# Self-Assembling Cavities: Present and Future

**Javier de Mendoza***

**Abstract:** The construction of artificial receptors to encapsulate any but the smallest substrates becomes prohibitively difficult by a covalent approach as the size of substrates increases, and the cavities thus produced are often poorly accessible. As an alternative, noncovalent interactions can be used for the self-assembly of smaller, simpler fragments into the desired cavities. One such method, namely the design of hydrogen-bonded host species to accommodate guests of different shapes and sizes, and current approaches to chiral recognition are discussed here.

**Keywords:** aggregation · cage compounds · hydrogen bonds · self-assembly · supramolecular chemistry

## Introduction

Molecular recognition is based on complementarity in size, shape, and functional groups between host molecules and substrates. For cavities tailored around spherical or globular targets, positioning of binding sites requires the controlled formation of a number of covalent bonds in long, often impractical multistep syntheses. As sizes needed to encapsulate even relatively small substrates increase, the covalent approach to artificial receptors becomes prohibitive from the synthetic point of view. Moreover, in molecular cavities based on covalent frameworks the windows allowing substrates to penetrate and to exit are frequently smaller than the inner volumes available, so encapsulation (or decomplexation) becomes too slow or simply not possible. Thus, energy barriers separating free and complexed species are directly related to the size of the openings.

Replacement of some covalent bonds in a cavity by noncovalent, complementary interactions, such as hydrogen bonds or those between metal centers or hydrophobic surfaces, may result in smaller, simpler fragments with enough molecular information to spontaneously reassemble into the desired cavity under favorable conditions, such as in the presence of suitable solvents or substrates. The economical use of a maximum of information in a minimum of structural complexity is a common lesson learned from nature, viral capsides or the quaternary structures of many proteins being classical examples. However, since noncovalent interactions are generally much weaker than covalent bonds, large areas of complementarity are necessary to allow the self-assembling process to occur, overcoming the entropic cost of the organization of components into the final ordered state. Some of the most fascinating designs in the field have been based on hydrogen bonds, whose selective and directional nature is ideally suited for the construction of complex molecular architectures.[1, 2] The formation of cavities by the use of components designed to hydrogen-bond together is discussed in this Concepts article.

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## Discussion

Dimerization of bowl-shaped molecules, mostly calixarenes or resorcinarenes endowed with sticky edges, has been demonstrated in a number of cases over the last few years. The first example was reported by Aoyama, who showed in 1992 that glucopyranosil derivatives were encapsulated between two resorcinol tetramers **1** (R = undecyl) by means of hydrogen bonds.[3] Somewhat later, Sherman and co-workers reported the inclusion of *N*-methylpyrrolidin-2-one and other small molecules, such as dioxane, DMSO, or pyridine, within a cavity formed by two cavitand tetrols **2**, whose semideprotonated forms dimerized through hydrogen bonding.[4] The substrates acted as templates to covalently link both halves into a carcerand cavity, pyrazine being the most effective guest.

A number of calixarene derivatives have been shown to self-assemble through hydrogen bonding in apolar solvents. The fruitful combination of pyridine and carboxylic acid functionalities has been exploited for the assembly of two calix[4]arenes in either lower-rim/upper-rim[5] or in upper-rim/upper-rim[6] modes, although encapsulation of substrates has not been reported for such systems. More recently, dimerization of the larger calix[6]arenes bearing three carboxylic acids in alternate positions at the upper rim has been observed.[7] The cavity is large enough to encapsulate simple pyridinium salts.

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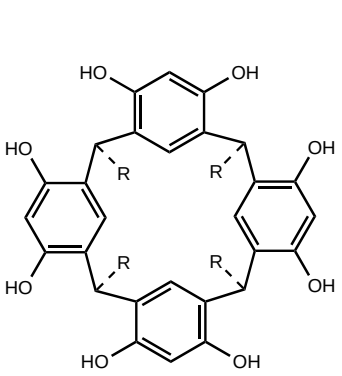
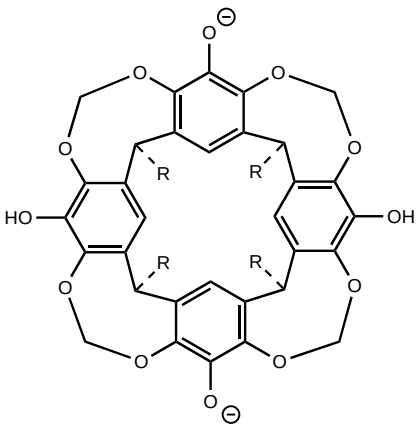
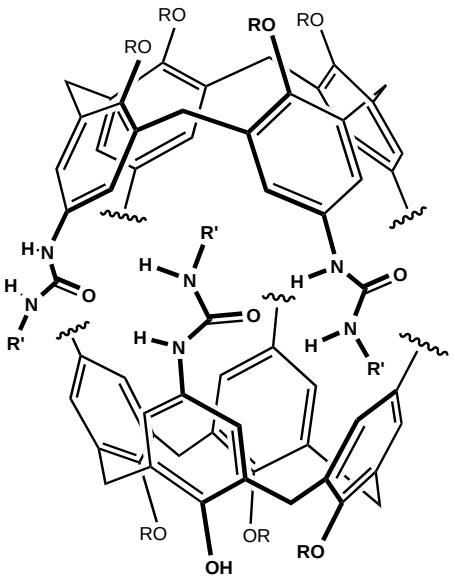


1



2

Dimerization of calix[4]arenes containing ureas at the upper rim (i.e. **3**) has been thoroughly studied by Rebek and Böhmer independently.[8] All eight ureas interdigitate in a head-to-tail directional array of 16 hydrogen bonds, leaving a sizable cavity where small guests, no larger than benzene, can be accomodated, as has been demonstrated both in the solid state (X-ray crystallography) and in solution (NMR). Interestingly, the $^1$H NMR spectrum of a 1:1 mixture of two different calix[4]arene tetraureas in apolar solvents ($CDCl_3$ or $C_6D_6$) shows independent signals for each of the three different combinations (two homodimers and the heterodimer), owing to the slow rates of assembly and dissociation. Only two compounds were observed in a more polar solvent ([$D_6$]DMSO), where hydrogen bonds are broken.

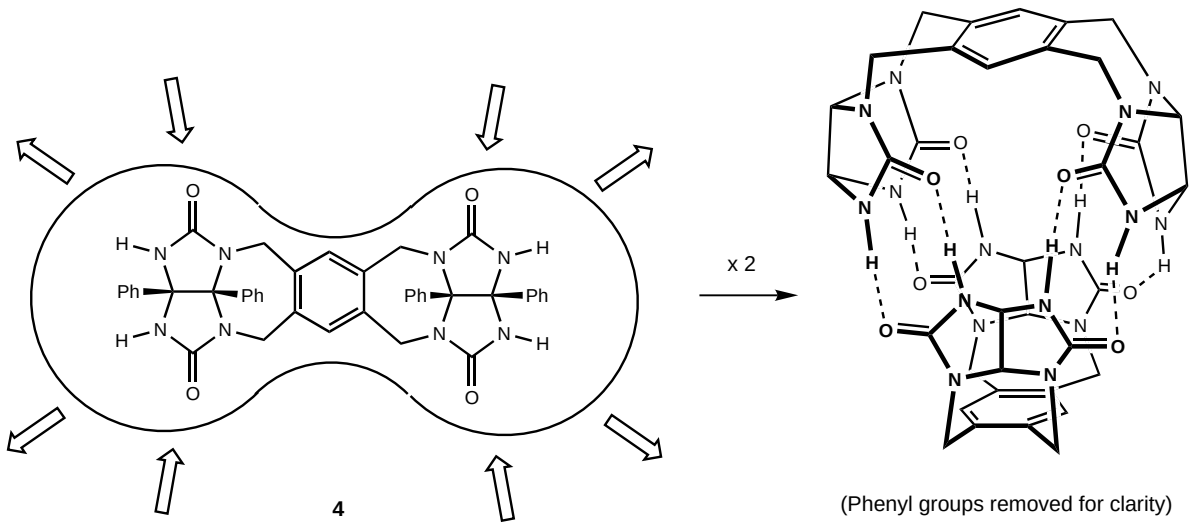


3

(Some ureas are omitted for clarity)

The successful combination of curvature and complementary hydrogen bonds has been exploited in the design of capsular dimers based on glycoluril. The first example was described in 1993 by Wyler, de Mendoza, and Rebek.[9] Structure **4** features two diphenylglycoluril subunits attached to a central durene spacer. In the self-assembled dimer, maintained by eight hydrogen bonds along the seam of a quasispherical structure that resembles a tennis ball (Scheme 1), a cavity of 50 – 55 Å$^3$ inner volume results. The cavity has been shown by Rebek and co-workers to encapsulate xenon, methane, and other small molecules in nonpolar solvents, such as chloroform. Assembly of the dimer can be also observed in more competitive solvents, such as DMF, provided suitable guests that could act as nucleators are present. Also, small variations on the size of the central spacer (within 1 – 2 Å) permit the preparation of heterodimers by recombination.

To develop self-assembling dimers capable of encapsulating larger molecules, Rebek and co-workers further expanded the spacer between the two glycoluril units while keeping the curvature and hydrogen-bonding features necessary for dimerization.[10] In this softball design (compound **5,** R = H), eight strong hydrogen bonds (of DD – AA type) are again involved, but dimerization can be further favored over other forms of aggregation by incorporation of suitable phenolic groups (**5**, R = OH), which results in an additional set of eight



4

(Phenyl groups removed for clarity)

Scheme 1.



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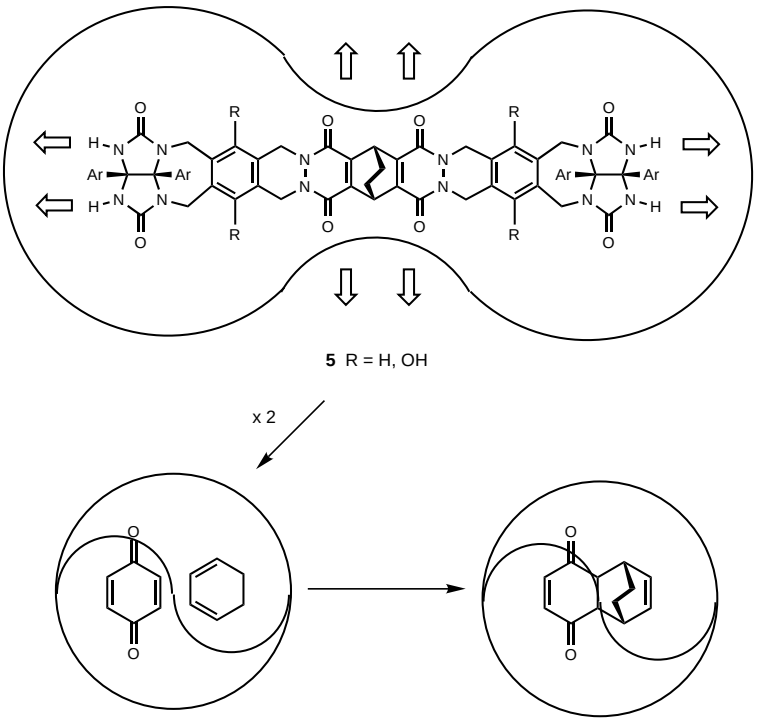
hydrogen bonds. The dimeric capsules are roomy enough to complex guests the size of adamantane. More interestingly, encapsulation of guests is entropically driven by the liberation

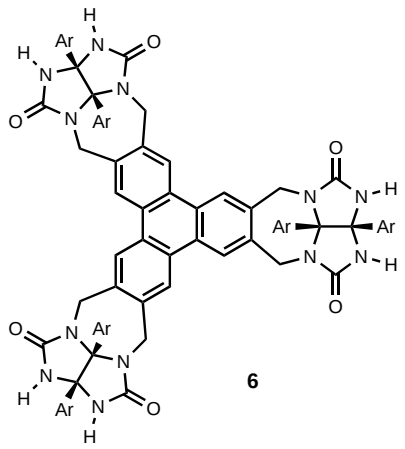


**5** R = H, OH

Scheme 2.

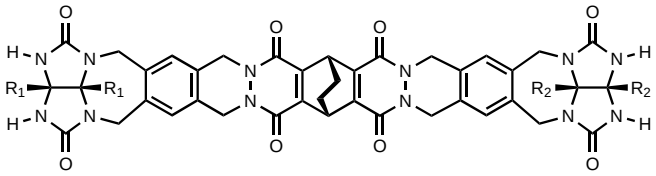
of more than one solvent molecule (i.e. benzene). This opened the possibility of using the capsules as reaction chambers to accelerate a reaction. Thus, the reaction of *p*-quinone and cyclohexadiene takes place with a 200-fold rate acceleration (Scheme 2), although no turnover was observed, the resulting Diels–Alder adduct causing strong product inhibition.

Up to three glycoluril subunits have been attached to a central triphenylene scaffold (compound **6**). The shape of the resulting structure resembles a jelly doughnut, and the aromatic surfaces are linked together through 12 strong hydrogen bonds. The cavity was shown to display selectivity for disk-shaped guests such as cyclohexane.[11]



**6**

The interesting possibility of using self-assembling capsules for chiral recognition has been recently adressed by Rebek in three different ways: asymmetric outer surfaces, asymmetric cavity linings and asymmetric cavities.[12] The former were illustrated by softballs **7** with differently substituted glycolurils at each end.[12a] The resulting capsules are chiral (they contain a $C_2$ axis but no longer the typical planes of symmetry of softballs with the same glycolurils). Although diastereomeric complexes were formed with camphor, no chiral recognition was evidenced. Presumably, the asymmetry of the system is limited to the outer surface and does not extend inside the cavity.

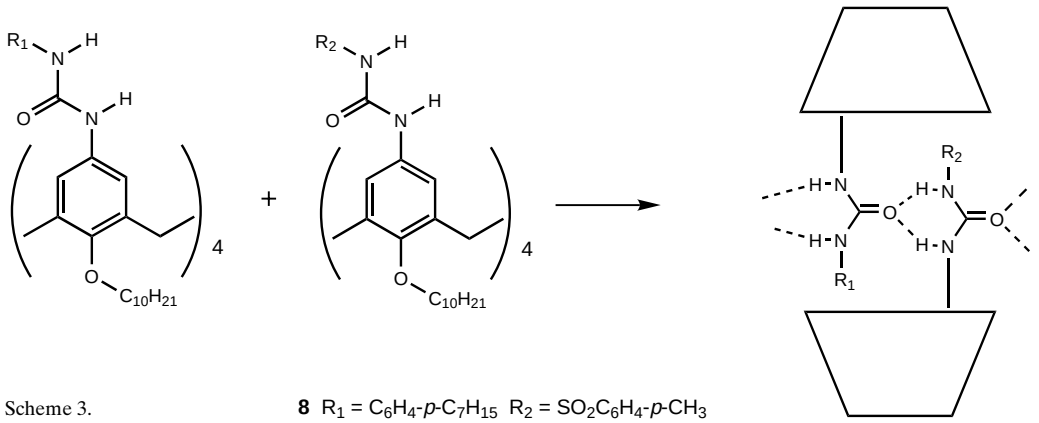


**7** $R_1 = CO_2iPen$ ; $R_2 = p\text{-}C_6H_4OC_6H_{15}$

The second approach was based on heterodimeric calix[4]arene tetraureas, that is, capsules with chemically nonequivalent top and bottom halves, like **8**. As a result of the directionality of the circular array of hydrogen bonds, these capsules are chiral too (Scheme 3). As for the softball examples mentioned above, well-positioned diastereomeric complexes are formed with chiral substrates, such as nopinone, but no enantioselectivity was proven.[12b] Finally, a substantial discrimination was observed with chiral cavity-shaped capsules, made of softball-like structures such as **9** with two different spacers in the same monomer. Although the monomers are achiral (they maintain a plane of symmetry), the dimers are chiral (Scheme 4), and one enantiomer is formed preferentially in the presence of enantiomerically pure guests, with differences in stabilities of up to 0.4 kcal mol$^{-1}$ (ca. 35% diastereomeric excess) in the most favorable cases.[12c]

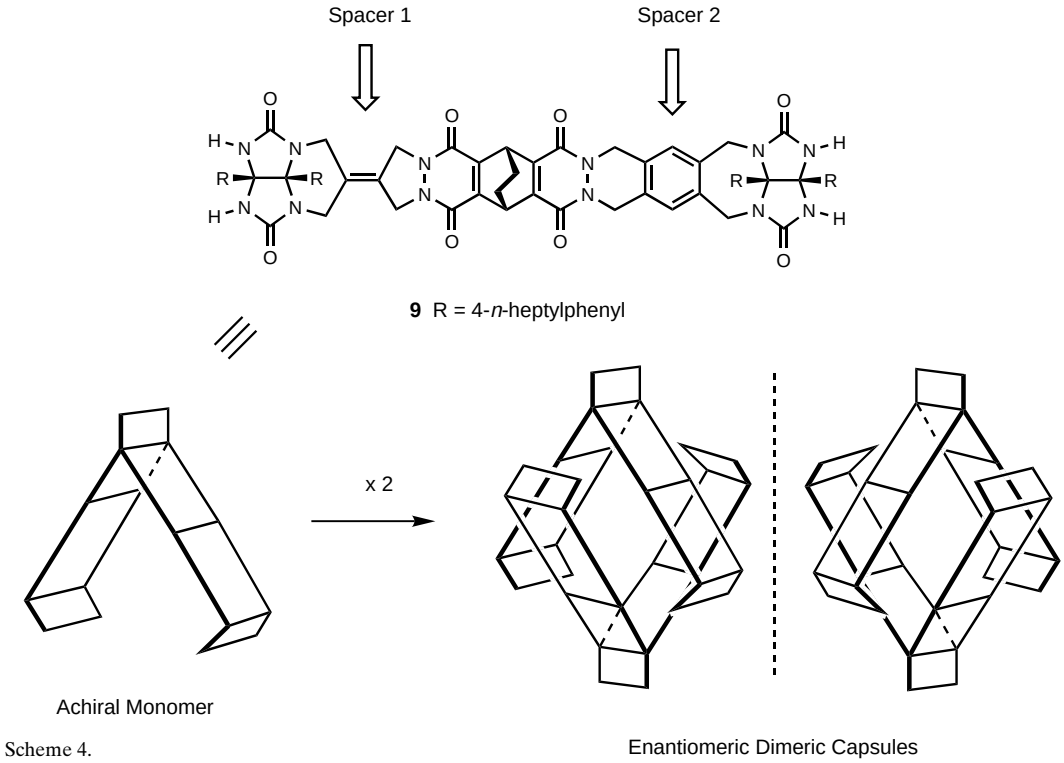
## Conclusions

Future progress in the field will be strongly dependent on the degree of control chemists can achieve of the self-assembling process and of the rules of the game for encapsulation. However, the two phenomena appear to be closely related. So far, the precise state of aggregation of monomeric entities is poorly understood, although in most instances well-characterized dimers are formed only in the presence of suitable guests or solvents which act as nucleating species. As larger capsules are to be designed, the lack of solvents of appropriate size and shape constitutes a severe limitation. Also, most of the cavities based on hydrogen bonding so far described are just dimers, entropy conspiring against higher order oligomers with such weak interactions. As larger cavities will probably require more than two monomers, better enthalpic contributions should be employed.[13] As nature clearly shows in the quaternary structures of proteins, a combination of different



Scheme 3.

**8** $R_1 = C_6H_4\text{-}p\text{-}C_7H_{15}$ $R_2 = SO_2C_6H_4\text{-}p\text{-}CH_3$




**9** R = 4-*n*-heptylphenyl

Scheme 4.

noncovalent interactions, such as hydrogen bonds, contacts between hydrophobic surfaces, or even coordination with metals,[2] could be the best strategy.

Molecule-within-molecule (covalent or self-assembling) complexes have been shown to stabilize reactive intermediates, to provide new forms of stereoisomerism to the incarcerated guests, or to act as molecular reaction vessels to accelerate reactions. Application of such self-assembling devices to transport drugs and other useful biomolecules across membranes are challenging goals for the years to come. Finally, the design of a capsule whose shapes and functional groups could truly catalyse a chemical process, without substantial product inhibition, is another dream in the field. Certainly, increased attention should be paid in the future to the forces oriented *inwards* into the cavities, and not only to the binding sites at the *edges* of the monomers, designed simply to allow the capsules to form.

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[2] Designs based on metal coordination (i.e. metallocyclophanes) will not be covered here. For a recent review, see P. J. Stang, *Chem. Eur. J.* **1998**, *4*, 19 – 27; see also P. Jacopozzi, E. Dalcanale, *Angew. Chem.* **1997**, *109*, 665 – 669; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 613 – 615.



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[13] Large aggregates of many components linked through hydrogen bonds, e.g. molecular rosettes or boxes, are well-known (G. M. Whitesides, E. E. Simanek, J. P. Mathias, C. T. Seto, D. N. Chin, M. Mammen, D. M. Gordon, *Acc. Chem. Res.* **1995**, *28*, 37–44; P. Timmermann, R. H. Vreekamp, R. Hulst, W. Verboom, D. N. Reinhoudt, *Chem. Eur. J.* **1997**, *3*, 1823–1832), but these systems are usually flat, collapsed surfaces without large holes left for guest complexation. For cavities, an exceptional assembly of six resorcinol tetramers **1** ($R = CH_3$) and eight water molecules has been recently reported in the solid state (L. R. MacGillivray, J. L. Atwood, *Nature* **1997**, *389*, 469–472). A more lipophilic derivative ($R =$ undecyl) seems to aggregate similarly in apolar organic solvents (NMR, osmometry), although this hexameric self-assembly deserves further study.

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