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# The quest for a molecular capsule assembled *via* halogen bonds

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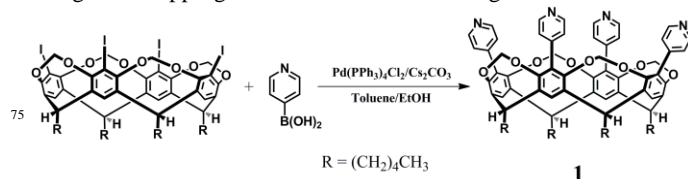
DOI: 10.1039/b000000x

A halogen-bonded capsule is obtained *via* directed assembly of a rigid tetra(3-pyridyl) cavitand and a flexible tetra(4-iodotetrafluorophenyl)calix[4]arene. The pyridyl nitrogen atoms from one cavitand molecule interact with the iodine atoms of a single calixarene molecule through short and directional I...N halogen bonds. The flexibility of the ethylenedioxy moieties on the calixarene platform results in positional flexibility of the iodotetrafluorobenzene sites which, coupled with a supramolecular chelating effect, allow for an effective partner-induced geometric fitting between four nitrogen atoms on the cavitand and four iodine atoms on the calixarene.

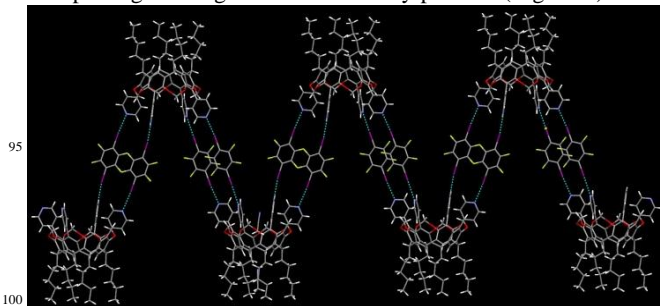
The deliberate use of precise self-assembly processes for combining two or more complementary molecular building blocks into discrete capsular structures has received considerable attention in recent years.<sup>1-5</sup> The motivation for synthesizing architectures with well-defined and accessible inner cavities is driven by a need to achieve selective encapsulation of molecular guests of different shapes, sizes, and chemical characteristics.<sup>6</sup> Such assemblies can be used for chemical separation<sup>7</sup> and gas encapsulation,<sup>8</sup> as reaction chambers<sup>1a</sup> and chiral receptors, in catalysis, social isomerization,<sup>9</sup> and drug-delivery. Covalent interactions, which tend to produce very rigid systems,<sup>6,8-10</sup> metal-ligand interactions,<sup>11,12</sup> and hydrophobic effects,<sup>13</sup> have been used for capsule construction. Hydrogen bonds (HBs) have also been successfully employed for the self-assembly of numerous molecular capsules, with the added advantage that synthetic errors can be corrected through thermodynamic equilibration, and synthetic short-cuts can be devised through multi-component assembly.<sup>2d,14-18</sup> There are, however, some practical limitations with HBs since molecules with multiple HB-donors typically require very polar solvents, and they tend to be functional only within certain pH ranges. As a result, new non-covalent interactions capable of driving the assembly of capsules is highly desirable.

The halogen bond (XB)<sup>19</sup> has emerged as a promising tool in the field of non-covalent synthesis. Despite the fact that HBs and XBs share many characteristics such as directionality and strength,<sup>20</sup> no structurally characterized halogen-bonded capsule has been reported so far.

Analogous to hydrogen-bonded heteromeric capsules that use 4-pyridyl moieties attached to calixarene platforms,<sup>3</sup> in our first attempt at making a halogen-bonded capsule we opted for the C-pentyltetra(4-pyridyl)cavitand **1** as it provides a combination of four pre-organized XB-acceptor sites with a rigid interior and good solubility. The tetra-pyridyl cavitand **1** was combined with 1,4-diiodo-tetrafluorobenzene (**A**) which can operate as a linear bidentate XB-donor when interacting with pyridine derivatives. We synthetic target was a hexameric capsule where four diiodotetrafluorobenzene units bridge two capping cavitands *via* a total of eight I...N XBs.



The covalent synthesis of **1** was achieved in reasonable yields through a Suzuki reaction (see Supporting Information). The reaction between cavitand **1** and diiodotetrafluorobenzene **A** was carried out by combining the cavitand (0.020 g, 0.0178 mmol) in 5 mL of acetonitrile, with an excess of **A** (0.029 g, 0.0712 mmol) in 5 mL of ethanol. The resulting solution was warmed and allowed to stand at r.t. Slow evaporation of the solvent produced colourless, cubic crystals after 4 days. The bands in the IR spectrum relative to those in the starting modules<sup>21</sup> were consistent with halogen bonded-adducts, but the crystal structure showed that the resulting supramolecular architecture only partly succeeded in completing the targeted self-assembly process (Figure 1).



**Fig. 1** Undulated infinite 1-D array **1•A<sub>2</sub>** formed *via* XB-driven self-assembly of one cavitand **1** and two diiodotetrafluorobenzene **A**.

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<sup>†</sup> Electronic supplementary information (ESI) available: Synthesis files and crystal data for **1•A<sub>2</sub>** and **2•B**. See DOI: 10.1039/b000000x

As expected, cavitand **1** does behave as a tetradentate XB-acceptor and all four nitrogen atoms are engaged in I...N XBs with iodine atoms from molecules of **A** which, in turn, function as bidentate XB-donors (I...N distances; 2.78-2.87 Å; C-I...N angles; 170-180°). However, when four diiodotetrafluorobenzene units **A** bind to the nitrogen atoms of **1**, the linear arrangement of the iodine atoms on **A** and the directionality of the formed XBs produce a divergent orientation of the nitrogen atoms of **1**. A pentameric adduct with a concave shape is thus formed where the external iodine atoms are too far apart from each other to match the four nitrogen atoms of a single incoming cavitand molecule **1**. In fact, instead of the desired capsule, a highly undulated infinite ribbon is formed wherein the cavitands alternate with pairs of diiodotetrafluorobenzene linkers.

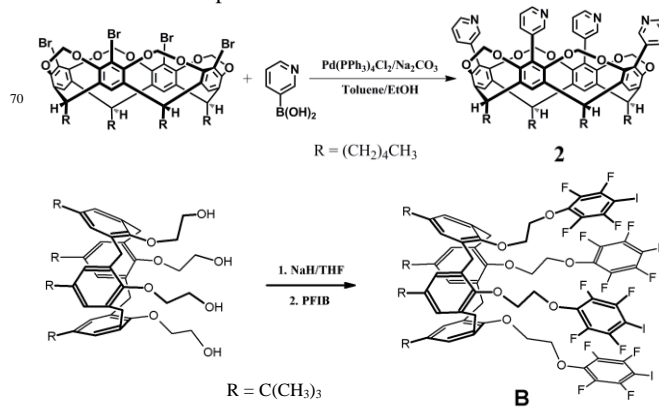
XBs are usually described as being more directional, *i.e.* less flexible, than corresponding HBs, as a consequence of the strong localization of the positive region of the electrostatic potential surface of halogen atoms, *i.e.* the  $\sigma$ -hole, which is responsible for the occurrence of XBs.<sup>22</sup> Therefore, since a convergent self-assembly process is necessary for the construction of a discrete heteromeric capsule, the actual positions of the nitrogen atoms in **1** when matched with the iodine atoms of **A**, are not ideally suited for the assembly of such a supramolecular species. For this reason, we decided to pursue the tetra(3-pyridyl)cavitand **2**, which, thanks to the *meta* orientation of the pyridyl nitrogen atoms, is potentially better suited as a XB-acceptor platform for the assembly of a molecular capsule.

On the other hand, even if all of the pyridyl nitrogen atoms of **2** were conveniently oriented in a convergent manner, a linear bridging molecule is not inherently tailored to fulfil the specific geometric requirements associated with the formation of a discrete heteromeric capsule. With the idea of exploiting a supramolecular “chelating” effect to obtain a capsule, we thus pursued the synthesis of the calix[4]arene derivative **B** where four XB-donor sites are attached to a calix[4]arene platform *via* flexible ethylenedioxy glycol chains. Our hypothesis was that by pairing one molecule of **2** with one molecule of **B**, once the first I...N bond between **2** and **B** is formed, additional I...N bonds are kinetically favored to take place between the same two molecules, instead of involving a third and/or fourth molecule (as long as the geometries of the components allow for such pairings to take place).

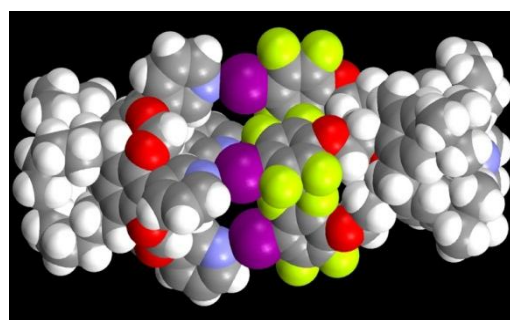
The rationale behind the selection of the *p*-*tert*-butyl-calix[4]arene tetra-2-(4-iodotetrafluorophenoxy)ethyl ether **B** as XB-donor subunit of the heteromeric capsule was that: 1) the calix[4]arene scaffold allows for a straightforward pre-organization of the four XB-donor sites at the lower rim of the molecule, 2) the synthesis of 4-iodotetrafluorophenoxy derivatives is easy and the iodine atoms give rise to strong XBs with pyridyl residues,<sup>23</sup> and 3) the conformational flexibility of the -OCH<sub>2</sub>CH<sub>2</sub>O- bridges separating the calixarene platform and the peripheral iodotetrafluorobenzene moieties, allows for an effective partner-induce fitting between the four XB-donor sites on **B** and the four XB-acceptor sites of a single cavitand **2**.

The C-pentyltetra(3-pyridyl)cavitand **2** and the

calix[4]arene **B** were synthesized according to literature procedures<sup>23,24</sup> and isolated as white crystalline solids (see Supporting Information). The non-covalent combination of the two modules was realized by adding the cavitand **2** (0.006 g, 0.0053 mmol) dissolved in 5 mL of ethanol to a solution of calix[4]arene **B** (0.010 g, 0.0052 mmol) in 5 mL of the same solvent. The resulting solution was warmed and allowed to stand for slow evaporation at r.t.



IR data were again consistent with the formation of a new halogen-bonded species. The single crystal structure determination of **2·B** was very complicated (see Supplementary Information) but it was possible to establish the existence of the heteromeric capsule, thanks to the pairing of one tetra(3-pyridyl)cavitand **2** and one tetrakis-iodotetrafluorophenylcalix[4]arene **B** via four N...I XBs (N...I distance in the range 2.79-2.89 Å, N...I-C angle in the range 169-177°) is realized in 60% of the cases (Figure 2), while for the remaining 40% the capsule is partially opened (N...I distance in the range 2.78-3.12 Å, N...I-C angle in the range 154-177°), one of the N...I XBs being disrupted (N...I distance: 5.18 Å) (ESI).



**Fig. 2** Space filling representation of the closed dimeric capsule **2(E)·B(A)** (see ESI for numbering scheme) held together by four I...N XBs between one cavitand **2** and one calix **B**. Colour code: Grey, carbon; white, hydrogen; red, oxygen; blue, nitrogen; yellow, fluorine; violet, iodine..

In the complex **2·B**, the four (or three) pyridyl rings of **2** are all inwardly oriented and converge towards the same XB-donor **B**. The four iodotetrafluorophenyl arms of the closed capsule are confined in a very crowded manner which may be explained, at least in part, by the strict energetic and

geometric requirements of the strong and linear N...I XBs. However, the congestion of the four arms requires that one of the N...I XBs is sacrificed in the partially opened capsule.

The capsules' packing is relatively open with cavities filled by very mobile chlathrated molecules of CH<sub>3</sub>CN. We have identified at least two solvent molecules inside the cavity of the capsule, one in the aromatic cavity of the calix[4]arene **B** and one among the four pentylic arms of the cavitand **2**; all these solvent molecules have unitary population factors, while at least other two molecules with population factor being 0.75 were localized out of the capsule and at 'the gate' of the opened capsule. The structure contains more solvent molecules having partial population, but it was impossible to fix them adequately for the refinement.

The effectiveness of I...N XBs in the directed assembly of structurally complex and polydentate tectons to give solid 1D, 2D, and 3D networks has been widely proven in recent years.<sup>19</sup> The few examples of formation of discrete adducts are obtained from simple and monodentate tectons.<sup>25</sup> In this study we demonstrate that the careful design of interacting tectons can produce the desired discrete heteromeric capsule, driven by four I...N XBs. **2•B** is the first halogen-bonded capsule reported to date and its structural similarity with some hydrogen-bonded heteromeric capsules<sup>3,5</sup> is a further indication of the analogies existing between XB and HB. The formation and structural characterization of **2•B** underscores that the strength and directionality of co-operative I...N XBs are likely to make these intermolecular interactions very valuable additions to the supramolecular tool box when it comes to non-covalent synthesis of complex heteromeric architectures. Our findings also highlight the importance of supramolecular chelation<sup>26</sup> in the formation of discrete capsular structure from the interaction between two moieties with complementary molecular-recognition sites.

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