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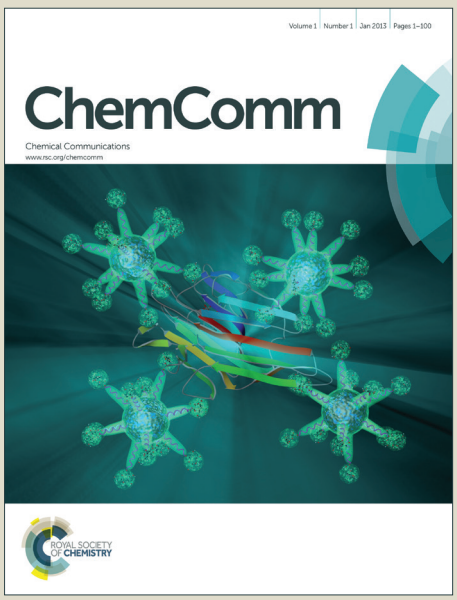

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Communication

Remarkably Selective Non-linear Allosteric Regulation of Anion Binding by Tetracationic Calix[4]pyrrole Homodimer

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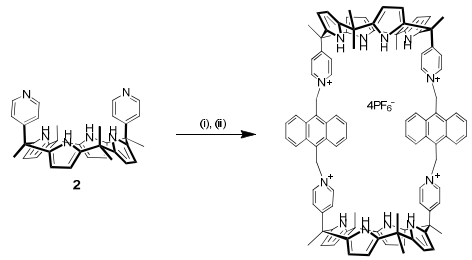
A covalently coupled, dimeric tetra-cationic calix[4]pyrrolehomodimer bearing anthracene linkers displayed distinctive cooperativity and fluoride selectivity with positive allosterism. The exclusive and successive binding of fluoride anions accompanied with large 'turn-on' of fluorescence (K_2/K_1=311).

Allosteric cooperative guest binding involving abiotic receptors[1] bearing multiple binding sites has drawn immense attention in recent years because such interactions play a central role in many biological processes[2] such as dioxygen binding to hemoglobin,[3] hexamerization of arginine repressor,[4] etc. Allosteric cooperativity could be either positive or negative depending on whether the initial interaction favors or disfavors the subsequent binding and vice versa.[5]This cooperativity is usually achieved by conformational change of the host upon binding of analytes. Positive or negative allosterism can be further classified as homotropic or heterotropic depending on whether the subsequent binding is by the same species or different species. Synthetic molecular analogues capable of eliciting positive homotropic allosterism[6] are more difficult to achieve than analogues capable of eliciting negative or heterotropic allosterism.[1f, 1g, 7]Particularly, it is even more difficult to achieve a positive allosteric response in recognition of monofunctional guests. Such a system (positive homotropicallosterism) is characterized by a non-linear sigmoidal response depending on the analyte concentration. However, to achieve high specificity and sensitivity for similar target analytes found in nature, it is necessary to develop artificial receptors that can mimic the binding process found in nature. This strategy would be a very useful and elegant approach in designing novel chemosensors that can detect the target analytes with high sensitivity and selectivity.

Selective recognition of anionic species is one of the key issues in supramolecular chemistry due to their crucial role in chemical, environmental and biological processes.[8] High selectivity and sensitivity toward specific analytes are often difficult to achieve due to their diverse geometry, low charge to radii ratios, narrow pH window and high solvation energy. Although host-guest complexation can be driven enthalpically, entropically, or by a combination of both, most abiotic host-guest complexation processes are driven enthalpically. This complexation could be achieved by proper installation of recognition sites around the binding domain or placing complementary functionalities for interacting with guests. In general, minimizing the overall free energy change (ΔG) by appropriate enthalpy–entropy compensation is important in the favorable binding event. Among the various anions, fluoride anion has received special attention due to its potential toxicity in various living systems. Although much progress has been made in the area of fluoride recognition and sensing,[9] there are only a few easy-to-use chemosensors that operate with high sensitivity due to fluoride's high charge density and hydration energy. Moreover, although there are a large number of receptors reported in literature, the clear allosteric binding systems for fluoride anion were not studied and remain a challenge.

The positive homotropicallosterism ($K = 10^{6.6}$ and n= 2.0±0.1, K = association constant, n = Hill coefficient)[10] for fluoride anion binding has been reported by Swager *et al.* in 2001 using a doubly strapped porphyrin having two small hydrogen bonding cavities.[11]Sessler and co-workers reported a quinoxaline-based porphyrinoid system that can bind with fluoride anion and $H_2PO_4^-$ in an allosteric manner ($K = 10^{11}$ and n= 2.2 for F^-, $K = 10^{3.8}$ and n= 1.9 for $H_2PO_4^-$).[12] More recently, Rosenthal *et al.* reported a series of phlorinmacrocyles that can bind with fluoride anion cooperatively.[13] This conclusion for the cooperative binding mode is based on the calculated Hill coefficient ranging from 5.0 to 8.6. However, such high values are highly incongruous and unfavorable in 1/2 host-guest binding stoichiometry.[14] No supporting ^{1}H NMR spectral data have been documented for the evidence of the formation of hydrogen bonding complexes.[15,16]



Scheme 1 (i) 9,10-bis(chloromethyl)anthracene, DMF-CH_3CN(2:80, v/v), reflux at 80 °C, 4 days (ii) NH_4PF_6,DMF/MeOH, H_2O, rt, 1 h.

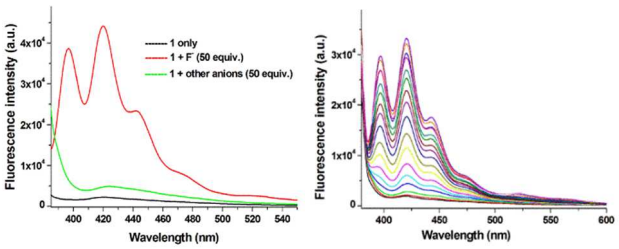
Herein, we report conformationally flexible fluorescent tetracationicbis(calix[4]pyrrole)macrotricylic receptor **1** that can bind fluoride anion in a distinctive allosteric fashion. Each individual binding event has been characterized thermodynamically. Calix[4]pyrroles are known to have excellent halide (mainly fluoride and chloride) binding ability and many

modified systems have been reported in the literature.[17,18]Inspiration came from the previous studies on two-wall calix[4]pyrrole (two aromatic rings occupying the alternate *meso*-positions with *cis*-configuration), which revealed that upon binding with anion, two aromatic rings at *meso* positions come close to each other due to the simultaneous interplay of N-H--anion hydrogen bonding and anion-π interaction.[18a-b, 18e, 19] With this result in mind, we anticipated that anion binding at one end of the macrotricycle**1** would lead to the conformational change, which in turn could facilitate the binding of the second anion thereby showing positive allosteric control. As detailed below, this outcome is indeed found to be the case.

The synthesis of the macrotricycle**1** is outlined in Scheme1. Compound **2** was synthesized according to the literature procedure.[18a] High-dilution coupling of **2** with 9,10-bis(chloromethyl) anthracene afforded the tetrachloride salt of the macrotricyle**1,** which gave the desired compound **1** as the tetra-hexafluorophosphate salt in appreciable yield on subsequent anion exchange reaction with excess NH_4PF_6.Compound **1** was thoroughly characterized by conventional spectroscopic methods (SI).

Preliminary anion binding affinities of receptor **1** toward various anions were examined using fluorescence spectroscopic titration. The receptor **1** displayed a very weak broad emission band approximately at 421 nm (λ_{ex} = 370 nm) in CH_3CN. At first, we examined the fluorescence changes of receptor **1** (17.5 μM) upon addition of 50 equivalents of various anions (F^-, Cl^-, Br^-, I^-, $HP_2O_7^{3-}$, $H_2PO_4^-$, NO_3^-, HSO_4^-, ClO_4^-, SCN^-, CH_3COO^-, $PhCOO^-$, phthalate, isophthalate, terephthalate, 1,4-phenylenediacetate, succinate, glutarate, adipate, pimelate, suberate, azelate and sebacate as their tetrabutylammonium salts) to the receptor solution (Figure 1(a) and SI). The initially weak emission of **1** was *switched on* only in the presence of fluoride anion. No other tested anions induced any appreciable change in the emission profile of **1**. These results led us to conclude that the receptor **1** is highly selective for fluoride anion. Such high fluoride-only selectivity of **1** is ascribed to the conformational restriction imposed in receptor **1**. This preventsthe favorable interaction of other anions with calix[4]pyrrole core.[20]To obtain more detailed insight into fluoride binding, we performed the fluorescence titration experiment with TBAF in CH_3CN. The incremental addition of F^-anion to the solution of receptor **1** (17.2 μM) resulted in a large fluorescence enhancement, which was saturated at ~0.6 mM of anion concentration. At the same time, the initial broad emission bands were well resolved into well-defined bands, which are characteristics of anthracene emission. Such increase in emission is ascribed to the binding induced conformational locking of macrotricyle**1** whose emission was originally quenched due to conformational flexibility. In addition, a weak emission band of approximately 525 nm was also noticed. This band clearly indicates that the fluoride anion binding to both ends of the inner cavity must bring the two anthracene units into close proximity leading to the formation of an excimer complex. The remarkable increase in emission intensity was noticed at the addition of 0.2 mM of fluoride anion (Fig.1b).

Most importantly, when the extent of complexation ($\Delta I/\Delta I_{max}$) is plotted as a function of fluoride anion concentration, a clean sigmoidal curve is obtained (Fig.2).This non-linear binding isotherm indicates that the binding of fluoride anion is cooperative (positive homotropicallosterism).



(a)(b)

Figure 1.(a) Changes in emission of receptor 1 upon addition of 50 equivalents of various anions. (b) Changes in emission of receptor 1 (*c* = 17.2 μM)with incremental addition of fluoride anion (as its tetrabutylammonium salt), λ_{ex} = 370 nm.

Binding of one fluoride anion to one of the calix[4]pyrrole binding moieties enhances the second fluoride anion binding. The significantly broadened absorption bands of free receptor **1** became sharp upon addition of fluoride anion (SI). The absorption spectrum of free receptor **1** exhibited three sets of split bands at 361, 370 and 380, 386 and 401, 409 nm, along with a shoulder band at 347 nm (SI). However, in the presence of fluoride anion each of the three split band becomes a single sharp band appearing at 365, 385 and 406 nm, respectively. These spectral changes clearly indicate the formation of rather rigid host-guest assembly upon anion binding.

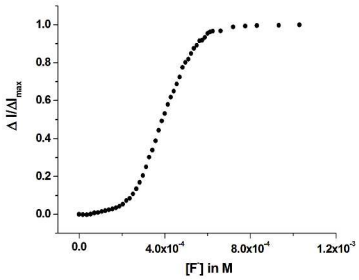


Figure 2. Binding isotherm based on fluorescence titration of 1 (17.2 μM) with tetrabutylammonium fluoride, measured at λ_{max} = 421 nm.

To quantify each binding event (formation of 1:1 and 1:2 complexes) and measure the cooperativity factor of the binding process, we performed an isothermal titration calorimetry (ITC) experiment for the complexation of **1** and TBAF in CH_3CN at 298K. In contrast to other spectroscopic analysis, ITC allows one to study the overall free energy change of the system, including the solvent effect. Thus, it provides direct access to the energetics of the binding event without the necessity of a structural probe that may or may not reflect the entireness of the binding processes (e.g., NMR spectroscopy). The stepwise addition of receptor **1** (1.35 mM in CH_3CN) to a solution of TBAF (0.127 mM in CH_3CN) resulted in gradual release of heat owing to the exothermic binding process. The normalized, integrated data displayed a sigmoidal binding isotherm with two inflection points at molar ratio ~ 0.5 and ~1.0 (see SI). The appearance of two distinct inflection points is consistent with the formation of 1:2 and 1:1 host/guest complexes, respectively. The formation of 1:2 complexes was further confirmed by Job plot, which displayed a

clear inflection point at the stoichiometric ratio of 1:2 (**1**/TBAF) (SI). In addition, the ITC data were well fitted to the theoretical isotherm obtained from the two binding sites model. The magnitude of first binding constant(K_1) is slightly lower than that observed for the monovalent congener (K = 6.94 x 10^6 M^{-1}) previously reported by us (SI).[18a] This is ascribed to the fact that the increased rigidity of calix[4]pyrrole core, imparted by conformational restriction imposed in **1,** is not positive for initial binding.[21] This is also consistent with relatively lower enthalpic contribution observed for the first fluoride anion binding. In contrast, the magnitude of the second binding constant (K_2) is ~311-fold larger than that of the first binding constant (K_1) and the interaction parameter (α) for this system is calculated to be ~1244 ($\alpha = 4K_2/K_1$).[22]

This high value of α clearly indicates that fluoride binding proceeds in a positive allosteric fashion. Such findings unambiguously lead to the suggestion that one fluoride anion binding to the cavity of the calix[4]pyrrole moiety in receptor **1**favors the second fluoride anion binding. Furthermore, the thermodynamic parameters obtained from the ITC analyses revealed that the formation of the first 1:1 complex is both enthalpically and entropically favorable (each term contributes almost equally to the free energy change (ΔG_1) with the entropic term being marginally larger). Larger entropic contribution is attributed to the net sum of the dissociation of fluoride-bound water molecules and the release of solvent molecules from the binding cavity to the bulk solution. In contrast, the second binding process (formation of 1:2 complexes) is not entropically favorable but driven entirely enthalpically. The positive allosteric binding can also be visualized in terms of the free energy difference ($\Delta\Delta G_{12} = \Delta G_2 - \Delta G_1$). The large negative free energy difference ($\Delta\Delta G_{12}$ = -3.73 Kcal/mol) between the first and second binding event is in accordance with the observed positive cooperativity.

The interaction of the receptor **1** with F^- was also realized by ^{1}H NMR spectroscopy in CD_3CN. The signal of the pyrrole N-H protons was shifted downfield (Δδ = 1.86 ppm) upon complexation (see SI). At the same time, protons on the pyridinium rings (H_a and H_b) underwent Δδ = 0.06 ppm up-field shift. Such up-field shift of the pyridinium protonsareattributed to the interaction of F^- anion with the face of the aromatic π-surfaces of the pyridinum rings (probably through anion-π and electrostatic interactions), but not with the C-H groups of the pyridinium rings involving CH---F^- hydrogen bonds.The up-field shift of the methyl protons H_f (Δδ = 0.2ppm) provide additional support for the proposed anion-πand coulombicinteractions (SI). No changes in the proton signals of the counter cation (tetrabutylammonium) were noticed during the course of the titration. These observations clearly indicate that the complexation takes place inside the macrocyclic cavity. Conformational changes from 1,3-alternate to cone triggered by one fluoride anion binding must occur first. Then, convergent hydrogen bonding, anion-pi interaction, and coulombic charge interactions cooperatively stabilize the complex. Apparently, only the smaller fluoride anion with high affinity seems to fit into the cavity. The pyrrole N-H protons corresponding to [**1**•F^-] complex formation was not observed at one equivalent of fluoride anion possibly due to peak broadening, but the appearance of a signal at δ = 0.7 ppm (H_f) undoubtedly confirms the formation of [**1**•F^-] complex (SI). The signals for free receptor completely disappeared upon addition of 5.0 equivalents of TBAF indicating the formation of a strong host-guest complex. Receptor **1** binds with fluoride anion relatively weakly at lower concentration, but the binding affinity is increased at high concentration of fluoride anion. This observation is an important aspect of a nonlinear binding (cooperative binding) process. The fact that the N-H proton resonance of fluoride bound receptor split into a doublet (J = 47.25 Hz), presumably due to the coupling with bound fluoride anion, at room temperature also supports the strong complexation.

DFT-based, energy minimized structure of the fluoride complex of the receptor **1** shows well fit of the fluoride anions to the cavity.[23]The cooperative actions of the one pre-organized binding domain must enhance the second fluoride complexation resulting in conformationally locked structure as shown in Figure 3. The structure also indicates that the intermolecular π-π interaction that can bring fluorescence quenching is interrupted. On the other hand, the two anthracene units are separated far apart in the optimized structure of the free host **1** resulting inconformationallyflexible geometry causing fluorescene quenching.

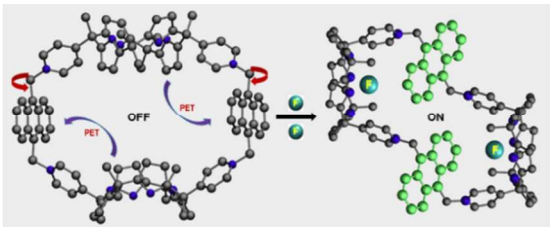


Figure 3. Energy minimized structure of the host 1 and [1•2F^-] complex.

In conclusion, we have demonstrated that homoditopiccapsular receptor **1**acts as a selective fluorescent chemosensor for fluoride anion by exhibiting a nonlinear *turn-on* fluorescence response. The two identical binding sites, which are suitable to accommodate fluoride anion, exhibited highly cooperative binding. The clean sigmoidal binding isotherms clearly indicate the positive allosteric binding behavior of the designed host. Moreover, each binding event was distinctly characterized thermodynamically. The development of such *non-linear* fluoride binding architectures would be very useful for the construction of highly sensitive and selective sensory systems as well as fluoride transport agents.[24]

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Notes and references

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14 Hill equation is described as following: $\log[y/(1-y)] = n\log[guest] + \log K$ where K ; association constant, y; extent of complexation, and n : Hill coefficient. The slope and the inter-cept of the linear Hill plots allow estimating binding constant K and Hill coefficient n. A higher value of n is related to the higher degree of cooperativity and the maximum value corresponds to the number of binding sites present in the host. Therefore, for 1/2 host- guest binding stoichiometry, the maximum value of n could be 2.0.[1g, 6a, 11]

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TOC

A covalently coupled, dimeric tetra-cationic calix[4]pyrrole homodimer bearing anthracene linkers displayed distinctive cooperativity and fluoride selectivity with large positive allosterism.