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Unexpected halide anion binding mode in *meso*-bis-ethynyl picket-calix[4]pyrroles: Effects of *meso* - π (ethynyl) extension

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***Meso*-ethynyl extended aryl-picket calix[4]pyrroles 2 and 3 are designed and synthesized by directly anchoring arylethynyl groups at diametrically opposed *meso*-positions. Critical roles of direct ethynyl linker are manifested through the isolation of unexpected host-anion conformers of *meso*-arylethynyl calix[4]pyrroles and significant enhancement in halide binding affinities.**

A 'Picket Calix[4] pyrrole' represents a calix[4]pyrrole bearing aryl groups at diametrical *meso*-positions in *cis*-fashion when it becomes a cone conformation. The cavity created by the tetrapyrrolic core along with the axial aryl groups is suitable for inclusion of mono and polyatomic anions. In recent years, a variety of picket calix[4]pyrroles possessing various aryl groups at diametrical *meso*-positions are developed and explored for anion recognition, sensing and transport in some cases.[1] For instance, Ballester and co-workers have extensively studied energetics between differently substituted aromatic moieties of picket calix[4]pyrroles and anions.[2] We have investigated anion recognition properties of these classes of hosts using fluorescence dye displacement assay technique.[3] As the results, fluorescence '*Turn-on*' type of recognition and selective sensing of different anions using various *meso*-aryl picket calix[4]pyrroles have been reported. For example, high fluoride anion selectivity was seen upon introduction of 4-fluorophenyl groups as *meso*-picket.[3a] Exceptionally high affinity toward dihydrogen pyrophosphate anion was observed when 4-methyl pyridinium groups were introduced as a picket component.[3b] Most recently, high selectivity toward bicarbonate anion was reported when the 2-benzimidazolium groups were introduced as the picket components.[3c] Due to conformationally flexible nature and low energy barrier between different conformers, calix[4]pyrroles adopt many different conformations depending on the solvents and the *meso*-substituents. For instance, the octamethylcalix[4]pyrrole **1** exists as a 1,3-alternate conformer in solid state wherein the adjacent pyrrole rings are oriented in opposite direction.[4] Theoretical calculation reveals that the stability order between the different conformers in **1** is: 1,3-alternate > partial cone > 1,2-alternate > cone conformation.[5] The macrocycle usually adopts a cone conformation upon complexation with anions. In the case of the *meso*-aryl picket calix[4]pyrroles, the anions usually occupy the deep pocket created by the two, axially positioned *meso*-aryl groups. The tetrapyrrole moiety and the *meso*-aryl substituents undergo dramatic changes in spatial orientation during complexation process. This type of pocket-side binding along with the conformational changes of the host molecules have been reported with a wide variety of *meso*-aryl substituted calix[4]pyrroles.[6] The trend of the deep pocket binding holds even in the case of the hexyl armed calix[4]pyrrole in chloride anion complexation.[7] DFT calculations also show this binding conformation to be the most stable. In order to clarify the binding modes of the *meso*-picket calix[4]pyrroles upon anion binding, we design and synthesize *meso*-picket calix[4]pyrroles **2**, **3**, **4** and **5** as shown in **Fig. 1**. Indeed, the detailed binding studies showed unexpected anion binding modes depending on the nature of the *meso*-pickets. We found that the aryl ethynyl arms occupy the equatorial positions in the sold state and the anion binds to the opposite side of the pocket in cases of **2** and **3**. The systematic binding studies were performed for in-depth understanding of this unexpected binding modes in *meso*-ethynyl extended calix[4]pyrroles **2** and **3**.

The synthesis of receptor **2** is outlined in Scheme S1 (ESI†). Briefly, *meso*-[2-ethynylphenyl)methyl]dipyrromethane (**8**) is synthesized in 52% yield by acid-catalyzed condensation of 4-phenyl-3-butyn-2-one, **6** with freshly distilled pyrrole at 0 °C. It is noteworthy to mention that longer reaction time at elevated temperature (rt) led to formation of *meso*-[2-phenyl]methyl)dipyrromethane **10** and **11** presumably *via* the cleavage of triple bond thorough Meyer-Schuster rearrangement[8] followed by retro Aldol type reaction (ESI†). Compounds **10** and **11** were isolated and verified. Mechanistic details of such transformation are provided in ESI.

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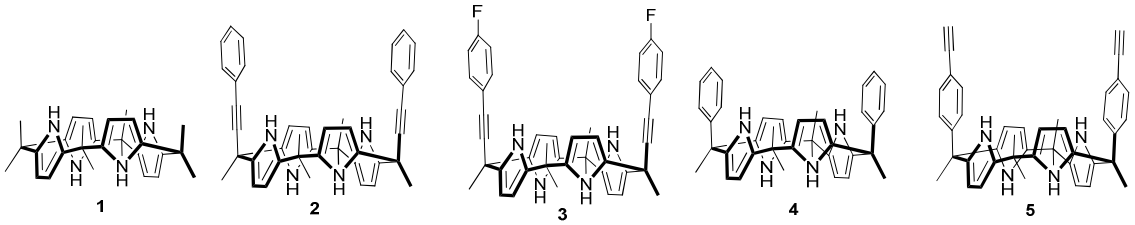

Fig. 1 Chemical structures of calix[4]pyrroles **1**, **2**, **3**, **4** and **5**

Condensation of **8** with excess of acetone in presence of $BF_3.Et_2O$ as catalyst afforded the *cis*- and *trans*-isomers as a mixture. Repeated column chromatography on silica gel yielded pure **2** in 7% yield, with characteristic *meso*-methyl protons as three distinct singlets in 1/1/1 ratio in ^{1}H NMR spectrum (ESI†). Structural analysis of single crystals of compound **2** obtained from a mixture solvent (ethyl acetate/hexane) revealed that the calix[4]pyrrole core adopted a 1,3-alternate conformation in the solid state and the phenyl ethynyl pickets adopted *pseudo*-axial conformation, whereas a partial cone conformer with bound solvents was obtained when the crystals were grown from acetone/methanol (ESI†). In this case one of the *meso*-phenylethynyl group occupied the axial position. Receptor **3** bearing *meso-para*fluorophenylethynyl picket was synthesized in 12% yield and characterized following a similar protocol (ESI†). Hosts **4**[2c] and **5**[9] were synthesized for the comparison study and will provide crucial information regarding the electronic and positional effects of ethynyl groups on the anion binding.

Solution state anion binding studies of receptor **2** with various halide anions (as their TBA salt) were performed by ^{1}H NMR spectroscopy in CD_3CN. Incremental addition of fluoride anion (0.25 equiv.) to a solution of **2** in CD_3CN (~10 mM) induced splitting of the pyrrolic N-Hs signals into two sets along with large downfield shift (Δδ = 5.40 ppm). Upon the addition of *ca.* 1.0 equiv. of F^-, the signals corresponding to the free host disappeared completely (ESI†). This result indicated slow complexation/decomplexation kinetics with high binding affinity. Noticeably, 0.13 ppm downfield shift of *ortho*-C-Hs of the *meso*-phenyl groups were observed while other phenyl-Hs remained unperturbed. These results ruled out presence of any anion-π interactions which is generally associated with up-field shift of aryl protons. All the *meso*-methyl protons endured slight downfield shift during titration. These findings suggested equatorial alignment of *meso*-phenylethynyl groups rather than axial orientation which is unprecedented in the anion binding of *meso*-aryl picket calix[4]pyrrole family. Fairly similar observations were noted during ^{1}H NMR titration with chloride anion (ESI†). Complexation induced chemical shift changes was calculated to be 3.85 ppm (Δδ) for chloride with slow complexation-decomplexation kinetics. Moreover, change of counter cations from tetrabutylammonium to tetraethylammonium did not alter the binding mode as clearly evident from ^{1}H NMR titration with tetraethylammonium chloride (ESI†). On the other hand, broadening of NH signals along with concomitant downfield shift was observed during titration with bromide anion, which was saturated after addition of one equiv. of bromide anion (ESI†). Chemical shift changes of aryl and *meso*-methyl protons were consistent with the equatorial alignment of *meso*-phenylethynyl groups. While small yet detectable downfield shift of NH protons of **2** was observed during titration with iodide anion (ESI†). Only few picket calix[4]pyrroles with highly electron withdrawing *meso*-aryl substituents were known to display response for iodide anion.[2c] This indicated that receptor **2** possesses high affinity towards anions in general. Similar observations were noted during titration of receptor **3** with halides. Equatorial alignment of *meso-para*fluorophenylethynyl pickets was evident from chemical shift changes of aryl-CH and *meso*-methyl protons. Details of titrations for **3** with different halides are provided in the ESI.

In case of *meso*-phenyl calix[4]pyrrole **4**, upon incremental addition of fluoride anion (as its TBA salt), the pyrrolic NHs resonance first disappeared due to peak broadening and then reappeared upon addition of ~1.0 equiv. of fluoride anion along with concomitant downfield shift (ESI†). 0.25 and 0.11 ppm up-field shifts were observed for the proton signals corresponding to phenyl groups indicating interaction of fluoride anion with the face of the π-surface of the phenyl ring but not with the C-H groups involving CH•F^- hydrogen bonds. The up-field shift observed for the signal corresponding to methyl protons (set a) provide an additional support for the existence of anion-π interactions operating between phenyl ring and bound F^- anion. Similar ^{1}H NMR spectral changes were noted with chloride anion indicating pocket side binding of anion (ESI†). Relatively smaller downfield changes in NH protons were observed in case of bromide indicating weaker hydrogen bonding interactions compared to fluoride and

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Table 1. Comparative chloride and bromide binding affinities for **1**, **2**, **3**, **4** and **5** in CH_3CN as determined by isothermal titration calorimetry at 298 K.

Binding Constant (K_a)	**1**[a]	**2**	**3**	**4**[b]	**5**
K_a(TBACl)	2.2×10^5	$4.25 \times 10^5 \pm 1.41 \times 10^4$	$5.73 \times 10^5 \pm 2.28 \times 10^4$	2.65×10^4	$5.53 \times 10^4 \pm 1.6 \times 10^3$
K_a(TBABr)	3.6×10^3	$7.15 \times 10^3 \pm 0.52 \times 10^3$	$1.10 \times 10^4 \pm 0.22 \times 10^3$	0.8×10^3	$0.92 \times 10^3 \pm 0.58 \times 10^2$

[a]value from ref[4b], [b]value from ref[2c]

chloride anions. However, pocket side binding of bromide in association with anion-π interaction was evident from the ^{1}H NMR spectral changes of *meso*-aryl and *meso*-methyl protons. ^{1}H NMR titration spectral pattern of **5** with chloride and bromide anion were consistent with the trend observed in case of **4** (ESI†). Pocket side binding of anion was established as preferred binding mode in cases of *meso*-aryl picket calix[4]pyrrole receptors with variety of aryl groups. Thus, the observed halide binding mode in case of receptors **2** and **3** is unique in *meso*-substituted calix[4]pyrrole family.

The stability constants and Gibbs free energy (ΔG) of binding for the 1/1 stoichiometric complexes of **2** and **3** with halide anions were determined by isothermal titration calorimetry (ITC) in acetonitrile at 298 K and summarized in Table S1-S2 (ESI†). The highest binding affinity was observed for the fluoride anion, which benefited from a favorable entropic term. The binding affinity values followed the order $F^- > Cl^- > Br^- > I^-$ as expected for typical calix[4]pyrroles. Interestingly, the binding affinity values of **2** were much higher compared to the *meso*-phenyl congener **4** (Table 1). For example, sixteen fold enhancements in chloride binding affinity was calculated for **2** over **4**. Similarly, nine fold increments in bromide binding affinity was found for **2** over **4**. The measured halide binding affinities of receptor **3** also followed the trend observed for **2**. For example, twenty two and fourteen fold increment in chloride and bromide binding affinity values are calculated respectively for **3** over **4**. Noticeably, two fold enhancements in chloride and bromide binding affinities were measured respectively for **2** over *meso*-octamethylcalix[4]pyrrole **1**. Differences in binding energies between picket calix[4]pyrroles and octamethylcalix[4]pyrrole (no picket) was the direct consequence of attractive or repulsive anion-π interactions between the anion and aromatic walls.[2a-2c] Taking chloride anion as a representative case, higher affinity of **2** compared to **1** clearly indicated no repulsive anion-π was present between phenylethynyl groups and chloride, indeed no anion-π interaction was operating in case of **2** (*vide supra*). Two other factors also contributed to the observed higher binding affinity of **3** for halides. In general, the binding energies of calix[4]pyrroles is the outcome of primary hydrogen bonding interactions between anion and tetrapyrrolic core. The complexation induced chemical shift value for **2** with chloride was found to be 3.85 ppm (Δδ) which is significantly higher compared to the values (Δδ = 3.0-3.23 ppm) found in cases of picket calix[4]pyrroles with varying degree of *meso*-substitutions.[2c] We postulate that the tetrapyrrolic core of **2** offered much stronger hydrogen bond donors for anions compared to reported picket calix[4]pyrroles thus far. Further evidences of such stronger hydrogen bonding interactions came from the relatively shorter N•••Cl bond distances of the crystal structure of chloride complex of **2**. Moreover, the additional CH•••Cl interactions in case of **2** contributed to the enhanced binding affinity. However, effect of counter cation on halide binding affinity value for **2** was minimal. For instance, slightly higher binding affinity (~1.3 fold) is calculated for **2** with chloride from ITC measurement when counter cation was changed from TEA to TBA species (ESI†). On the other hand, *meso*-phenyl calix[4]pyrrole **4** displayed relatively lower binding affinity than **2** as consequence of repulsive anion-π interactions between phenyl groups and halide (Table 1).[2c] Calix[4]pyrrole **5** bearing terminal ethynyl groups showed slightly higher binding affinity for chloride and bromide than that of **4** (Table 1). Thus, higher anion binding affinity of **2**, **3** and **5** compared to **4** indicated electron withdrawing nature of ethynyl groups. However, lower affinity of **5** than **1** suggested repulsive anion-π is still operational between ethynylphenyl groups and halides albeit to a lower extent.

Unambiguous confirmation of halide binding was obtained from the X-ray crystal structure analysis of the chloride complex of **2** (Complex **1**). Crystal structure analysis of complex **1** [(**2**)•(TEACl)] revealed the tetrapyrrolic core adopted a cone conformation to encapsulate the chloride anion (**Fig. 2**). The tetrapyrrolic core offered four strong hydrogen bond donors for chloride anion. The average N--Cl bond distances and N-H•••Cl bond angles were calculated as 3.26 Å and 174° respectively (ESI†). Notably, several CH•••Cl interactions contributed to the chloride binding. Intermolecular CH•••Cl interactions were observed between *ortho*-CH protons of two phenylethynyl groups and chloride anion which further ruled out presence of anion-π interactions between aryl group and anion (*vide infra*). The TEA countercation occupied the π-rich cavity generated by four pyrrole groups. Further evidence of such unique conformation is obtained from the crystal structure analysis of fluoride complex of **3** [Complex **2,**

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(**3**•TBAF•H_2O•CH_3CN)]. Single crystals of complex of **3** and TBAF revealed trapping of monohydrated fluoride anion by **3** (**Fig. 2**). Notably, *meso*-*para*fluorophenylethynyl groups were oriented in the *pseudo*-equatorial positions. Details of hydrogen bonding parameters for complex **2** were provided in ESI. Significant conformational differences were noted in the orientation of the *meso*-arylethylnyl groups compared to the trend observed for *meso*-aryl picket calix[4]pyrroles. Generally, the *meso*-aryl groups of picket calix[4]pyrroles adopt face-to-face orientation to create a pocket for anion, while the *meso*-methyl groups occupy the equatorial positions. In cases of complex **1** and **2**, *meso*-methyl groups are axially oriented while the *meso*-arylethynyl groups are pointed equatorially. The binding of halide anions are occurred in this cavity side rather than the pocket side created by *meso*-arylethynyl groups. Possible explanation for such unique spatial arrangement of aryl groups could be obtained from one of the crystal structure of **2**. Crystals of partial cone conformer of **2** was obtained with bound water molecule where one of the *meso*-phenylethynyl group occupied the axial position (ESI†). Distance of the bound water (hydrogen bond acceptor) to the centroid of phenyl group is clearly out of range for any weak interaction. In this analogy, anion-π interaction is ruled out

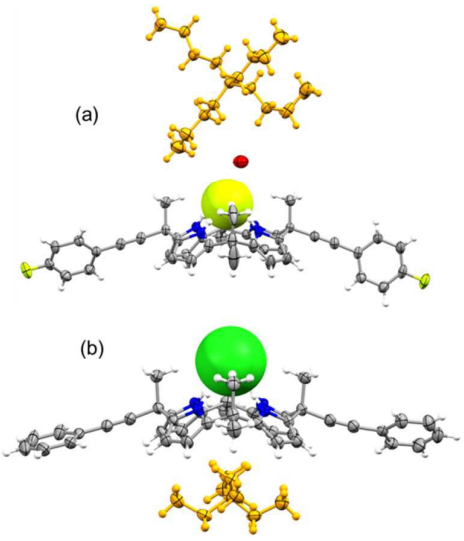

Fig. 2 Crystal structures of TBAF complex of **3** (a) and TEACl complex of **2**(b).

between phenyl group and chloride in this conformation. However, repulsive interaction between anion and π-cloud of triple bond is likely as evident from the contact distance (ESI†). Such repulsive interaction could enforce the *meso*-phenylethynyl groups to orient towards equatorial direction. Lesser steric repulsion could also contribute to the observed equatorial orientation of *meso*-arylethynyl groups in cases of **2** and **3**. Proposed anion binding mechanisms for *meso*-aryl and *meso*-arylethynyl calix[4]pyrroles are given in the ESI.

In summary, we have designed and synthesized new picket calix[4]pyrroles bearing arylethynyl groups at the diametrically opposed *meso*-positions. These alkynyl extended calix[4]pyrroles **2** and **3** are established as a superior halide anion receptor than the analogous *meso*-aryl congener. Single crystal X-ray structure analysis as well as solution state binding study of the halide-host complexes demonstrate *pseudo*-equatorial alignment of the *meso*-arylethynyl groups, which are unprecedented and quite different from *meso*-aryl calix[4]pyrroles reported thus far. These results indicate that the repulsive anion-alkyne interaction is stronger so that the equilibrium favour the unexpected conformer. Further exploration of the anion–triple bond interaction paradigm in conjunction with analogous receptors with varying substituents on the ethynylaryl groups are currently in progress.

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There are no conflicts to declare.

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