

# RESORCINARENE-BASED HYDROGEN-BONDED MOLECULAR CAPSULES

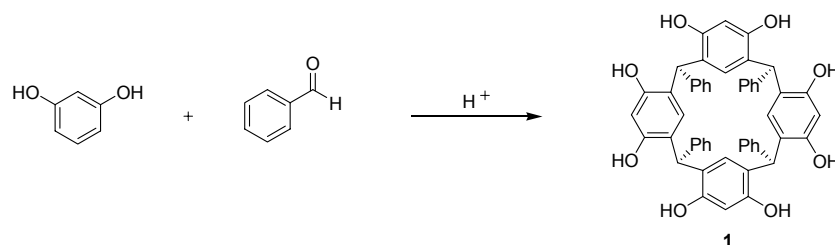
Reported by Emily G. Schmidt

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## INTRODUCTION

The acid-catalyzed condensation reaction between resorcinol and benzaldehyde was first reported by Baeyer in 1872.<sup>1</sup> Although Niederl and Vogel proposed the correct structure of the product in 1940,<sup>2</sup> it was not proven conclusively until Erdtman and coworkers reported the crystal structure of the cyclic tetramer, resorcin[4]arene (**1**), in 1968.<sup>3</sup> Since that time, the readily available resorcinarenes have been found to have interesting complexation and material properties. In addition, resorcinarenes serve as the basis for cavitands and carcerands.

Scheme 1 Synthesis of resorcin[4]arene.



Resorcinarenes are capable of forming 1:1 complexes with other molecules in solution. For example, in basic media half of the phenol groups are deprotonated and the resulting bowl-shaped tetraanion has a high affinity for alkylammonium cations. In addition, as an octol, the cyclic tetramer can bind polar organic molecules such as D-ribose and dicarboxylic acids through hydrogen-bonding interactions.<sup>4</sup>

Resorcinarenes are also the starting materials for the synthesis of cavitands, generated by covalently linking hydroxyl groups on adjacent aromatic rings (**2**, Figure 1).<sup>5</sup> The resulting rigid, bowl-shaped synthetic compounds form inclusion complexes with a variety of solvents including acetonitrile and chloroform. Covalently linking two cavitands at their upper rims forms a carcerand (**3**, Figure 2).<sup>6</sup> During the process of covalently linking the cavitands, small organic molecules can be trapped inside the complex. Once incarcerated, the guest molecules can only be freed by breaking covalent bonds.

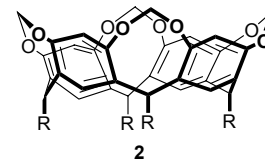


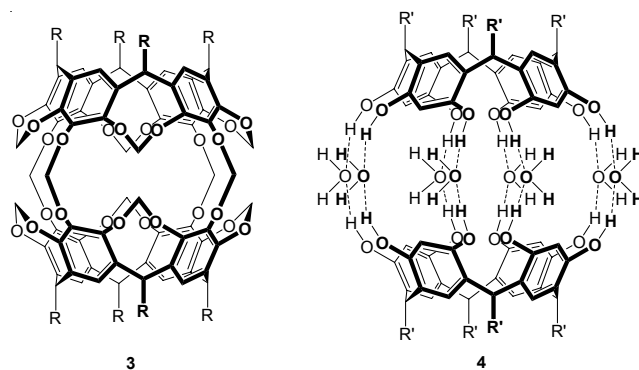
Figure 1 An example of a cavitand with bridging methylene units.

The report of the first carcerand by Cram in 1985<sup>7</sup> has inspired chemists to create similar structures in which the subunits are joined by noncovalent linkages. While these “capsule” complexes still protect the guests from solvent and other molecules outside, the weaker noncovalent interactions

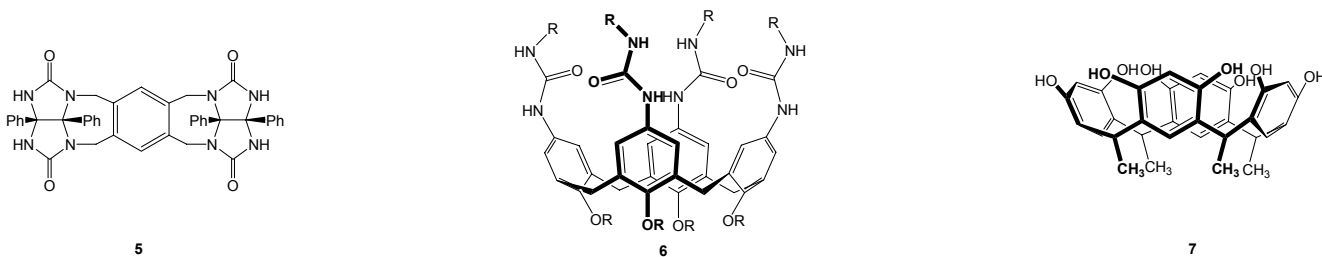
allow the guests to be reversibly entrapped (Figure 2). Analogous to the covalent links between the cavitand subunits in carcerands, bridging solvent molecules are necessary for the assembly of supramolecular capsules. The hydrogen-bonding molecules serve as spacers to help avoid steric interactions between the resorcinarenes.

The formation of these capsule complexes involves two important processes: assembly of the subunits and encapsulation of the guest molecule(s). In order for capsule assembly to occur and for the structure to hold together, the subunits must be able to participate in reversible, noncovalent interactions. Two common strategies utilize hydrogen bonds and metal-ligand interactions. In both cases, symmetrical subunits are generally used in order to make as many weak, reversible interactions as possible to generate robust capsules.<sup>8,9</sup>

Several different types of subunits have been found to generate hydrogen-bonded supramolecular capsules. Figure 3 shows examples of glycoluril- and cyclophane-based monomers. Cyclophane-based capsules have been constructed utilizing bowl-shaped calixarenes and resorcinarenes. This report will focus on the resorcinarene-based hydrogen-bonded molecular capsules.<sup>4,5</sup>



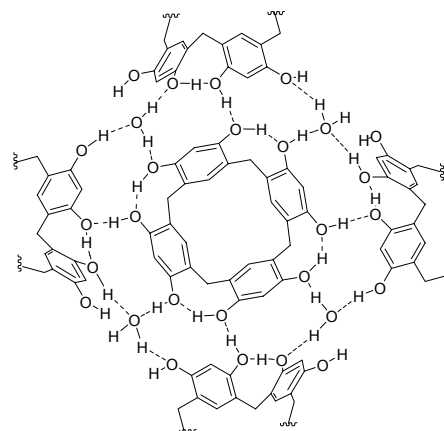
**Figure 2** A carcerand **3** and a resorcinarene-based hydrogen-bonded dimeric capsule **4**.



**Figure 3** Types of subunits that form hydrogen-bonded capsules. A glycoluril-derived subunit (**5**), a calixarene (**6**), and a resorcinarene (**7**).

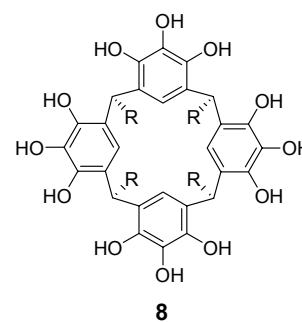
## HEXAMERIC CAPSULES

In 1997, MacGillivray and Atwood reported the formation of an impressive spherical hexamer composed of six resorcin[4]arene subunits and eight water molecules in the solid state (Figure 4). This hexameric assembly, held together by sixty hydrogen bonds, had an internal volume of approximately 1375 Å<sup>3</sup>. Although x-ray analysis data indicated that guest molecules were present, their identity



**Figure 4** Spherical hydrogen-bonded assembly of resorcin[4]arene subunits.

could not be determined.<sup>10</sup> Shortly thereafter, Mattay and coworkers reported the formation of a similar hexameric capsule formed from hydroxyresorcinarene units (**8**, Figure 5). This slightly larger hexameric assembly had a cavity of approximately 1520 Å<sup>3</sup>. Encapsulation of ten acetonitrile molecules was observed in the crystal structure. Although the resorcin[4]arene hexamer was reportedly quite stable, the hydroxyresorcinarene analog appeared to be more fragile as additional attempts to isolate the hydroxyresorcinarene hexamer failed.<sup>11</sup>



**Figure 5** Hydroxyresorcinarene subunits with alkyl groups at methine bridges.

Atwood and coworkers demonstrated the reproducible formation of robust hexameric hydroxyresorcinarene capsules, both in solution and in the solid state.<sup>12</sup> These large assemblies were observed using <sup>1</sup>H NMR spectroscopy for a variety of hydroxyresorcinarenes by varying the alkyl groups attached at the methine bridges and the solvent polarity. Capsules containing longer alkyl groups were found to be more soluble in nonpolar solvents while the presence of shorter alkyl groups increased the solubility in polar solvents. For example, the *n*-pentylhydroxyresorcin[4]arene (**8**, R = *n*C<sub>5</sub>H<sub>11</sub>) was soluble and stable in a 1:1 mixture of D<sub>2</sub>O and acetone-*d*<sub>6</sub>.

Knowing from previous work that resorcinarene-based cavitands have a high affinity for ammonium cations,<sup>13</sup> Rebek and Shivanyuk added a variety of quaternary ammonium and phosphonium guests to solutions of resorcin[4]arene. By <sup>1</sup>H NMR spectra, 6:1 complexes of resorcin[4]arene to guest were observed for the tetraalkylammonium salts with alkyl groups containing three to seven carbon atoms. In general, assemblies containing the larger tetraalkylammonium salts were more stable in solution. Although complexation was also observed with smaller tetraethylammonium and phosphonium cations, these guests were encapsulated by just two resorcinarenes, forming dimeric complexes.<sup>14</sup>

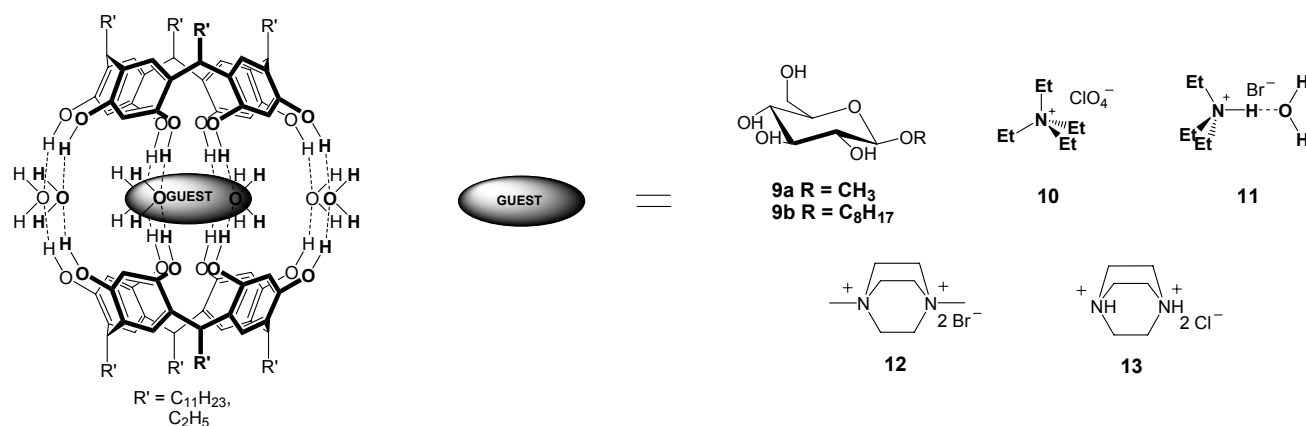
Subsequently, it was shown that the covalent compounds Bu<sub>4</sub>SbBr and Ph<sub>4</sub>SbBr could also drive the self-assembly of hexameric capsules.<sup>15</sup> In previous investigations with a similar assembly, Mecozzi and Rebek found that optimal encapsulation occurred when the guest molecules occupied approximately 55 % of the cavity volume.<sup>16</sup> With this in mind, aromatic guests were added to solutions containing the antimony compounds to determine if coencapsulation would occur. Since the antimony (V) bromides only occupy an estimated 25 % of the cavity, coencapsulation of benzene, toluene, and *p*-xylene was observed as well.

After it was shown that tetraalkylammonium salts and covalent antimony bromides could drive the formation of the hexamer, Kaifer and Philip demonstrated that the electrochemically-generated ferrocenium ion had a similar effect.<sup>17</sup> In a solution with a resorcinarene present, a lower potential was

observed for the oxidation of ferrocene to its cation, suggesting the stabilization of the electrochemically-generated ferrocenium ion through noncovalent interactions in the capsular assembly. Once entrapped, the electrochemical behavior of ferrocene changed noticeably. In the presence of six equivalents of resorcinarene, the reduction of the ferrocenium ion was inhibited, indicating complete encapsulation.  $^1\text{H}$  NMR data were also consistent with the formation of a hexamer. Due to the paramagnetic character of the ferrocenium cation, the diamagnetic cobaltocenium ion was used in its place. In the presence of six equivalents of host, free guest was no longer observed in the NMR spectrum while the resonance for the entrapped guest reached full development.

## DIMERIC CAPSULES

In 1992, Aoyama and coworkers reported the formation of a 2:1 complex between resorcin[4]arene and methyl  $\beta$ -glucopyranoside (**9a**, Figure 6) in  $\text{CDCl}_3$ . Analysis of the interaction between the same resorcinarene cyclic tetramer and octyl glucoside (**9b**) revealed the formation of a 1:4 host to guest complex. The difference in the stoichiometry for the assemblies was attributed to the difference in the solubility of the two glucosides in chloroform. While **9b** is readily soluble, solvophobic **9a** was only solubilized upon encapsulation.<sup>18</sup>

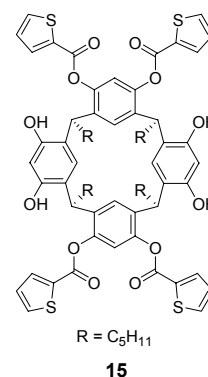


**Figure 6** Dimer of resorcinarene with an entrapped guest. Guests: methyl glucoside (**9a**), tetraethylammonium cation (**10**), triethylammonium-water hydrogen-bonded complex (**11**), 1,4-dimethyl-DABCO dibromide (**12**), and DABCO dichloride (**13**).

More recently, crystal structures of a variety of dimeric capsules with entrapped cations have been reported. In these cases, cation- $\pi$  interactions between the guests and the resorcinarene hosts are expected to play an important role in capsule formation. Two to one complexes of tetraethylresorcin[4]arene with the tetraethylammonium ion (**10**),<sup>19</sup> the hydrogen-bonded complex  $\text{Et}_3\text{N}^+-\text{H}\cdots\text{OH}_2$  (**11**),<sup>20</sup> or 1,4-dimethyl-1,4-diazoniabicyclo[2.2.2]octane (1,4-dimethyl DABCO) dibromide (**12**)<sup>21</sup> have been observed in the solid state. In each case, the two resorcinarenes were eclipsed with respect to each other and the counterion(s) resided in the pockets created by the ethyl

groups on the methine bridges of the resorcinarenes. Analysis of the dimeric capsule with the DABCO dication entrapped revealed a slightly modified assembly. In the crystal structure, the chloride counterions bridged the two resorcinarene molecules, and the two halves of the capsule were staggered with respect to each other, allowing them to come closer together.<sup>17</sup>

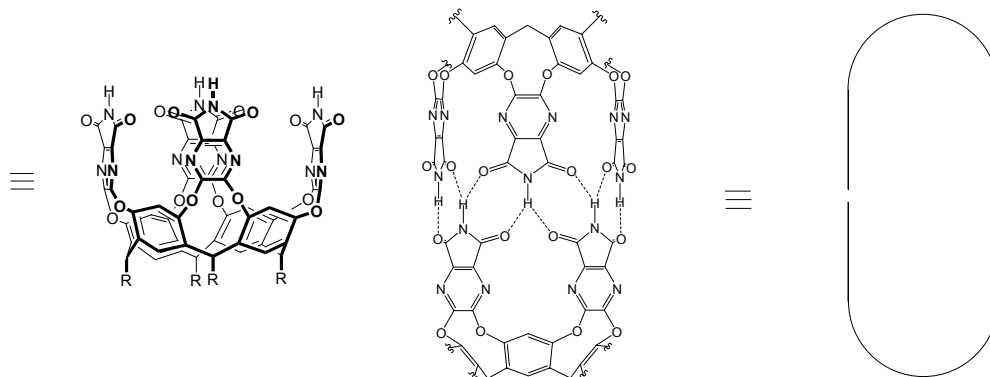
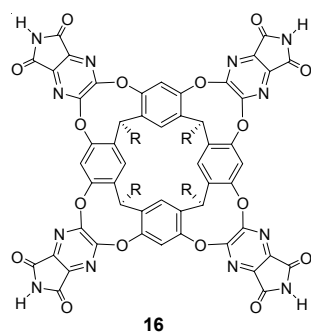
Bohmer and coworkers observed the formation of dimeric capsules composed of two molecules of resorcinarene tetraester **15**. In this case, the four unmodified hydroxyl groups on one molecule and the four ester carbonyl oxygens of another participate in hydrogen bonds in the presence of a suitable guest. Capsule formation in the presence of the tropylium cation led to the formation of a charge-transfer complex, as indicated by the intense orange-red color of the solution.<sup>22</sup>



### CAVITAND-BASED DIMERIC CAPSULES

In addition to the dimeric capsules described above, similar assemblies have been generated using resorcinarene-based cavitands. The covalently linked hydroxyl groups on adjacent aromatic rings of cavitands enforce a concave cavity in which small molecules can bind.

Rebek and coworkers have extensively studied the dimeric assembly formed by pyrazinedicarboximide-bridged cavitand **16** (Figure 7). The cylindrical dimeric capsule held together by a seam of eight bifurcated hydrogen bonds (Figure 8) can encapsulate a variety of guests, including *p*-xylene and dicyclohexyl carbodiimide (**17**, Figure 9). Smaller guests such as toluene are entrapped in pairs.<sup>23</sup> To further probe the dimensions of the internal cavity, they tested a series of aromatic amides of known size and shape, including anilide **19**. Using <sup>1</sup>H NMR spectroscopy to monitor encapsulation and to determine at which point the amide became too long or wide to be fully encapsulated, they estimated the cavity dimensions to be approximately 14.7 Å by 5.7 Å.<sup>24</sup> A variety of *N*-protected amino acid esters were studied and it was found that longer guests, such as the L-alanine derivative **20**, was encapsulated in a more compact conformation.<sup>25</sup>

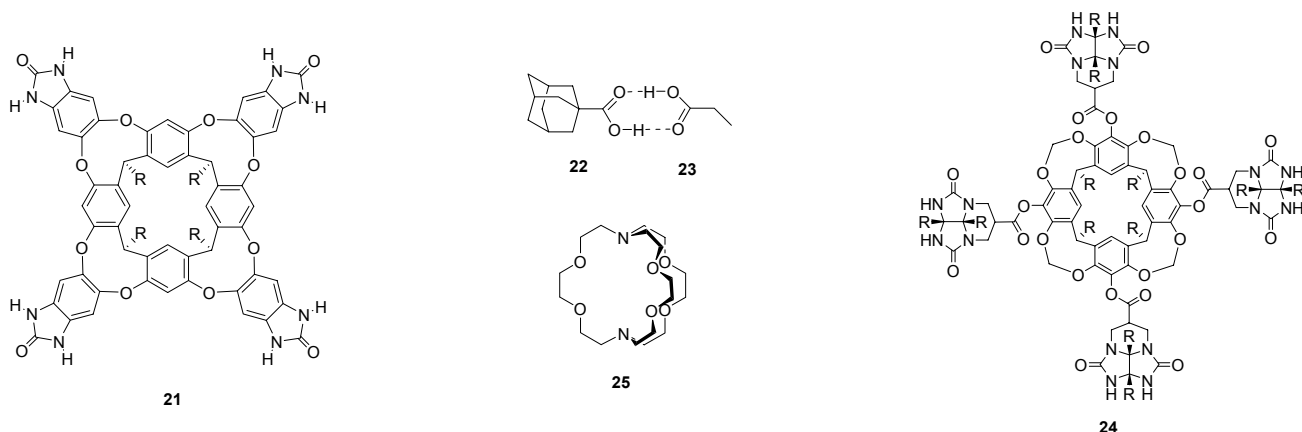


**Figure 7** Pyrazinedicarboximide-bridged cavitand **16** shown flat and in the actual vase shape.

**Figure 8** Hydrogen-bonded dimer of imide-bridged cavitand **16**.

Additionally, it was shown that benzoyl peroxide could be encapsulated by this cavitand-based system. The encapsulated peroxide no longer reacted with external agents and was protected from thermal decomposition. Destruction of the capsules through addition of a more polar solvent released the entrapped peroxide, allowing it to oxidize PPh<sub>3</sub> in solution.<sup>21</sup> The same cavitand-based cylindrical capsules also sequester anions such as tosylate (TsO<sup>-</sup>), hexafluorophosphate (PF<sub>6</sub><sup>-</sup>), and chloride (Cl<sup>-</sup>) in solution. Among the anions tested, binding appeared to be independent of anion size, geometry, and hydrogen-bonding ability.<sup>26</sup>

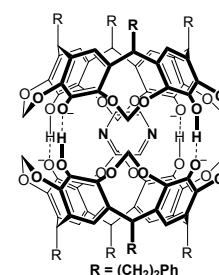
Similar cylindrical capsules composed of cavitands with 2-benzimidazolone bridges (**21**, Figure 10) were reported by Ebbing and coworkers.<sup>27</sup> These dimeric assemblies encapsulated dimers and heterodimers of carboxylic acids. For example, pairwise encapsulation of 1-adamantanecarboxylic acid (**22**) and propionic acid (**23**) was observed.



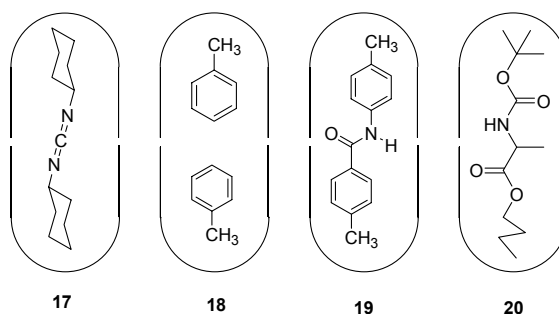
**Figure 10** The hydrogen-bonded dimer of cavitand **21** entraps the heterodimer formed between the carboxylic acids **22** and **23**. The glycoluril-functionalized cavitand **24** forms a hydrogen-bonded dimer that encapsulates cryptand **25**.

Using a different approach, Rebek and coworkers attached glycoluril groups to a tetrahydroxy cavitand through ester linkages (**24**).<sup>28</sup> The resulting dimeric assembly, held together by sixteen hydrogen bonds, had a cavity volume of approximately 950 Å<sup>3</sup>, large enough to encapsulate cryptand **25**.

Subsequently, it was shown that dimeric capsules could be generated from tetrahydroxycavitands in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (Figure 11). Addition of enough DBU to deprotonate half of the



**Figure 11** Tetrahydroxycavitand dimer with pyrazine guest.

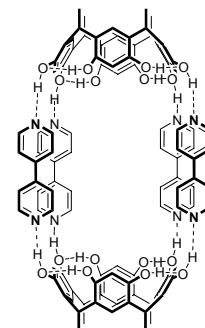


**Figure 9** Dimeric capsules of **16** with encapsulated dicyclohexyl carbodiimide (**17**), toluene (**18**), anilide **19**, and L-alanine n-butyl ester **20**.

hydroxyl groups of the resorcinarenes led to complete capsule formation. The resulting dimeric complexes, held together by four O $\cdots$ H-O charged hydrogen bonds, were highly selective for the guest pyrazine.<sup>29</sup>

## DIMERIC CAPSULES WITH ORGANIC MOLECULE BRIDGES

In addition to resorcinarene-based assemblies connected directly by hydrogen bonds or through bridging water or solvent molecules, multi-component capsules with bridging organic molecules have also been reported. Capsules consisting of two resorcin[4]arene and four terpyridine<sup>30</sup> or 4,4'-bipyridine<sup>31</sup> units held together by eight hydrogen bonds have been observed in the solid state (Figure 12). A related structure composed of two cavitand tetracarboxylic acid molecules and four 2-aminopyridines bridged by sixteen hydrogen bonds has also been reported.<sup>32</sup>



**Figure 12** Resorcinarene dimer with four 4,4'-bipyridine bridges.

## CONCLUSION

The field of resorcinarene chemistry has progressed considerably since the first reported crystal structure of the cyclic tetramer thirty-five years ago. From the stoichiometric (1:1) complexes with small organic molecules to the synthesis of covalently linked carcerands, resorcinarene chemistry has now expanded to include hydrogen-bonded capsules. While interesting in their own right, these assemblies hold promise for applications in drug delivery, catalysis, and chemical sensing.

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