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ARTICLE

N-Alkyl ammonium resorcinarene salts: Multivalent halogen bonded deep cavity cavitands

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*N-Cyclo*hexyl ammonium resorcinarene halides, stabilized by an intricate array of hydrogen bonds into a cavitand-like assembly, forms multivalent halogen bonded deep cavity cavitands with perfluoroiodobenzenes. From macromolar to infinite concentration range through crystal growth and single crystal X-ray analyses, the four 1,4-diiodotetrafluorobenzene form moderate halogen bonds with the bromides of the *N-cyclo*hexyl ammonium resorcinarene bromide leading to a deep cavity cavitand-like structure. In this assembly, the *N-cyclo*hexyl ammonium resorcinarene bromide also act as a guest and sits in the upper cavity of the assembly interacting with the 1,4-diiodotetrafluorobenzene through strong $\pi\cdots\pi$ interactions. Solvent molecules acts as guests and are located deep in the cavity of the resorcinarene skeleton. In the millimolar range, ^{1}H and ^{19}F NMR spectroscopic analyses confirms halogen bonding in solution. Fast exchange binding of electron rich fluorophores (naphthalene, anthracene and pyrene) in the upper layer of these assemblies was also observed in the millimolar range while in the micromolar range via fluorescence analysis, no binding of the fluorophores is observed.

Introduction

Multivalency is a key phenomenon in system chemistry whereby strong yet reversible interactions lead to complex and functional architectures.[1,2] Multivalency, which describes molecular recognition phenomena between two binding partners involving more than one binding site is prevalent in biology and biochemistry.[3,4] The utilization of weak interactions in the mimicking of biological and covalent systems is a constant challenge in nanochemistry since in most cases, the final assemblies results from a compromise between the competing weak interactions and the geometrical constraints of the building blocks.[5,6]

Hydrogen bond (HB) is arguably the most used weak interactions in the design of supramolecular architectures.[6,7] Recently, the halogen bond (XB) which results from the charge transfer interaction between polarized halogen atoms and Lewis bases, and similar to HB in terms of strength and directionality was defined and extensively reviewed.[8] XB has been widely studied in crystal engineering[9,10,11] and also in materials chemistry.[12,13] Receptors capable of utilizing both HB and XB and working cooperatively are uncommon. There are reports of several receptors that can selectively recognize anions utilizing either XB or both HB and XB as a result of distinct preferences in either or both of the interactions.[14] A more recent report shows the recognition of oxoanions by a bis(triazolium) receptor through HB and XB with high stability constants.[15]

Resorcinarenes are very important supramolecular hosts systems by virtue of their ease to synthesize, the possibility to further functionalize and their interior cavities suitable for guest recognition.[16,17] The concave cavity of resorcinarenes in the C_{4v} conformation can be utilized to bind a variety of guests through multiple weak interactions.[16] The aromatic rings, the phenolic hydroxyl groups and lower rims of resorcinarenes provide a platform for further functionalization.[17] A six-member ring is formed between resorcinarenes and primary amines through Mannich condensation.[18] This six-member ring can be opened in the presence of mineral acids to form *N*-alkyl ammonium resorcinarene salts.[19,20] These cavitand-like structures are stabilized by a strong circular intramolecular hydrogen bonded cation-anion seam formed between the –NH_2^+-R moieties and the anions (usually halides). Chlorides and bromides are optimum in maintaining the C_{4v} symmetric nature of these large organic salt compounds through their size, electronic and HB acceptor affinity.[21]

In this contribution, we present the formation of halogen bonded deep cavity cavitand between *N-cyclo*hexyl ammonium resorcinarene halides **1-3**, and perfluoroiodobenzenes **4-5** (Figure 1). The effect of guest binding through $\pi\cdots\pi$ interactions at different concentrations (macromolar/infinite, millimolar and micromolar) is analyzed. The guest compounds include naphthalene **6**, anthracene **7**, and pyrene **8** (Figure 1). In the solid state, the aromatic regions of the resorcinarene **1** act as a guest, and sits in the upper cavity of the XB assembly (Figure

3). These assemblies are analyzed in the solid state through single crystal X-ray diffraction studies and supplemented in solution through NMR and fluorescence spectroscopic studies.
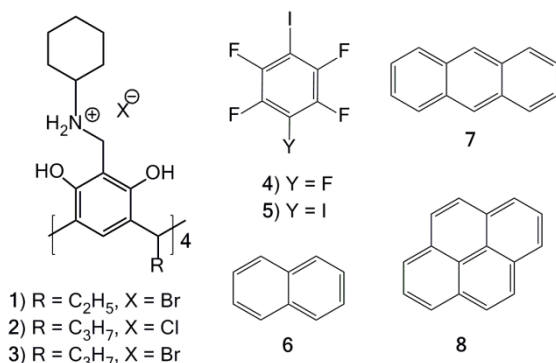

Figure 1. *N-Cyclo*hexyl ammonium resorcinarene salts **1-3**, XB donors **4-5** and guests **6-8**.

Results and discussion

X-Ray Crystallography.

Three *N-cyclo*hexyl ammonium resorcinarene chloride and bromide salts (**1-3**) were synthesized (Figure 1) according to reported procedures.[19,21] Single crystals of the *N-cyclo*hexyl ammonium resorcinarene bromide **3**, were obtained via slow evaporation from a mixture of ethanol (EtOH) and 1,2-dichloroethane ($C_2H_4Cl_2$). In the structure, EtOH_$C_2H_4Cl_2$@**3**, the resorcinarene bromide stack in a head-to-tail motif with a single cavity that is filled with EtOH and $C_2H_4Cl_2$ molecules (Figure 2). The EtOH is located deep in the cavity of the receptor and interacts through two HBs (EtOH$\cdots$Br$^-$ and NR'R''H$_2^+\cdots$OHEt) and CH$\cdots\pi$ interactions between the methyl groups and the electron rich resorcinarene moiety. The disordered 1,2-dichloroethane is located close to the cavity edge between the cyclohexyl rings, wherein it donates weak HB interactions to Br$^-$ (CH$\cdots$Br$^-$) and to O atom of EtOH (CH$\cdots$O).
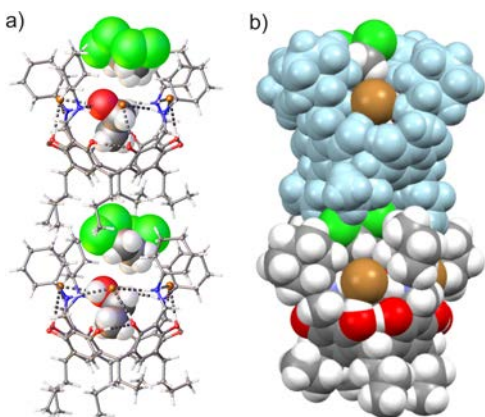

Figure 2. Head-to-tail arrangement in the solvate crystal structure EtOH_$C_2H_4Cl_2$@**3**: a) Ball and stick presentation with the solvent guests in CPK, b) CPK presentation.

Cocrystallization of the resorcinarene bromide **1** and slight excess of 1,4-diiodotetrafluorobenzene **5**, in CHCl$_3$ resulted in single crystals of the assembly CHCl$_3$@[**1•(5)$_4$**] (Figure 3) analyzed by X-ray

crystallography. In the structure CHCl$_3$@[**1•(5)$_4$**], the strong circular HB seam ($\cdots$NR'R''H$_2^+\cdots$Br$^-\cdots$NR'R''H$_2^+\cdots$Br$^-\cdots$)$_2$ maintains the cavitand-like structure.[19,21] Anions being good Lewis bases are also suitable XB acceptors. Four molecules of **5** are halogen bonded to the bromide anions resulting in an analogue of a deep cavity cavitand (Figure 3).[22] The 1,4-diiodotetrafluorobenzene **5** molecules bind to the open space between cyclohexyl rings of the resorcinarene tetracation with both Br$^-\cdots$IC$_6$F$_4$I XBs and van der Waals (IC$_6$F$_4$I)$\cdots$*cyclo*hexyl interactions. The interaction ratio R$_{XB}$ (R$_{XB}$=d$_{XB}$/(X$_{vdw}$+B$_{vdw}$))[23,24] can be used as a rough measure of the strength of the halogen bond. The R$_{XB}$ ratios between 0.7–0.8 can be regarded as "strong" XB, while 0.8–0.9 are "moderate" and 0.9–1.0 "weak". The four I$\cdots$Br$^-$ halogen bonds are relatively short (3.25Å) resulting in the XB ratio $R_{XB} = 0.85$ with C–I$\cdots$Br$^-$ angle of 170.28^o thus demonstrating moderate XB acceptor character of the large organic salts (Figure 3). The halogen bonded IC$_6$F$_4$I molecules together with the *cyclo*hexyl rings form a wall on the upper rim thus resulting in a deep cavity. The height of the cavity is *ca.* 14.90 Å defined by the centroid-to-centroid distance of the four aromatic hydrogens on the lower rim and the four uppermost iodines of the halogen bonded IC$_6$F$_4$I molecules. The effective diameter of the upper cavity in CHCl$_3$@[**1•(5)$_4$**] defined by the closest van der Waals surfaces between the opposite uppermost iodine atoms of IC$_6$F$_4$I molecules is *ca.* 15.76 Å. The solvent accessible cavity void volume was calculated to be *ca.* 644.16 Å^3 (see ESI).
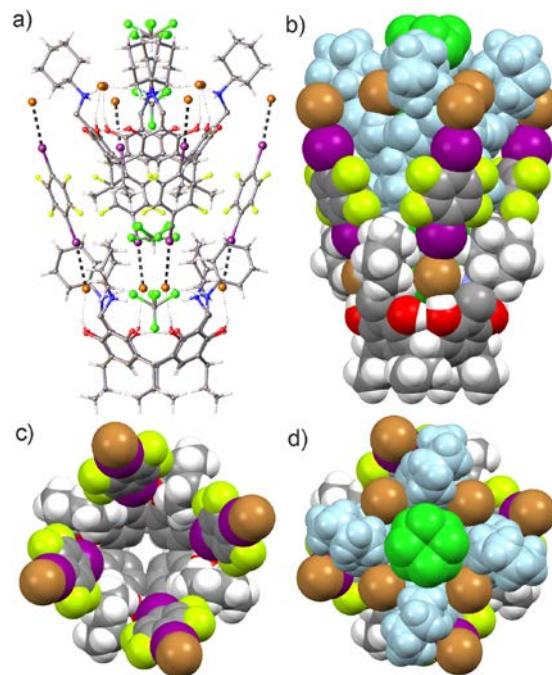

Figure 3. Crystal structure of halogen bonded deep cavity cavitand CHCl$_3$@[**1•(5)$_4$**]. The disordered CHCl$_3$ molecule sits deep into the cavity of the assembly. A second resorcinarene molecule is self-included in the upper cavity of the assembly and interacts through strong $\pi\cdots\pi$ stacking between electron poor phenyl rings of **5** and the electron rich phenyl rings of the resorcinarene **1**, resulting to an assembly that could be described as [CHCl$_3$+**1**]@[**1•(5)$_4$**] and extends into a polymeric herringbone or cup-pile arrangement.

A disordered $CHCl_3$ molecule is located in the cavity of $CHCl_3@[\mathbf{1}\bullet(\mathbf{5})_4]$ which is split over two positions. One part of the $CHCl_3$ in the bottom of the cavity has one C–Cl on the four-fold symmetry axis with another two Cl atoms averagely situating above over four positions due to the four-fold symmetry; while, another part of the disordered $CHCl_3$ molecule sits in the middle of the cavity. The three C-Cl bonds are rotating around the four-fold axis, which can be observed in 8 positions. The cavity is large enough for the lower half of another resorcinarene moiety to barge into the upper cavity position of the halogen bonded assembly. Thus each $CHCl_3@[\mathbf{1}\bullet(\mathbf{5})_4]$ assembly acts as a pocket for the next assembly resulting to a polymeric herringbone or cup-pile arrangement in one direction (Figure 3). The arrangement is stabilized by four relatively strong $\pi\cdots\pi$ interactions between the electron rich phenyl rings of **1** in guest assembly and the electron poor phenyl rings of **5** in host assembly with the closest phenyl ring centroid-to-centroid distance of 4.68 Å (centroid-to-centroid of benzene dimer is 4.96 Å).

The other iodine ends of the four XB donors IC_6F_4I in the $CHCl_3@[\mathbf{1}\bullet(\mathbf{5})_4]$ assembly, are each halogen bonded to the bromides of the next assembly in the opposite direction forming $Br^-\cdots IC_6F_4I\cdots Br^-$ XB system and resulting in a 3-D polymeric arrangement resembling an egg-crate-like supramolecular network (Figure 4). The tightly packed supramolecular network looks like a pile of egg crates (Figure 4c).
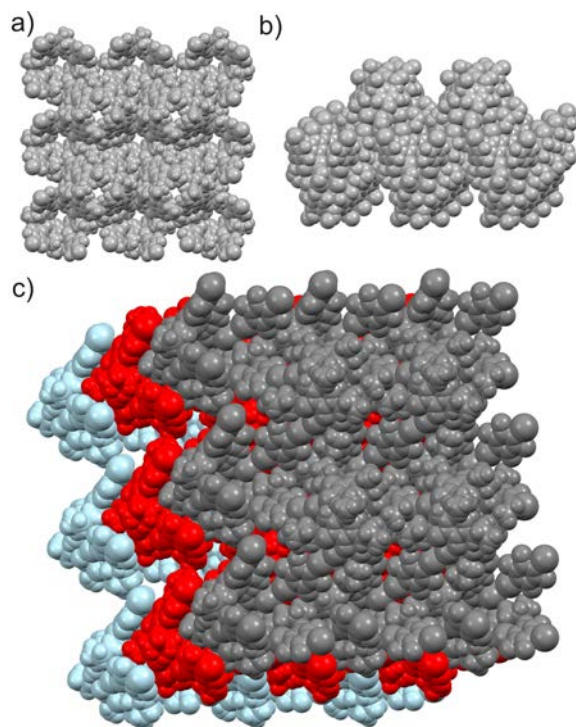

Figure 4. Top view (a) and side view (b) of the partial packing diagram of the complex assembly $\mathbf{1}\bullet(\mathbf{5})_4$ resembling an egg-crate. c) The packing of the 3-D supramolecular network looking like a pile of egg crates.

NMR Spectroscopy

The strong $\pi\cdots\pi$ interactions between the π rich surface of the resorcinarene skeleton of one receptor interacting with the π poor surface of the XB donor IC_6F_4I prompted us to investigate the possibility of these halogen bonded supramolecular structures to form host-guest complexes with electron rich guests **6-8**. Solvent interference makes demonstrating halogen bonding in solution a rather tedious and sometimes an elusive process. However, recent reports have shown NMR spectroscopy to be the most effective tool to study halogen bonding in solution.[25,26,27,28] Though ^{19}F NMR is suitable for halogen bonding involving perfluorinated compounds, comparative monitoring[25,29] of ^{1}H NMR chemical shift changes has been utilized for the detection of XB formation.[25] Single crystal analyses clearly show the halogen bonded deep cavity cavitands resulting from an infinite concentration range in the solid state. These assemblies were then probe in the millimolar concentration range in solution via a series of NMR analyses.
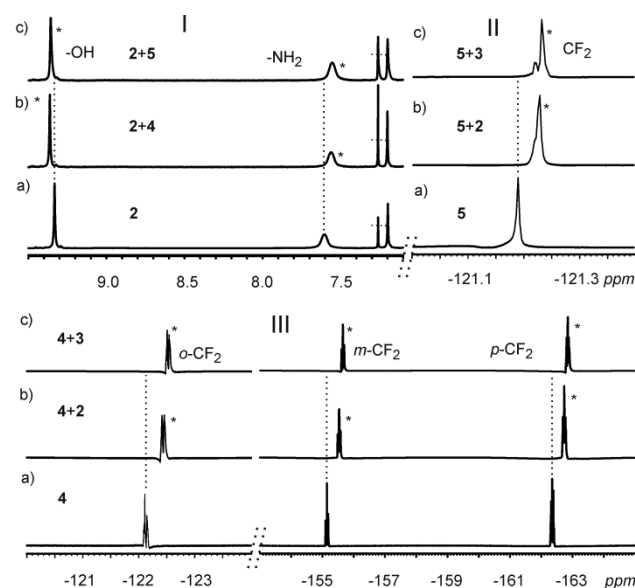

Figure 5. I: ^{1}H NMR (in $CDCl_3$ at 303 K) of: a) **2** (30 mM), b) 1:4 mixture of **2** and **4**, c) 1:4 mixture of **2** and **5**. II: ^{19}F NMR of: a) **5** (30 mM), b) 4:1 mixture of **5** and **2**, c) 4:1 mixture of **5** and **3**. III: ^{19}F NMR of: a) **4** (30 mM), b) 4:1 mixture of **4** and **2**, c) 4:1 mixture of **4** and **3**.

In the experiment, several samples containing the resorcinarene hosts **2-3** and the XB donors **4-5** in 1:4 ratio with concentrations of *ca* 30 mM were prepared, and their ^{1}H and ^{19}F NMR were recorded at 303 K in $CDCl_3$. The –OH and $-NH_2$ groups of the hosts are involved in the strong HB seam involving the halides. The formation of XBs with the halides will thus change the electronic environment and therefore has a synergetic effect on the –OH and $-NH_2$ protons. Indeed, distinct changes in the –OH and $-NH_2$ signals were observed thus confirming the existence of XBs in solution under these conditions (Figure 5I, SI). ^{19}F NMR analysis was also utilized to further probe the existence of halogen bonding in solution. Resonance changes as a result of the formation of XBs of the –CF protons of **4** and **5** in the presence of **2** and **3** in a 4:1 ratio were observed (Figure 5II, 5III). It is then concluded that the XB system that was clearly observed in the solid state at an

infinite concentration is also observed in solution at the *ca* 30 mM concentration range.

The X-ray structure clearly shows $\pi\cdots\pi$ interactions between the electron poor π surface of the XB donor IC_6F_4I **5** and the electron rich π surface of the phenyl rings of the resorcinarene skeleton. We then proceeded to investigate the possibility of these assemblies to similarly bind electron rich phenyl rings of the guest **6**-**8**. ^1H and ^{19}F NMR measurements of a series of samples containing the host **2**-**3**, the XB donors **4**-**5** and the aromatic guests **6**-**8** with electron rich π surfaces, in a 1:4:2 ratio were analyzed. It is generally difficult to observed $\pi\cdots\pi$ interactions in solution at low concentrations. Since the main driving force is the $\pi\cdots\pi$ interaction between the guests **6**-**8** and the XB donor situated at the upper cavity of the XB deep cavity cavitand, it thus expected that the binding process will be very fast on the NMR timescale.
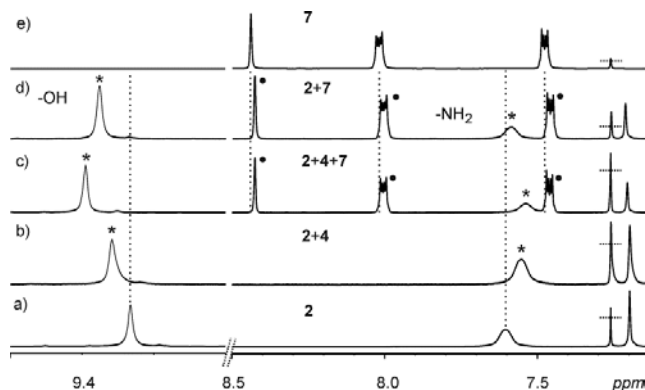

Figure 6. ^1H NMR (in $CDCl_3$ at 303 K) of: a) **2** (30 mM), b) 1:4 mixture of **2** and **4**, c) 1:4:2 mixture of **2**, **4** and **7**, d) 1:2 mixture of **2** and **7**, e) **7** (30 mM).
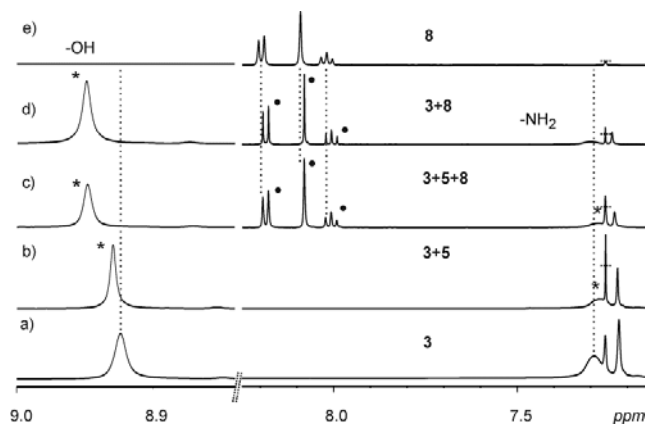

Figure 7. ^1H NMR (in $CDCl_3$ at 303 K) of: a) **3** (30 mM), b) 1:4 mixture of **3** and **5**, c) 1:4:2 mixture of **3**, **5** and **8**, d) 1:2 mixture of **3** and **8**, e) **8** (30 mM).

Minor up field shifts in the ^1H NMR resonances of the guest protons were observed from the samples and attributed to $\pi\cdots\pi$ interactions. Changes in the –OH and –NH_2 signals of the host also confirms the interactions between the host and the guests (Figure 6&7, SI). The presence of the guests **6**-**8** in the upper cavity of the assembly interacts with the XB donors **4**-**5** and thus affects their XB interactions with the host halides resulting

in synergetic changes to the –OH and –NH_2 signals. ^{19}F NMR of these samples also shows minor changes in the –CF_2 signals in the presence of the guests (Figure 8, SI).
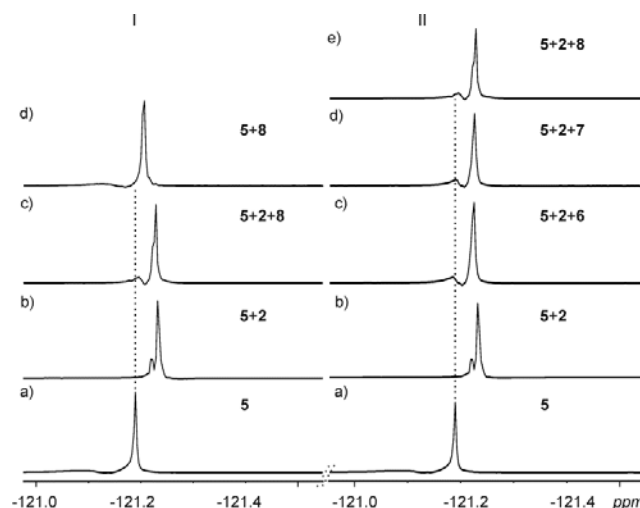

Figure 8. I: ^{19}F NMR (in $CDCl_3$ at 303 K) of: a) **5** (30 mM), b) 4:1 mixture of **5** and **2**, c) 4:1:2 mixture of **5**, **2** and **8**, d) 1:1 mixture of **5** and **8**. II: ^{19}F NMR of: a) **5** (30 mM), b) 4:1 mixture of **5** and **2**, c) 4:1:2 mixture of **5**, **2** and **6**, d) 4:1:2 mixture of **5**, **2** and **7**, e) 4:1:2 mixture of **5**, **2** and **8**.

Fluorescence Spectroscopy

As aromatic fluorophores **6**-**8** were used as guests for the studies, it was imperative to look for manifestations of host-guest interactions through fluorescence spectroscopy. However to eliminate the possibility of excimer formation (and loss of vibrational fine structure), the emission studies were carried out at micromolar concentrations.[30,31] Unfortunately, no considerable changes in the fluorescence spectra of pyrene were observed in the presence of host **2**-**3** and the XB donor **4** (Figure 8). The constant I_1/I_3 ratio also indicated that there has been little or no change in the pyrene environment[30,31] even in the presence of cavitand hosts. However, it should be noted that even at much higher concentrations (millimolar), only very weak host-guest interactions were observed by NMR studies. Considering the various competitive equilibria/interactions in solution, formation of host-guest complexes at micromolar concentrations would have been extremely difficult and hence was not reflected in any significant changes in the fluorescence spectra of pyrene or other guests **6**-**7** (see SI).
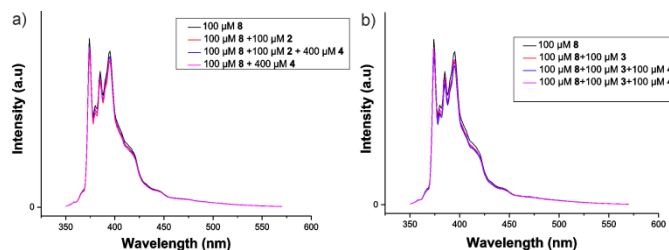

Figure 9. Fluorescence spectra of **8** (100 μM) in presence of **4** (400 μM) and a) **2**(100 μM) & b) **3**(100 μM) in $CHCl_3$. λ_{ext} = 330 nm.

Conclusions

In conclusion, we present examples of HB and XB working in tandem in a cooperative manner to form analogues of deep cavity cavitands between *N-cyclo*hexyl ammonium resorcinarene halides and perfluoroiodobenzenes **4-5**. X-ray crystallography confirms moderate XB between the XB donor **5** and the bromide acceptor in the resorcinarene salt **1**. These results show the formation of an analogue of a deep cavity cavitand, with a lager cavity size, larger than some reported covalent deep cavity cavitands.[32] The lower rim of the resorcinarene is located in the upper cavity of the halogen bonded assembly acting as a guest and held together by strong $\pi \cdots \pi$ interactions between the electron poor ring of the XB donor **5**, and the electron rich phenyl ring of the resorcinarene skeleton **1**. The ability of NMR spectroscopy to reliably observe nucleus specific information and thermodynamic information[26] was used to probe the existence of XB in solution via a series of ^{1}H and ^{19}F NMR analyses. The presence of guest molecules with electron rich π-surfaces did not dissociate the assemblies and even showed a fast exchange host-guest process at the millimolar concentration range. The XB process was determined to be concentration dependent as no changes were observed from several mixtures of the resorcinarene salts **2-3**, the XB donors, **4-5** and the guests **6-8** at the micromolar range through fluorescence measurements. Though perfluorinated iodocompounds are known to be good XB donors, the resorcinarene salts are proving to be suitable multivalent XB acceptors and careful organization of the components at suitable concentrations can lead to more sophisticated functional supramolecular architectures.

Notes and references

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