The self-assembly of benzyl alcohol derived deep-cavity cavitands: a new, highly efficient moiety for irreversible assemblies?†

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In the absence of an apparent (single) molecular template, the irreversible self-assembly of benzyl alcohol substituted, deep-cavity cavitands is shown to be a highly efficient process.

With aspirations to improve our understanding of self-assembly, chemists have begun to focus on systems where the convergence of the molecular subunits is not promoted by a single molecular template,[1–4] but rather where assembly occurs around multiple 'templates'.[5] When considering the nano-scale products which such manifold species 'templations' result in, two options are available. First, scientists have considered self-correcting systems as a means to product formation, an approach that utilizes thermodynamics to maximize the yield of the target.[6,7] Alternatively, using a (normally less efficient) irreversible process allows the potential isolation of intermediates, and hence a more detailed picture of the assembly process in question. In this latter paradigm, considerable work has been carried out in systems requiring a single template. Thus, extending the original work of Cram,[8–10] Sherman *et al.* have demonstrated how carceplex formation is governed by the topology of the molecular template so essential for their synthesis.[11] In contrast, probing irreversible self-assemblies that require manifold species 'templation' has been relatively unexplored, primarily because of a lack of suitable supramolecular motifs[12] that can effectively drive such assemblies. Thus in the formation of a number of large, cavity-containing molecules, it has been noted that when using phenol groups to form the supramolecular motif, yields have tended to decrease toward statistical or worse.[10,13,14] We report here on an irreversible assembly in which the subunit utilizes benzyl alcohol groups in its supramolecular motif. Although the assembly occurs in the absence of a single molecular template, and the eight new covalent bonds created in the process are formed in a non-correcting manner, each is formed with an efficiency greater than 97%. As a result therefore, the synthesis of the nanoscale host is highly efficient.

We recently demonstrated the stereoselective bridging of resorcinarenes with benzal bromide, a process which provided access to a new series of deep-cavity cavitands (DCCs) epitomized by structure **1**.[15] More recently, we have noted that this reaction can be applied to a range of benzal bromides to form a series of DCCs whose 'upper row' of aromatic rings may be substituted at the *o, m* or *p* position.[16] We chose one example of these, the *p*-Br derivative **2** as an entry point for the synthesis
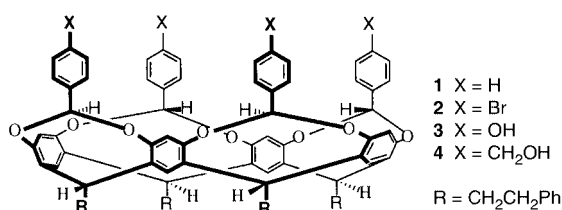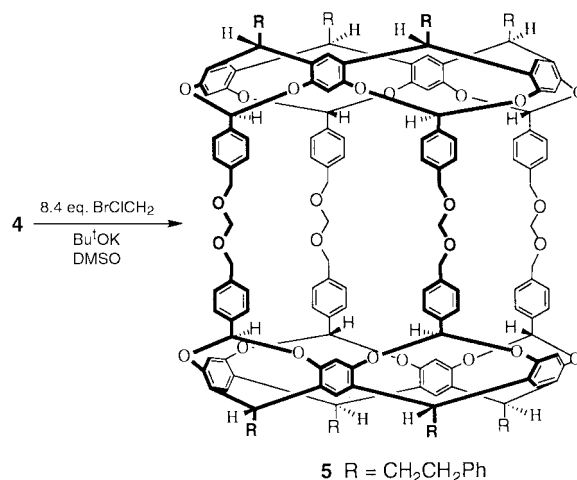
of DCCs **3** and **4** whose architecture should allow them to undergo an assembly process analogous to the carceplex reaction.[10,11] Our initial attempts to perform this 'dimerization' of DCCs centered around the tetrakis(4-hydroxyphenyl) derivative **3**. However, our studies showed that **3** was insufficiently stable in either acidic or basic conditions, a result we attribute to the ability of the electrons on the OH groups to conjugate through to the acetal bridges. Consequently, we synthesized DCC **4** whose essential nucleophilic centers possess slightly less preorganization, but are 'insulated' from the benzal bridging-carbon by the benzyl methylene group.

Our initial studies focused on the covalent joining of two molecules of **4** with the bis-electrophile CH_2BrCl (Scheme 1) in the absence of a large templating molecule. Our early results with a range of aprotic solvents[17] gave poor yields of **5**, the bulk of **4** being transformed into intractable polymeric material and trace quantities of DCC–solvent conjugates. DMSO on the other hand led to a considerable improvement, with a highly efficient[18] 80% yield of **5** being obtained under dilute conditions, a remarkable yield for an irreversible process.[19] Yields decreased at concentrations > *ca.* 2 mmolar, presumably because of the highly concentration-dependent formation of the superbase, methylsulfinyl carbanion.[20] However at these concentrations, yields could be increased by the addition of small quantities of water to generate the less basic hydroxide[21] and inhibit[20] the superbase formation.

Definitive formation of **5** came from an X-ray crystallographic determination (Fig. 1).[22] In the solid state, both hemispheres of **5** are rotated slightly with respect to each other, while the linker groups each display the anomeric effect with *gauche–gauche* conformations for the $CH_2OCH_2OCH_2$ units. A consideration of the salient inter-carbon atom distances indicates that the cavity of **5** is approximately 19 × 15 Å, while the portals are roughly 9.5 × 11.5 Å. Not surprisingly, disordered solvent molecules within the cavity precluded an accurate determination of its composition.

Although the assembly is highly efficient, DCC **4** is too large to fit within the cavity of the product. Thus, there is no suitable, single template to promote the formation of **5** over and above

1 X = H
2 X = Br
3 X = OH
4 X = CH₂OH

R = CH₂CH₂Ph

$$4 \xrightarrow[\substack{Bu^tOK \\ DMSO}]{8.4 \text{ eq. } BrClCH_2}$$
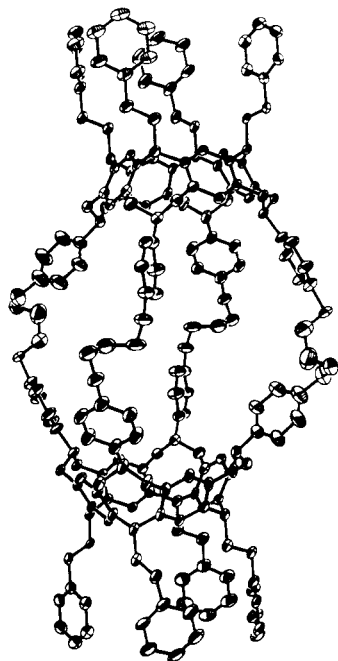
5 R = CH₂CH₂Ph

Scheme 1

Fig. 1 ORTEP diagram of DCC dimer **5**. Hydrogen atoms have been omitted for clarity.

random polymer. As it seems entropically unlikely that several species in solution organize themselves into a multiple species template; we surmise that this efficient assembly process is occurring 'around' bulk solvent.

What lies behind this efficient assembly? In normal cavitands, the supramolecular motif that drives the reaction is constructed with the phenol group, a moiety that in the presence of base can form a charged hydrogen bond (CHB) with its conjugate base.[23] As yet, we have been unable to definitively ascertain if an analogous process is occurring in the assembly of **4**. However, variations in the base utilized for the reaction tentatively support this hypothesis.[24] Furthermore, work by Kolthoff[25]—who demonstrated that weakly acid phenols formed stronger CHBs with their conjugate bases than their more acidic counterparts—suggests that the poorly acidic benzyl alcohol group[21a] should form very strong CHBs.

In summary, we have demonstrated an efficient, irreversible self-assembly that occurs in the absence of a single, molecular template. Investigations into the use of the benzyl alcohol group in other molecular subunits are currently underway.

Notes and references

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