basic nature, which result in its unusual chemical properties. Therefore, to design and synthesize novel receptors for F^- with high affinity and selectivity is a challenging mission for chemists.

Pillar[5]arenes[7] are a new type of macrocyclic hosts. Their repeating units are connected by methylene bridges at the *para*-positions, forming a unique pillar architecture, which is different from the basket-shaped structure of the *meta*-bridged calixarenes. The unique structure and easy functionalization of pillar[5]arenes afford them outstanding ability to selectively bind different kinds of guests and provide a useful platform for the construction of various receptors with different functions. However, although the complexation of pillar[5]arenes to cationic and neutral guests has been well studied, the binding of pillar[5]arenes to inorganic anions has not been explored yet.[7] Herein we want to report the design and preparation of a novel non-symmetric pillar[5]arene and its application in anion-binding. This non-symmetric pillar[5]arene is composed of the following three parts. First, the non-symmetric pillar[5]arene-based framework provides a rigid platform to connect binding sites for anions. Second, the triazole rings, which can be easily obtained through click chemistry, are sensitive to anions[8] because the electronegativities of the three nitrogen atoms combine to polarize the CH bond, and the lone pairs of electrons on the nitrogen atoms act to establish and orient along the CH–H-bond a large (5 D) dipole whose positive end points toward the H atom.[8b] Third, the naphthalene groups can be used as the fluorescent chromophores.

By condensation of **1** and paraformaldehyde with boron trifluoride diethyl etherate [$BF_3{\cdot}O(C_2H_5)_2$] as a catalyst, pillar[5]arene **2** was prepared. Compound **3**, which was obtained by treatment of 2-bromomethyl naphthalene with sodium azide in acetone/water (10 : 1) at 50 °C, reacted with **2** in the presence of $CuSO_4{\cdot}5H_2O$ and sodium ascorbate in DMF at 90 °C to afford four constitutional isomers **4a**, **4b**, **4c** and **4d** (Scheme 1a and ESI†),[7h] among which only the spectrum of **4a** was analyzable. The overlap of peaks in the spectra of the other isomers makes it impossible to assign these spectra. Given the rigid pillar structure and size of the pillar[5]arene cavity, five triazole rings on one side of **4a** may interact with anions *via* hydrogen bonding interactions cooperatively[9] (Scheme 1b). Therefore, we thought that this fluorescent pillar[5]arene should be a good receptor for a special anion with high affinity and high selectivity, enabled by the size of the rigid pillar[5]arene cavity.

To determine the binding constants of **4a** to halide anions, fluorescence titration experiments were carried out with the concentration of **4a** kept constant at 1.50×10^{-4} M and that of tetrabutylammonium halides (TBAX) varied from 0 to 9.00×10^{-4} M at 25 °C. Addition of the fluoride anion to a solution of **4a** in acetone resulted in a substantial decrease in the intensity of the emission band at 381 nm (Fig. S7, ESI†).



Scheme 1 (a) Synthesis of fluorescent non-symmetric pillar[5]arene **4a**; (b) binding of the fluoride anion by multiple triazole groups of **4a**; (c) chemical structure of model compound **5**.

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† Electronic supplementary information (ESI) available: Synthetic procedures and characterizations. For ESI see DOI: 10.1039/c2cc00125j

Titration with the other halide anions only reduced the corresponding intensity a little even after the addition of 6 equiv of Cl^-, Br^-, or I^-. The association constants for F^-, Cl^-, Br^-, and I^- with **4a** were calculated to be (1.25 ± 0.08) × 10^4 M^{-1}, 858 ± 73 M^{-1}, 614 ± 51 M^{-1} and 284 ± 19 M^{-1}, respectively, by using the Stern–Volmer equation.[10] It is found that the pillar[5]arene formed 1 : 1 complexes with all of the four halide anions. The measured binding constant between **4a** and F^- was the highest. It was almost 15-fold to that of Cl^- and about 20-fold and 44-fold to those of Br^- and I^-, respectively. These data show that the binding strength between **4a** and F^- is the strongest, and along with the reduction of halide anions' electronegativity, the association constants of complexation between **4a** and the halide anions decrease gradually. It should be noted that a gradual enhancement of fluorescence intensity was observed when trace amount of water was progressively injected into the solution. This phenomenon was caused by the reduction of hydrogen bonding between **4a** and the halide anions.

The interactions between triazole hydrogen atoms of **4a** and the fluoride anion were further confirmed by using model compound **5** (Scheme 1c), which contains only one triazole unit. Upon the addition of excess F^-, the triazole hydrogen signal shifted downfield slightly ($\Delta\delta$ = +0.096 ppm) (Fig. S18, ESI†). The K_a value was estimated by a fluorescence titration experiment to be 38 ± 2 M^{-1}. The quenching of fluorescence observed in the emission spectrum of **5** was not notable, indicating the weak binding ability of **5** with F^-. The association constant of F^- with **4a** is far higher than that of F^- with **5**. Triazole units on one side of **4a** wrapped up the F^- simultaneously as a result of multiple hydrogen bond interactions, which led to the high K_a value. The much higher binding constant of **4a** and F^- emphasizes the important geometric characteristic of the pillar[5]arene structure.

The binding of **4a** to halide anions was also studied through ^{1}H NMR spectra with TBAX as anion source. Fig. 1 illustrates ^{1}H NMR chemical shift changes of **4a** with the addition of different halide anions. Upon the addition of Cl^-, Br^- and I^-, the signal related to the triazole protons H_1 shifted downfield ($\Delta\delta$ = +0.449, +0.337 and +0.100 ppm, respectively). Compared with Cl^-, Br^- and I^-, the complexation of **4a** with

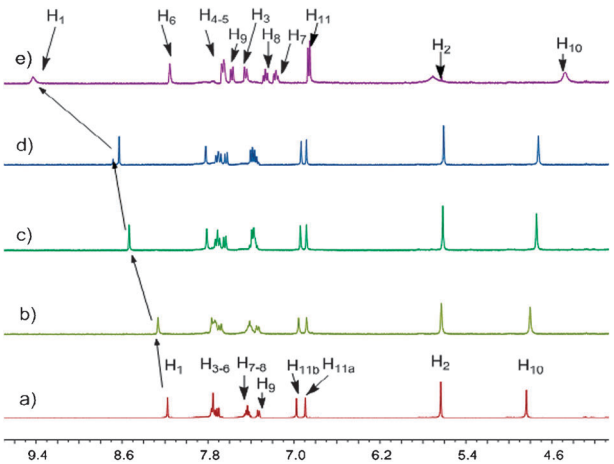

Fig. 1 Partial ^{1}H NMR spectra (400 MHz, acetone-d_6, 298 K): (a) **4a** (1.00 mM); (b) **4a** (1.00 mM) and 4 equiv. of TBAI; (c) **4a** (1.00 mM) and 4 equiv. of TBABr; (d) **4a** (1.00 mM) and 4 equiv. of TBACl; (e) **4a** (1.00 mM) and 4 equiv. of TBAF.

F^- led to specific changes in the ^{1}H NMR spectrum (no characteristic peaks related to HF_2^-), the peak related to triazole protons H_1 shifted downfield significantly, from 8.165 ppm to 9.556 ppm ($\Delta\delta$ = +1.391 ppm), which was caused by the formation of C–H···F^- hydrogen bonds between triazole protons on the pillar[5]arene host and the anion guest. Correspondingly, the signals related to protons H_{11a} and H_{11b} shifted upfield and coalesced into one peak, while there were almost no chemical shift changes for H_{11a} and H_{11b} when **4a** complexed with Cl^-, Br^-, and I^-. Meanwhile, when **4a** complexed with F^-, chemical shifts of protons on naphthalene rings of the host changed dramatically (Fig 1e). In addition, upfield shifts were observed for protons H_{10} ($\Delta\delta$ = −0.394, −0.108, −0.086 and −0.023 ppm for F^-, Cl^-, Br^- and I^-, respectively). These differences in chemical shift changes between the fluoride anion and the other three halide anions were caused by the particularity of the fluoride anion. The electronegativity and basicity of the fluoride anion are the strongest and its size is the smallest among the halide anions. When **4a** binds a fluoride anion, the C–H···F^- hydrogen bond forms easily and the repeating units rotate around the methylene bridge, so five triazole rings at one side of the pillar[5]arene are inclined to converge and interact with the F^- while the pillar architecture of **4a** changes into a conical structure. From comparison of ^{1}H NMR spectra we find that receptor **4a** has selectivity towards F^- over Cl^-, Br^-, and I^-.

^{1}H NMR titration experiments in acetone-d_6 were carried out to pinpoint the anion receptor sites and fully explore the interaction modes between the halide anions and **4a**. Fig. S19 (ESI†) shows the ^{1}H NMR spectral changes of **4a** upon the addition of F^-, Cl^-, Br^-, and I^-. For all of the halide complexes, chemical shifts of the triazole protons H_1 and the protons H_6 and H_9 on naphthyl rings all underwent downfield shifts, which indicated the formation of C–H···X^- hydrogen bonding interaction. The rest of the aromatic protons and H_{10} on the methylene bridge showed upfield shifts, which can be ascribed to the anion-induced through-bond shielding effect and the π–π stacking interactions between the naphthyl rings that take place as **4a** wraps around the anion. All of the proton resonances shifted more for F^- than for Cl^-, Br^-, and I^-. In addition, the peaks of **4a** became broad during the addition of F^-, indicating that the kinetics of the complexation were on the same time scale as the ^{1}H NMR experiment, consistent with the stronger anion binding.

In order to explore other evidence for the C–H···F^- interactions in solution, ^{19}F NMR spectra were carried out. Fig. S20 (ESI†) shows the ^{19}F NMR spectra of **4a** upon the addition of F^-, the resonance of free F^- appeared at −128.16 ppm. However, in the mixture of **4a** and F^- (1 : 1), the singlet of free F^- disappeared. A possible reason for this is that the F^- is located in the cavity of **4a** and shielded by its electron-rich cyclic structure after the formation of an inclusion complex between **4a** and F^-.[7c,e] Another reason is the host-induced broadening effect.[7e]

The phenomenon that the conformation of **4a** changed from the pillar architecture into the conical structure when **4a** interacted with F^- was further validated by NOESY NMR spectroscopy. The NOESY spectrum (Fig. S21, ESI†) of the uncomplexed **4a** shows no correlation between the protons on the naphthyl rings, indicating that the interproton distances between each other are large. When F^- was included into the cavity of **4a** and formed C–H···F^- hydrogen bonds, the NOE cross peaks (**A**, **B**, **C**, **D** in Fig. 2)

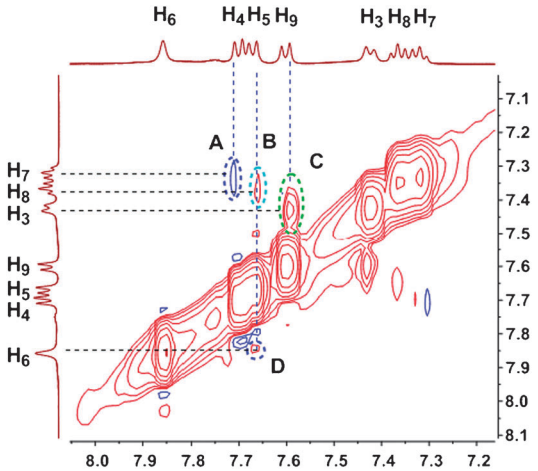

Fig. 2 2D ^{1}H–^{1}H NOESY spectrum of **4a** in acetone-d_6 at 298 K after addition of 2 equiv. of TBAF.

between naphthyl rings were observed. The associated changes (Fig. S22, ESI†) in through-space interactions arose from the conformation change in **4a** upon the formation of C–H···F$^-$ hydrogen bonding interactions and indicated that the distances between the naphthyl rings became closer on average.

In order to further demonstrate that **4a** can selectively bind the F$^-$, fluorescence titration experiments of **4a** against various anions were investigated. The addition of CF_3COO^-, NO_3^-, HSO_4^-, CH_3COO^-, ClO_4^-, and $H_2PO_4^-$ produced only a nominal change in the fluorescence spectrum of **4a** due to their low affinities towards **4a**. The corresponding association constants were far lower than that of **4a** and F$^-$ (Table S1, ESI†). As for PF_6^-, it could not get into the cavity and interact with **4a** due to its large size. No chemical shift changes were observed in ^{1}H NMR spectra after adding 4 equiv. of $TBAPF_6$ into the solution of **4a** (Fig. S24, ESI†). Compared with a wide range of anions, the strength of the binding between **4a** and F$^-$ is remarkable (Fig. S25, ESI†).

In conclusion, a novel fluorescent non-symmetric pillar[5]arene-based receptor **4a** with high selectivity and affinity towards the fluoride anion has been synthesized. Due to the unique geometric structure of **4a**, multiple C–H···F$^-$ hydrogen-bonding interactions between **4a** and the fluoride anion formed and greatly improved their affinity. This novel pillar[5]arene-based neutral anion receptor enriches the structural diversity of anion binding chemistry, and can be further used in the fabrication of sensing devices for the fluoride anion.

This work was supported by the National Natural Science Foundation of China (20834004, 91027006, 21172166), the Fundamental Research Funds for the Central Universities (2010QNA3008), National Basic Research Program (2009CB930104), and Zhejiang Provincial Natural Science Foundation of China (R4100009, Y4100783). Thanks to Mr. Xiaopeng Chen for his assistance with molecular modelling.

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