

Self-Assembly of Organic Supramolecular Capsules

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1 INTRODUCTION

1.1 Supramolecular capsules

Supramolecular self-assembled organic capsules are formed when more than one unit, characterized by the same or different chemical nature, spontaneously encounter in solution giving rise to an aggregate that forms a cavity where guest molecules can be accommodated. Driving forces for this “get together” that involves several partners can be driven by either the enthalpic advantage, when working in apolar media, or the entropic advantage when the aggregate forms in polar solvents. The aggregate behaves as a new chemical entity, and it often does not have much to share with the components. Usually, the subunits that compose the capsule feature concave shapes and are adorned with functional groups that in the aggregate are involved in weak intermolecular interactions like hydrogen bonding, ion pairing,

or hydrophobic interactions. For efficient aggregation, the presence of multivalent functional groups in every subunit is required and cooperativity between attractive interactions is often observed.¹ Usually, subunits present a certain degree of rigidity and a limited number of possible conformations because this strongly favors intermolecular interactions and reciprocal docking, but this observation should not be taken as a rule because in many cases it is the bound guest within the cavity that drives the formation of a certain aggregate imparting preferential conformations to the subunits that can be adopted if they are semiflexible. Overall, the formula for assembly is written in the specific kind of functional groups, in molecular curvature present in the subunits, together with adequate filling of the cavity.

An important feature of the self-assembled capsule is the reversibility of the aggregation process that can be inverted by correct changes in the experimental conditions. Capsules are not immobile systems, rather there is a continuous dynamic exchange of subunits at rates that are a function of the number and strength of intermolecular interactions. It is because of these phenomena that the cavity present in capsules can be accessed by external guests. Common methods of monitoring and characterizing guest exchange are several, like NMR (nuclear magnetic resonance), UV-vis, mass spectrometry, electrochemistry, and calorimetry.²

The same concepts are present in nature that has evolved examples of natural supramolecular capsules deputed to the transport and/or the storage of important chemical species. Examples are the tobacco mosaic virus characterized by a rodlike appearance and composed of 2130 molecules of coat protein that surround one molecule of genomic RNA 6400 bases long. Another important representative is apoferritin, which is a capsular aggregate with octahedral symmetry formed by 24 identical peptides that present a cavity of over 230 \AA^3 that can store up to 4500 iron atoms as ferric hydrous oxides.

2 Self-processes

1.2 Lifetime of capsules

As far as aggregation phenomena in solution are concerned, it is worth noting that when two molecules come together and no special attractive interactions are present among them, the lifetime of this encounter complex is on the order of $<10^{-9}$ s. This means that if we follow the fate of one single molecule for 1 s, this embarks in intermolecular contacts with several millions of solvent molecules in an extremely rapid change of partners. If we connect several of these solvent molecules and arrange them in a concave shape, the result is longer contacts between the molecule and the aggregates and reduced number of possible partners. If we extend this concept to a much smaller number of species, we observe the same phenomena that occur to guests in self-assembled capsules. The capsule acts as an organized solvent where different residues have been brought together and the entropic penalty for their organization has already been paid through the synthesis of the hosting subunits. This translates into much longer lifetimes for capsule–guest interactions that can last up to seconds. In other words, while in the bulk solvent a single molecule senses a huge number of other molecules for extremely short times, in capsules the guest interacts with the same capsule from 10^3 to 10^{-3} s, having enough time to be strongly reciprocally influenced.³

Ingress and egress of the guest from the capsule occur via different supramolecular mechanisms that can span from the temporary disassembly of one subunit creating a door through which the guest goes back and forth, or, alternatively, opening flaps of subunits with only partial dissociation, thus limiting the enthalpic cost. In detail, substitution of guests in capsules usually occurs via either a bimolecular guest substitution when an incoming guest appears in the rate expression (SSg2) or via unimolecular guest substitution (SSg1) when flap opening and guest release is the rate-determining step.

In order to follow capsule formation and guest binding, it is necessary to use tools that are able to “take snapshots” of the system at a rate faster compared to the process under investigation, thus allowing the detection of signals for each species present in solution. If the technique employed is not fast enough, only an average of the exchanging systems is observed because of the exchange that occurs during the time required for observation of the system, with signals in-between the species that exchanged during the shot. NMR spectroscopy is the most adequate/prevalent technique because, with the opportune tuning of the temperature, it is possible to regulate the exchange process between fast and slow exchange regime that, compared to the chemical shift timescale, falls in the range from 0.1 ms up to a few seconds. IR and UV–vis spectroscopy are instead in

the range of picoseconds; therefore, the systems observed almost always reside in the slow exchange regime.

Moreover, the encapsulation process can be easily studied because NMR resonances of the trapped guests are shifted upfield by the aromatic ring currents of the host, often kinetically stable, and in slow exchange on the NMR chemical shift timescale, revealing two distinct species for the encapsulated and free guests.

1.3 The viewpoint of the guest

The inner surface of a supramolecular capsule is not different from the surface of any other molecule; both require contacts with other molecular species in order to minimize the overall energy of the system as much as possible; basically, internal surfaces need to be solvated as much as other molecules in solution. Because of the closed structure and the prolonged contact times, the bound molecule is more strictly selected compared to solvation phenomena in the bulk and extra requisites are necessary to transform a simple molecule into a suitable guest. Matching of shape is obviously required and, as far as the size is concerned, again a parallel with what happens in solvents is natural. It has been observed that bulk solvents are characterized by packing coefficient (PC) values, that is, the volume of all the molecules that occupy a certain volume of a liquid, which is in the range of 45–55%. A close observation of several capsule–guest interactions demonstrated that the same criteria apply to encapsulation phenomena.⁶ In fact, good binding can be expected if the PC is in the range 0.55 ± 0.09 for liquid guests, while for gaseous guests the value is smaller, around 0.4, implying that the gas in the capsule behaves similar to gas molecules in the gas phase even in condensed matter.

Apart from the above-mentioned criteria, the guest interacts with the host, establishing attractive or repulsive weak intermolecular forces with the capsule following criteria that are well known in supramolecular chemistry like hydrogen bonding, π – π stacking, CH– π , cation and anion– π interactions, and so on. For large capsules that can accommodate more than a single guest, interguest contacts are possible with both being isolated from the rest of the solvent with the opportunity to observe molecule-to-molecule interactions.⁷ Encapsulation of guests⁸ allows new phenomena such as supramolecular stereochemistry^{9–11} restricted tumbling, and spinning and modified conformations to emerge,¹² most of which are described in the following.

The ultimate target of self-assembly of capsules and guest binding is the mimicry of what happens in nature. In particular, two phenomena are the source of inspiration: the transport of molecules where the capsule acts as a reversible carrier that takes up the guest in a place and releases it in

another upon opportune stimulus, and the catalysis where the capsule acts as an enzyme that binds substrates forming a complex that evolves to products and free catalyst ready for a subsequent cycle. Review articles covering various aspects of these phenomena are reported in the section titled "Further Reading".

Significant examples of organic self-assembled capsules that have been fully studied in solution along with a discussion on their peculiar encapsulation behaviors, catalogued on the basis of the kind of intermolecular force involved like hydrogen bonding, ion pairing, and hydrophobic effect in increasing order of number and kind of units that compose the supermolecule are illustrated in the following. The focus is on the interactions that emerge within the cavity between the guests bound and the self-assembled capsule, citing examples of capsules that do not show clear examples of encapsulation only if they represent in any way an advancement in the field.

2 HYDROGEN-BONDING HOMOMERIC CAPSULES

In the present section, capsules held together by hydrogen bond interactions in noncompetitive organic solvents in increasing size and complexity order from dimeric to multimeric aggregates are described. Capsules made of all equal units (homomeric capsules) are illustrated first followed by those comprising different units (heteromeric capsules).

2.1 Dimeric capsules

2.1.1 Tennis ball

The first hydrogen-bonded supramolecular capsule reported was developed by Rebek and collaborators and was based on the connection between two glycoluril units to a durene scaffold, giving rise to a U-shaped molecule featuring an array of hydrogen-bonding sites along its periphery that provide overall eight hydrogen bonds to seal the capsule and form a cavity of approximately 55 Å³.^{3,13} In chloroform-*d*, the system shows two species in agreement with an open and a dimeric closed structure in slow exchange on the NMR timescale (Figure 1). The cavity is rather small and can accommodate liquid guests like dichloromethane, but more singularly the capsule showed clear encapsulation of gaseous guests like methane, ethane, and ethylene with decreasing binding constants. A smaller capsule, where the aromatic residue was present on the scaffold, derived by durene was replaced by a tetrasubstituted double bond¹⁴ obtaining a self-assembled host system that did not encapsulate dichloromethane and that showed higher selectivity for gas binding with much higher affinity for methane compared to that for ethane. Substitution of the aromatic spacer of the monomer with electron-rich hydroquinone allowed encapsulation of fluorinated guests like CH₃F and CF₄ investigated by ¹⁹F NMR where separate signals for free and bound guest showed higher affinity for the former.¹⁵ Other permutations on this kind of capsule led to the formation of a chiral tennis ball starting from an achiral monomer where two different glycoluril residues were

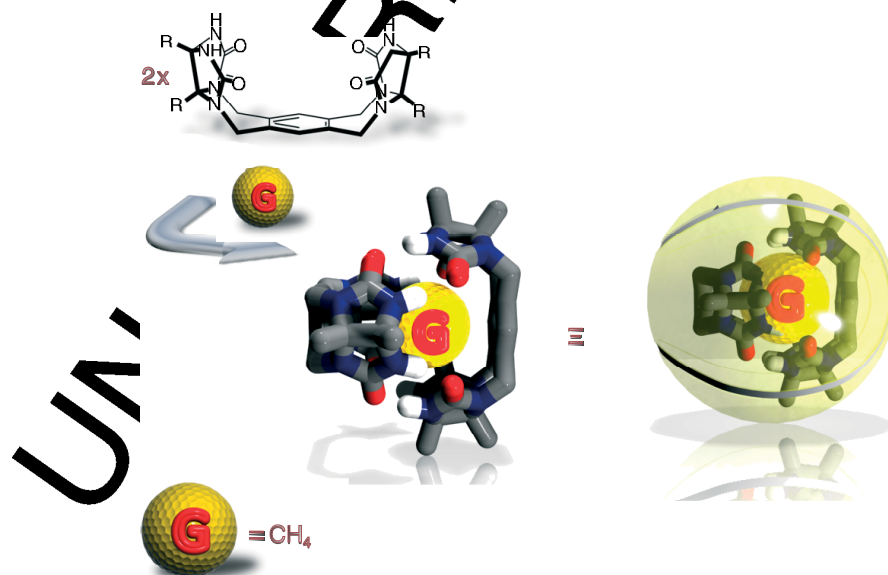


Figure 1 Homodimeric tennis ball encapsulating methane.

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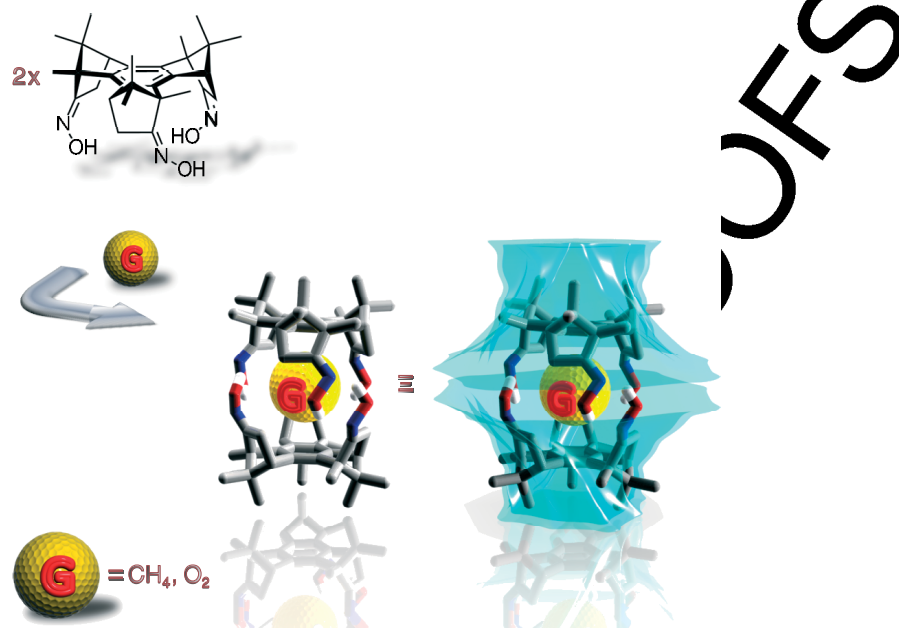


Figure 2 Self-assembling dimerization of the benzocyclotri(m) tris-oxime leading to molecular capsule for methane and oxygen hosting.

connected to the aromatic spacer,¹⁶ or the system was endowed with amino groups on the side chains of the glycoluril giving rise to enhanced solubility and encapsulation of argon and xenon, but also the reversible control over the association–dissociation process by means of addition of *p*-toluenesulfonic acid or sodium carbonate.¹⁷ Even heterodimeric capsules were prepared by simply mixing monomers characterized by different spacers like ethylene, benzene, and naphthalene etheno and racene, confirming the high dimerization ability of the glycoluril residue and the good complementarity provided by the curvature of the monomers forming hybrid capsules with disproportion equilibria driven by the employment of sized solvents as guests.¹⁸

2.1.2 Tris-oxime dimer

While there are several systems based on glycoluril or urea hydrogen-bonding groups for the preparation of dimeric self-assembled cages due to their intrinsic attitude to the formation of attractive interactions, much less has been investigated in the development of new hydrogen-bonding functional groups that are able to provide strong and directional interactions. Recently, Scarso and Fabris reported the preparation of a chiral benzocyclotri(meric) system adorned with three oxime residues that self-assembled in chloroform-*d*, forming a capsule characterized by a cavity of about 46 Å,³ which accommodates molecular

oxygen under fast exchange on the NMR timescale as confirmed by the broadening of the resonances of the capsule (Figure 2).¹⁹ This phenomenon is ascribable to the paramagnetic properties of molecular oxygen that cause the relaxation of nuclei positioned in proximity, thus acting as a probe molecule for determining its position in the equatorial portion of the cavity. Bubbling of inert gases like N₂ or CH₄ leads to sharp signals and encapsulation of the incoming gaseous guests, as confirmed at low temperature where exchange processes slowed down showing clear upfield signals for the encapsulated methane.

2.1.3 Tris(ureidobenzyl)amine

Self-assembling capsules are usually based on conformationally restricted systems in order to minimize entropy losses; therefore, aromatic surfaces connected by not more than one atom are preferred over flexible linear segments. Rigidity and preorganization favor self-recognition, but a certain degree of flexibility would allow the preparation of systems that more closely resemble biological receptors where flexibility and adaptation of the host to complement the guest are commonly observed. One of the dimeric self-assembling capsules characterized by flexible hydrogen bonding units is based on tris(ureidobenzyl)amines²⁰ with substitution in position 2 or 3 of the aromatic residue leading to monomeric species that show C_{3v} symmetry in polar solvents such as (dimethyl sulfoxide) DMSO-*d*₆ but

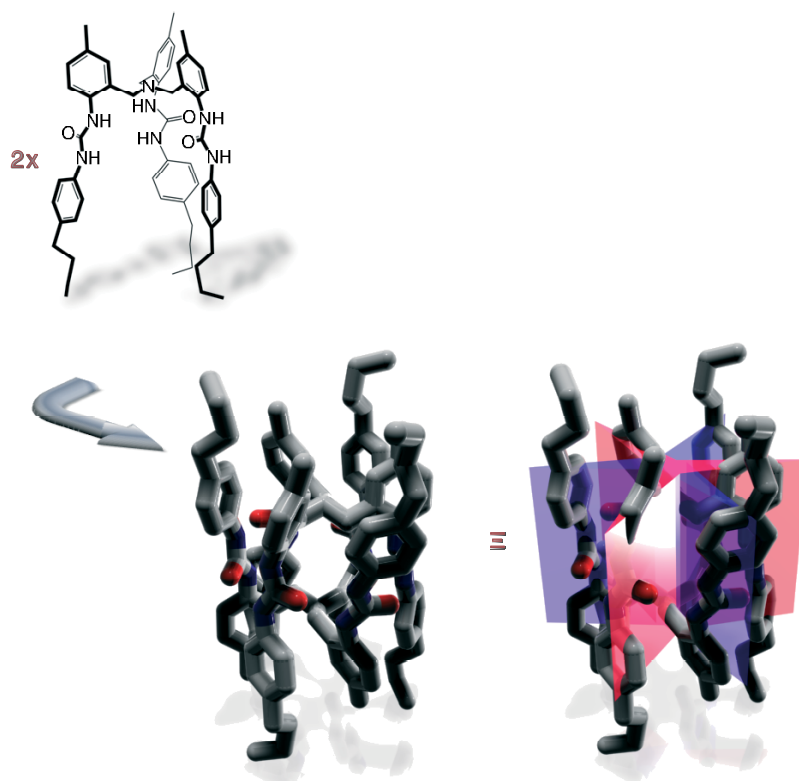


Figure 3 Homodimerization of urea-based tris(2-ureidobenzyl)amine, forming a capsule that is very small to accommodate guests. The larger tris(3-ureidobenzyl)amine showed the presence of one encapsulated solvent molecule.

form dimeric capsular assemblies in chloroform solvents in slow exchange between monomer and dimer on the NMR timescale. In particular, tris(2-ureidobenzyl)amine shows formation of enthalpically driven dimeric capsule²¹ via interplay of six hydrogen-bonded ureas with no guest included because of the small space available and with blocked conformation of the aromatic residues in a chiral-propeller-like structure with an overall C_3 symmetry derived by one clockwise and the other counterclockwise arrangement of the tris(benzyl)amino residues (Figure 3).

The larger tris(3-ureidobenzyl)amine forms analogous dimeric capsules with enough space to accommodate one molecule of guest, which could be CH_3NO_2 , dichloromethane, or CH_2I_2 in increasing order of affinity, using toluene-*d*₆ as a non-competitive solvent observing fast in-out of the guest at room temperature and requiring a temperature as low as 213 K to move to slow exchange observing separate resonances for free and bound guest.^{22,23} Using chiral racemic tris(3-ureidobenzyl)amine²⁴ characterized by the presence of a stereocenter in one arm of the tris(benzyl)amine led to the preferential formation in solution of only two isomeric capsules out of the seven possible

if considering the reciprocal position of the stereocenters of the two subunits; all driven by a point-to-helix chirality transfer, which means that the asymmetry present in the stereocenter steers the asymmetry of the helical assembly.

2.1.4 Calix[4]urea

The urea moiety provides a good combination of hydrogen bond donor and acceptor character in the same functional group, which can be implemented on different molecular scaffolds leading to self-assembling systems. Calix[4]arene scaffold is characterized by a semirigid concave surface and, if decorated with urea moiety on every aromatic residue, forms dimeric capsules with the shape of two facing square pyramids reciprocally rotated by about 45° toward each other. Tight binding between two units is ensured by a seam of 16 hydrogen bonds derived by interdigitating alternating urea moieties that, behaving like a zip, seal the equatorial region of the supramolecular structure forming a cavity of about 200 \AA^3 in a quantitative way for concentrations above micromoles.^{25,26} Such a cavity can host neutral solvent molecules with affinity in the order *p*-xylene < toluene < benzene \approx chloroform²⁷ as well as

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fluorobenzene, all in slow exchange on the NMR timescale. Alternative guests are cationic species like tetralkylammonium species of congruent sizes and shapes that can experience attractive cation- π contacts with the inner aromatic surfaces of the capsule. Hydrogen-bonded dimeric capsules based on the same calix[4]arene scaffold but endowed with different hydrogen bonding tags like tetraureidopeptide²⁸ moieties provided slightly larger capsules where extra hydrogen-bonding contacts were present.

Combinations of equimolar amounts of tetraarylurea and tetraatosylurea calix[4]arenes curiously led to the exclusive formation of heterodimeric capsules (Figure 4). The presence of different halves in combination with clockwise and counterclockwise head-to-tail arrangement of the hydrogen bond seam makes the assembly chiral²⁹ showing diastereoselective binding of chiral enantiopure guests like (+)-nopinone or (-)-myrtenal. Reasons for such specific

heterodimerization processes are still under debate; plausible explanations are the good match between the more acidic hydrogen-bond donor tosylurea combined with the more basic hydrogen bond acceptor urea and the fact that tetraatosylurea dimers are characterized by conformations that are sensibly higher in energy compared to those assumed in the heterodimers.³⁰ This class of heterodimeric capsules is the smallest chiral supramolecular aggregate that has displayed enantioselective binding. Interaction of a racemic guest characterized by a rigid bicyclic structure like norcamphor with heterodimeric capsule resulted in the formation of two diastereoisomeric assemblies in a 1.3:1 ratio (diastereoisomeric effect) d.e. 13%.³¹ The same level of stereoselectivity was observed using (*R*)-(+)-3-methylcyclopentanone as an enantiopure guest that is selectively bound only on the basis of steric interactions, indicating that, in order to achieve higher selectivities,

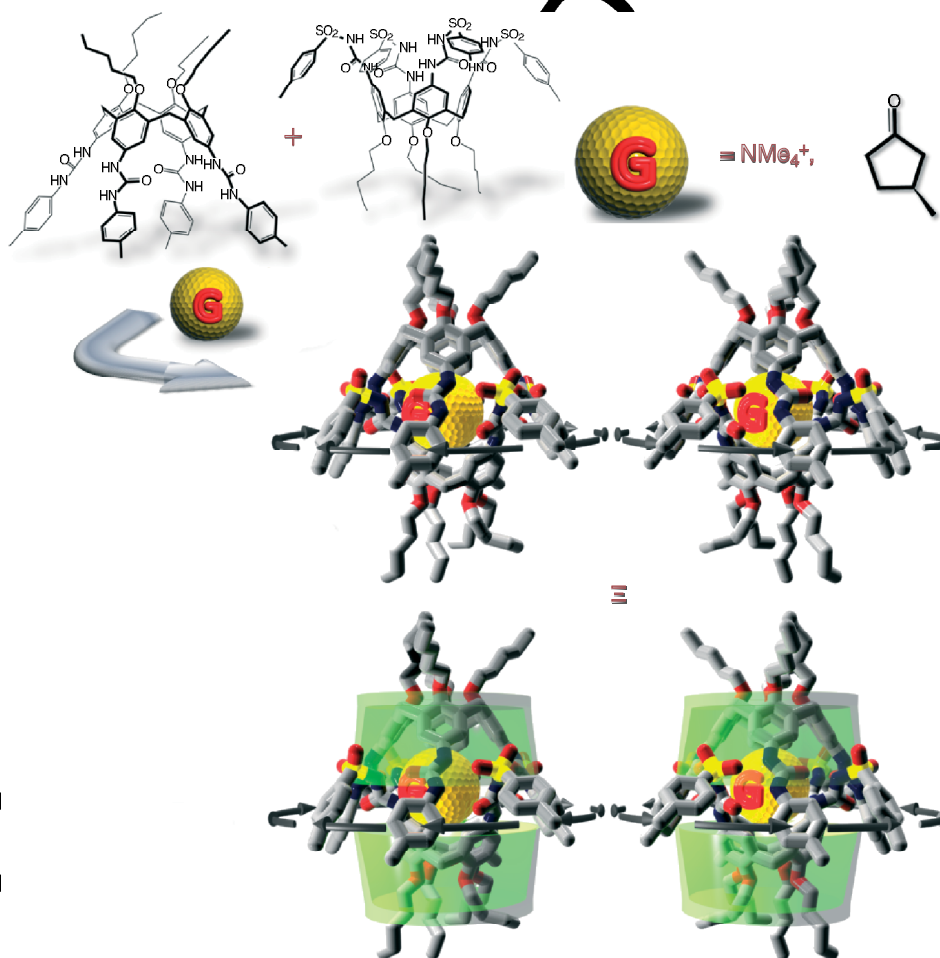


Figure 4 Preferential heterodimerization between tetraarylurea and tetraatosylurea calix[4]arenes leading to supramolecularly chiral capsules that can host cationic or neutral guests.

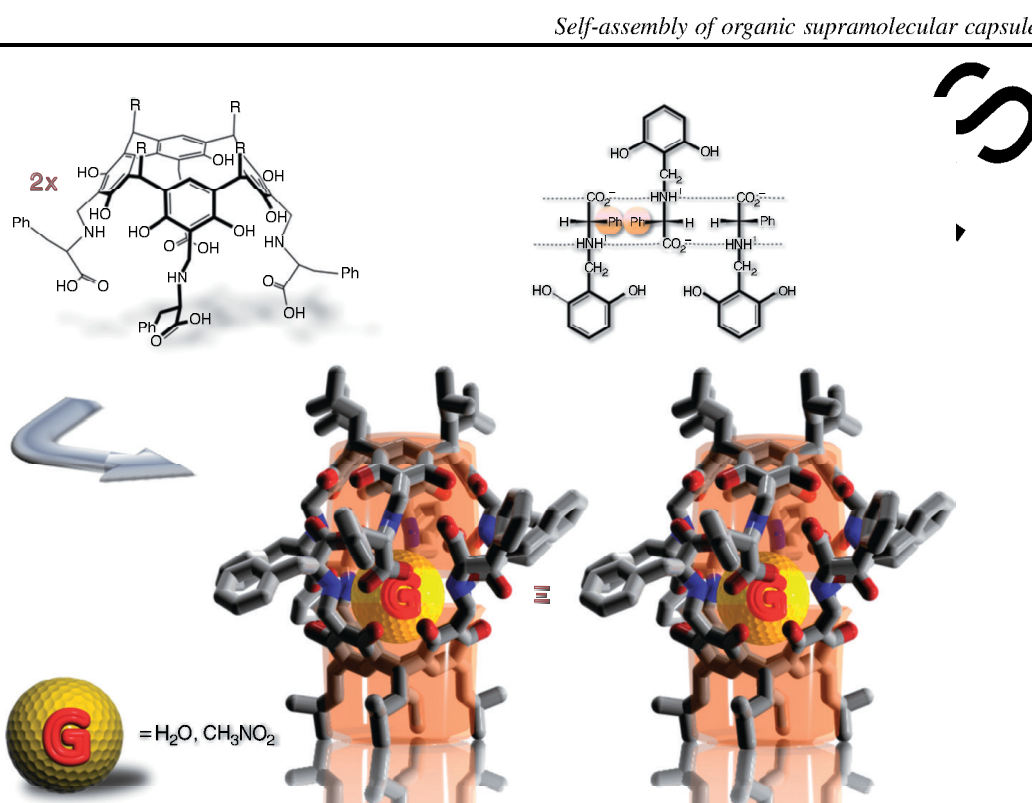


Figure 5 Homodimeric capsule assembled via a seam of charged hydrogen bonds between phenylalanine residues in apolar solvents.

closer contacts between the host and guest are required via attractive weak interactions. The exclusive heterodimerization process has been exploited for the construction of a large variability of functional molecular species like capsular polymers,²⁵ dendrimers,²⁶ and many others that are beyond the scope of the present contribution. Several permutations on the kind of substituents present on the urea moieties for homodimeric capsules allowed to observe supramolecular chirality only due to the mutual arrangement of the two achiral calix[4]arenes in the dimer.³²

2.1.5 *N*-linked phenylalanine-resorcin[4]arene

Tighter association constants were observed using resorcin[4]arene-based structures endowed with four *N*-linked phenylalanine residues that enable the self-dimerization of the system via formation of two seams of salt bridges formed between the amine and the carboxylic groups. Such a capsule is highly kinetically stable, with a cavity of about 310 Å³ large enough for coencapsulation of different guests that, contrary to what is commonly observed, need to be polar like nitromethane, alcohols, and, quite surprisingly, also water owing to the strong interactions via hydrogen bonding with the polar equatorial belt of the capsule under slow exchange on the NMR timescale (Figure 5).^{33,34} In particular, because

of the intrinsic chirality of the capsule, diastereoselective binding of chiral hydroxy acids was possible with d.e. up to 59% for coencapsulation of such guests together with one molecule of acetone-*d*₆ or water.³⁵

Similar strong hydrogen bonding between polar charged groups allowed dimerization in competitive solvents as observed for amino-calix[4]arene systems connected through the C-terminus to four alanine residues. Such polar cavitand self-assemble in methanol-*d*₄ containing 4% of D₂O as a polar solvent by means of a seam of hydrogen bonds between protonated terminal amino groups and carbonyl residues with an association constant of 29 000 M⁻¹.³⁶ This system represents a connection between uncharged capsules in apolar solvents and purely ionic capsules in polar solvents.

2.1.6 Tetraurea-calix[4]pyrrole

Orientation of guests within self-assembled capsules is usually driven by the size and shape selectivity as most of the subunits employed lack the presence of inwardly oriented functional groups that can bind the guest weakly and reversibly. Exceptions to this were discovered recently by the group of Ballester that reported the preparation of dimeric capsules based on the installation of urea functions in the para position of the $\alpha, \alpha, \alpha, \alpha$ -stereoisomer

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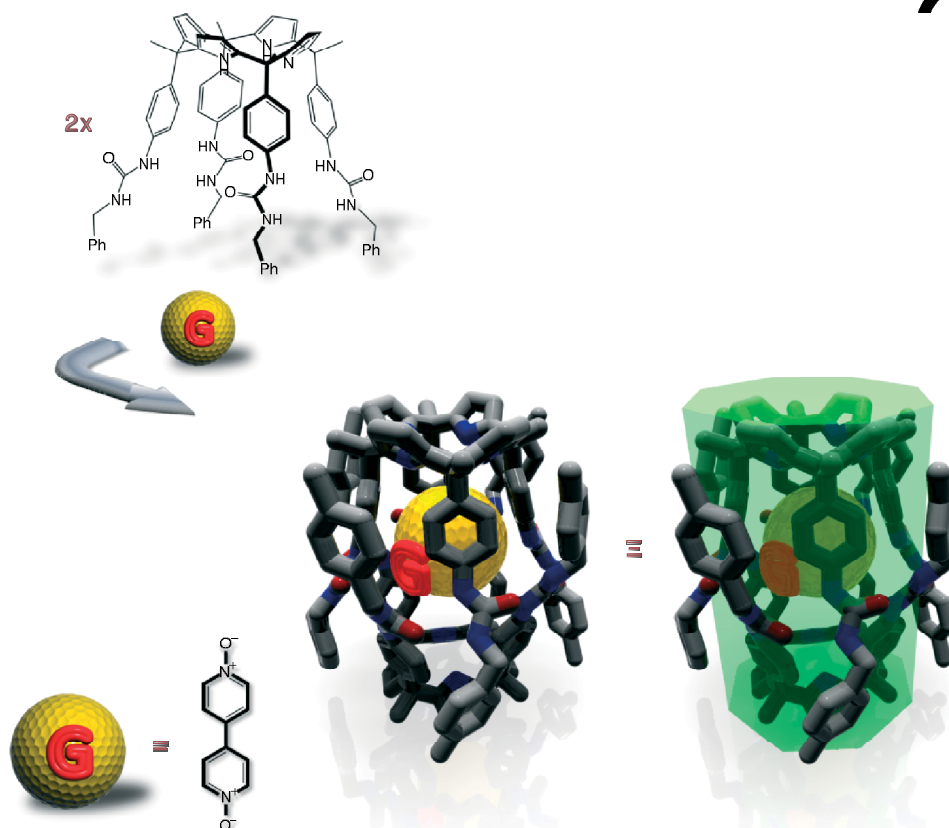


Figure 6 Homodimeric capsule formed by hydrogen bonding between urea moieties and guest encapsulation via attractive hydrogen bonding between the guest and the calix[4]pyrrole extremities.

of *meso*-tetraphenyl-tetramethyl-substituted calix[4]pyrrole (Figure 6).³⁷

The monomer presents urea moieties for the dimerization process and pyrrole NH residues that converge in the calix[4]pyrrole structure providing suitable hydrogen bond donors for suitable guests endowed with hydrogen bond acceptors at both extremities, like 4,4'-pyridine bis-*N,N'*-oxide.³⁸ In fact, the calix[4]pyrrole does not provide clear solutions in CD_2Cl_2 but clear signals appear upon addition of half equivalent of the pyridine bis-*N,N'*-oxide that has the correct size and shape to fill about half of the volume of the cavity ($\sim 210 \text{ \AA}^3$) with a PC close to ideality and that makes strong hydrogen-bond contacts with the electron-rich oxygen atoms to the calix[4]pyrrole top and bottom of the capsule.⁶ Smaller guests can be used but necessitate the presence of good hydrogen bond acceptor moieties like for trimethyl phosphine oxide and trimethyl ammine oxide that can be coencapsulated in the dimeric capsule, both oriented with the oxygen atoms toward the pyrrole residues. The head-to-tail directionality of the urea groups can be clockwise or counterclockwise and interconversion

is slow enough with an activation barrier of $16.6 \text{ kcal mol}^{-1}$ for the change of direction of the urea belt that makes chiral the dimer. When using chiral tetraurea calix[4]pyrrole scaffolds bearing stereogenic centers close to the urea residues, the dimeric capsules obtained with suitable guests acquire another element of asymmetry due to the *M* or *P* chirality induced by the urea belt. Overall, it is worth noting that, analogous to that observed with tetraureido-calix[4]arenes and tetraureido-calix[4]pyrroles, while enantiopure (*S*) monomer self-assemble into (*S, P · S, M*) dimer, when racemic tetraurea is used, there is preferential formation of achiral meso-(*S, P · R, M*) hetero dimer.³⁹

2.1.7 Softball

Glycoluril subunits, as versatile hydrogen bonding units, have been implemented into several polycyclic rigid structures bearing bridged bicyclic centerpiece giving rise to many dimeric pseudospherical aggregates generally known as "softballs." Here the cavity is rather large (from 200 to 400 \AA^3) and up to two guests can be accommodated

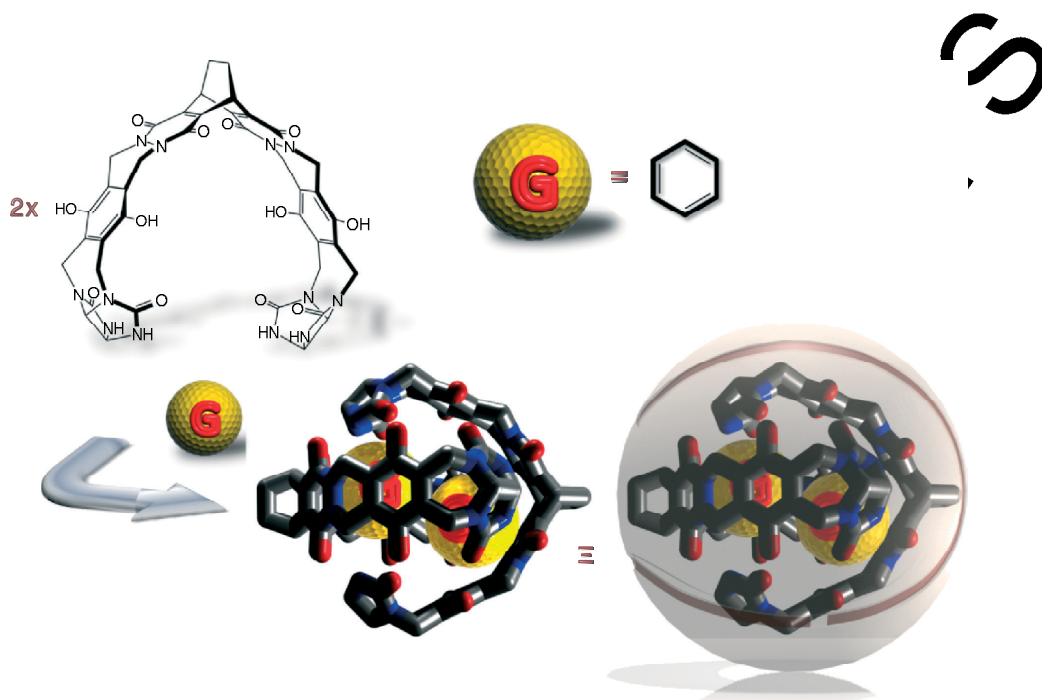


Figure 7 Homodimeric softball capsule hosting two molecules of benzene as guests.

(Figure 7).⁴⁰ These kind of capsules have found interesting applications in several fields; two in particular, are worth mentioning. The first is the synthesis of chiral racemic capsules for recognition of chiral guests. Two approaches are possible, one based on the employment of different glycoluril residues at the extremities of a symmetrical spacer⁴¹ and the other based on the same glycoluril structure connected to spacers bearing different bicyclic units. In both the cases, the monomers are achiral but the dimeric capsules are chiral as a typical example of supramolecular chirality.^{9,42}

Addition of chiral enantiopure guests to the first class of chiral softballs led to the formation of two diastereoisomeric host-guest systems, unfortunately in equal amounts because the cavity was too symmetric to sense the chirality of the guest. To provide selectivity in the binding due to stereorecognition, cluster interactions and tighter binding are pivotal requisites, and the second kind of chiral softballs achieved the goal.⁴³ In this case, the dissymmetric inner surface of the cavity easily sensed chiral guests, providing different diastereoisomeric complexes in different amounts. Each diastereoisomer is characterized by four different NH resonances because of the complete loss of symmetry of the complex. A total of six different glycoluril monomers with overall twenty 20 chiral enantiopure guests were investigated⁴⁴ observing that the presence of functional groups capable of hydrogen bonding to the host was crucial for affinity as well as selectivity. In a few cases, the

selectivity allowed d.e. above 50% and never more than 60% probably because the average distance between the capsule and the chiral content is not optimized and, even in the presence of a good fit and high PC; about half of the cavity's volume is still not filled and this space surrounds the guests.⁶

The high kinetic stability of softballs, which dissociates and therefore racemizes with rates much smaller compared to the in-out exchange of the guest, allowed the demonstration of the chiral memory effect concept (Figure 8). It was possible to template the formation of a chiral enantiopure capsule with a chiral enantiopure guest like (+)-pinanediol favoring one of the two enantiomeric host structures, then the guest was replaced by an achiral one like leaving a chiral nonracemic host capsule that slowly reequilibrates to the thermodynamically racemic mixture.⁴⁵

The second important application of softballs is their use as supramolecular catalysts in the Diels-Alder reactions.⁴⁶ In particular, after careful substrate selection, the system is optimized and true turnover ability is possible for the reaction of *p*-quinone and thiophene dioxide (Figure 9). The reaction is spontaneous in solution and provides 10 and 17% of cycloaddition products after two and four days respectively. With softball as catalyst, 55 and 75% conversion was achieved after the same time periods.⁴⁷ More importantly, the capsule provided true turnover because of the higher steric clashes of the product compared to the

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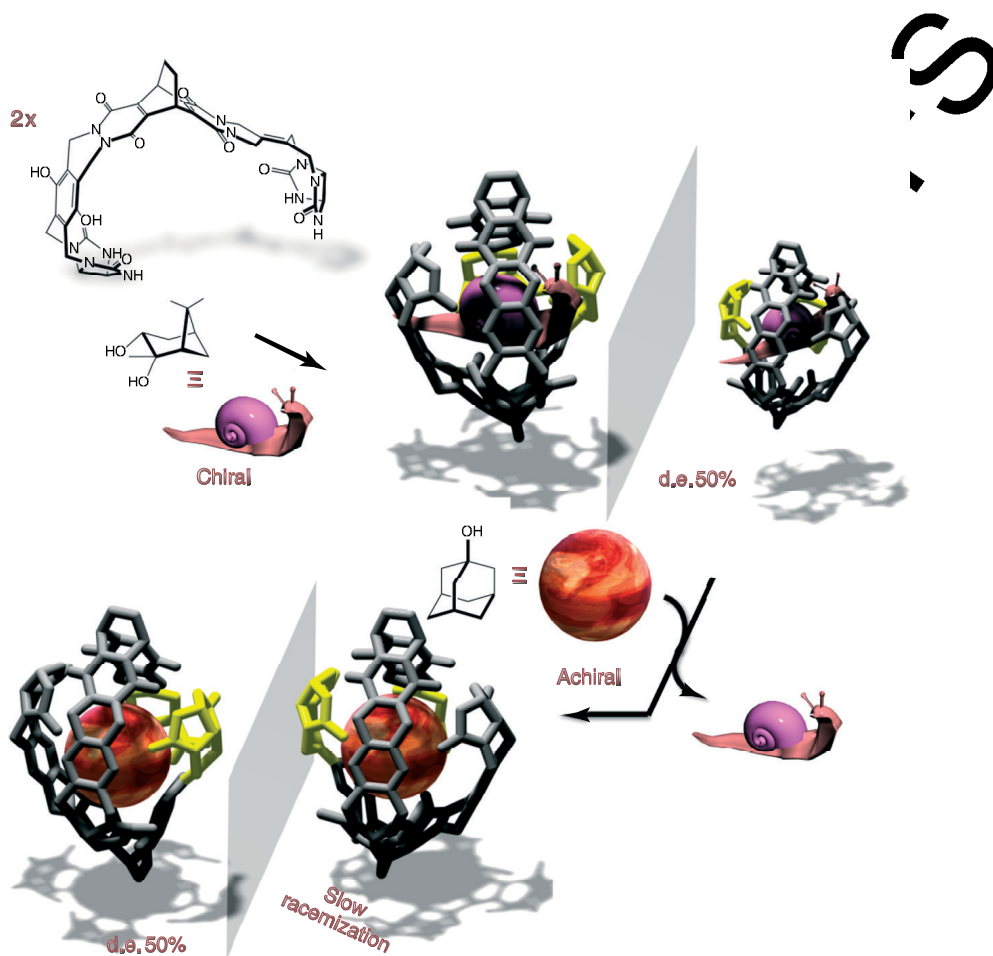


Figure 8 Chiral memory effect displayed by a softball capsule templated with a chiral guest that is subsequently replaced by an achiral one, leading to an enantiomerically enriched softball that slowly racemizes.

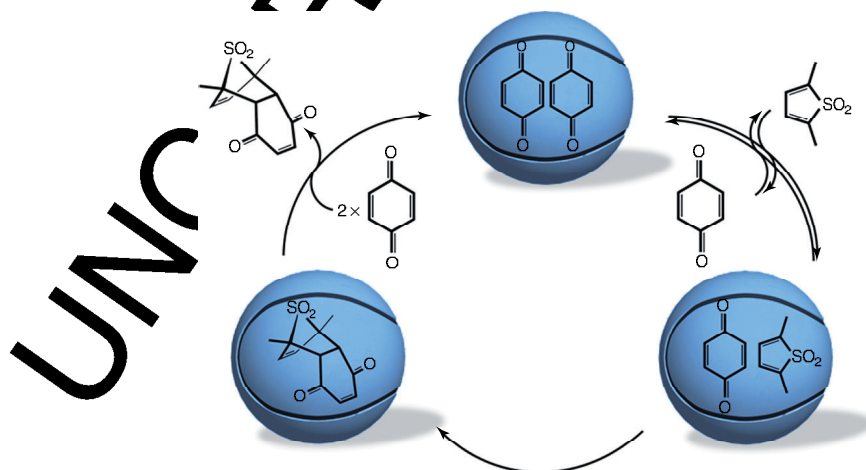


Figure 9 Catalytic Diels-Alder reaction mediated by the hydrogen-bonded softball capsule.

coencapsulation of two molecules of *p*-quinone, which was the resting state of the catalyst in the cycle.

2.1.8 Cylindrical capsule

Most of the hydrogen-bonded capsules are based in rather shallow cavitands adorned with hydrogen-bonding units on the rim. This leads to the formation of aggregates with a shape that can span from pseudospherical to egg shaped as a function of the depth of the cavitand employed and on the difference between the diameter of the aperture and the subunits employed. Only one example is known of a cylindrical capsule formed by dimerization of a deep cavitand. The latter features a resorcin[4]arene base to which four aromatic walls with imide functionalities on the top are attached. Two modules self-assemble through a network of eight bifurcated hydrogen bonds and result in a cavity of about 425 \AA^3 that can be filled with a very large combination of up to three guest molecules,⁴⁸ with preference for neutral or anionic species (Figure 10). Usually the solvent of choice for this kind of studies is mesitylene-*d*₁₂ because its size and shape hamper the encapsulation, leaving access to the cavity for other guest present in the solution even at a rather low concentration.

In decreasing order of number of guests, the cavity can be filled with three chloroform molecules giving rise to two signals, one for the guest that resides in the polar belt of the capsule and one for two molecules positioned deep in the cavity. Using racemic propylene oxide, three molecules are encapsulated and a total of six diastereoisomeric combinations of stereochemistry of the guests is possible.⁴⁹ Using accurately optimized combinations of anions and two organic solvents, it was possible to fill the cavity with three different guests, like PF_6^- anion in the polar middle and CD_2Cl_2 and C_6D_6 at the opposite ends.⁵⁰

With two guests, a new form of isomerism called *social isomerism*⁵¹ arose derived by the reciprocal interaction between the guest molecules that could assume head–head or head–tail proximity as a consequence of the restricted tumbling of elongated guests imparted by the shape of the cavity. For instance, chloroform and *p*-ethyltoluene give rise to two encapsulation aggregates: one with the methyl group toward chloroform, and one with the ethyl group facing the halogenated molecule in an 80:20 ratio in favor of the latter isomer. The cylindrical capsule provides a simple and direct method to formally isolate one-to-one molecular interactions from the bulk solvent, that is, a single-molecule solvation like in the case of solvent molecules coencapsulated with β -ketoesters where the ratio between

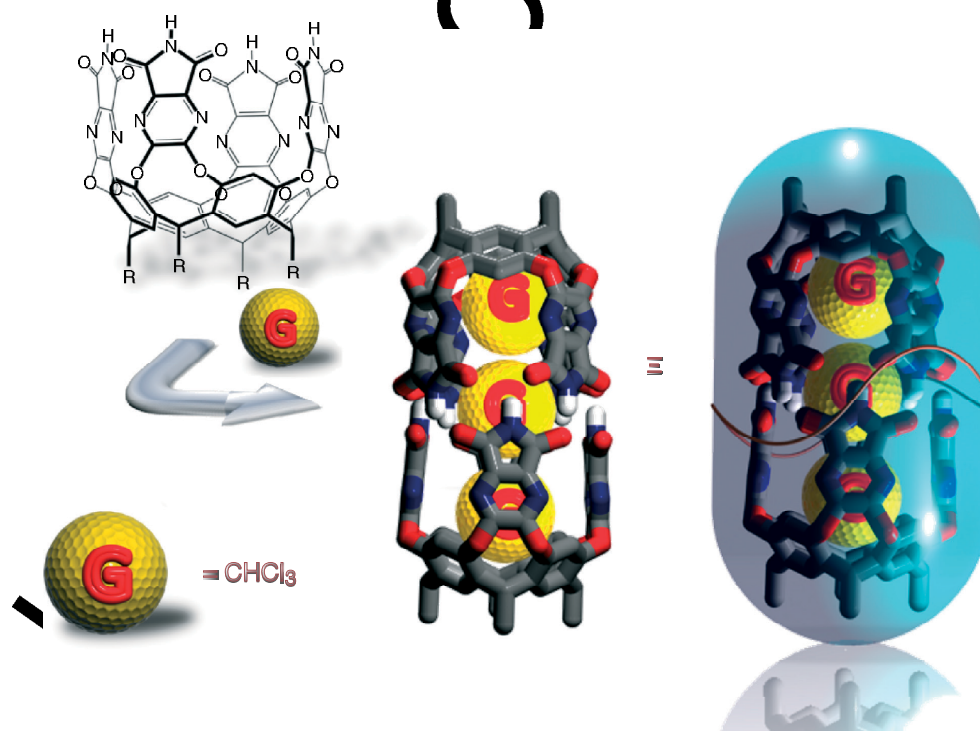


Figure 10 Cylindrical homodimeric capsule featuring an elongated cavity that can accommodate up to three guest molecules.

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the keto and enol form of the latter species within the capsule depends on the kind of second guest, while in the bulk solvent the two do not interact with each other and the keto–enol ratio is insensitive to the nature of the cosolvent.⁵² Using *p*-cyclophane as the primary guest that perfectly fits the square section of the cavity, it was observed that the size of a second coencapsulated guest can finely regulate the spinning rate of the first, also on the basis of steric interactions.⁵³ In the presence of rather large guests, it was possible to coencapsulate different gaseous guests like *p*-xylene-*d*₁₀ with ethane or anthracene with methane in the residual cavity.⁵⁴

In unimolecular guests, the kinetic stability of the ternary aggregate increases and the system withstands the presence of small amounts of protic solvents.⁵⁵ The cavity can accommodate long alkanes from decane through tetradecane, (Figure 11) but, while the former is encapsulated in its extended conformation, the latter is too long and enters the cavity adopting several gauche conformations assuming a helical shape that permits better CH– π contacts between the guest and the aromatic surfaces of the capsule, thus compensating the extra energy required for folding.^{56,57}

This kind of capsule was used to prove concepts related to chiral sensing and chiral induction across the space, both between species coencapsulated within the cavity and also between guests and chiral residues outside the capsule. In the first case, combinations of two molecules of chiral racemic species led to diastereoisomeric host–guest assemblies like in the cases of (\pm)-*trans*-1,2-cyclohexanediol,⁵⁸ (\pm)- α -halo, or (\pm)- α -hydroxy acids⁵⁹ with diastereoselective ratios up to 1.6:1. Concomitant encapsulation also allows the reciprocal interaction between two different chiral guests, for example, the stronger hydrogen bond donor

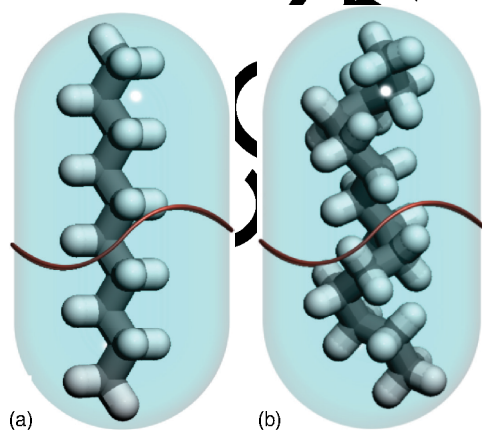


Figure 11 (a) *n*-decane encapsulated in the cylindrical capsule in an extended conformation; (b) *n*-tetradecane is too long to fit the cavity and it is encapsulated only assuming a shorter helical conformation.

like (*S*)-mandelic acid with (\pm)-2-butanol giving rise to two diastereoisomeric complexes, this time in the ratio 1.3:1 at 283 K, or between (*S*)-1-phenylethanol and (\pm)-3-methyl-2-bromo-butyric acid with a 1.5:1 diastereoselective ratio because of the presence of attractive intraguest hydrogen bonds that are instructed and favored by the shape and size of the cavity of the molecular capsule.⁶⁰

In the second case, a small guest like isopropanol was coencapsulated with *meso*-1,1'-benzene-1,4-diyl-diethanol containing one *R* and one *S* stereocenter with (1*R*,1'*R*)-1,1'-benzene-1,4-diyl-diethanol with both stereocenters with the same configuration. The signals of the methyl groups of isopropanol were diastereotopic because of the chiral environment created by the larger guest, but more importantly the difference in chemical shift between each couple of doublets was 0.1 ppm with the *meso* guest and 0.27 with the enantiopure guest. This low but significant difference implies that the isopropanol senses not only the asymmetry imparted by the stereocenter close to it but also the other stereocenter more than 10 Å away facing the bottom of the capsule. This phenomenon is not related to distortions or steric arguments of the hosting structure and is ascribable to magnetic asymmetry.⁶¹ A further step was disclosed on long-range chiral effects using cylindrical capsules bearing stereocenters on the alkyl chains of the resorcin[4]arene scaffold observing their effect from the outside of the capsule directly on the guest trapped in the inside. Using a biphenyl guest bearing an isopropyl ester moiety encapsulated in chiral footed capsules, it was clearly observed that the resonances of the isopropyl residue were diastereotopic as a consequence of the chirality of the host that induces its magnetic effects through the capsule to the bound guest.⁶²

Last but not the least, this kind of capsule has been largely employed as a nanometric reaction chamber for a vast range of reversible and irreversible chemical reactions with the aim of underlining the effect of encapsulation phenomena on product selectivity. Correct size and shape complementarity is crucial for the catalysis of bimolecular reactions with capsules. The cylindrical capsule preferred the coencapsulation of phenyl azide with phenylacetylene with both the aromatic residues near the tapered ends of the capsule leading to 1,3-dipolar cycloaddition reaction with specific formation of the 1,4-triazole isomeric product, while in solution both isomeric 1,4 and 1,5 products were observed in comparable amounts (Figure 12a).⁶³ Another example of product selectivity comes from the reaction between carboxylic acids and isonitriles,⁶⁴ which, when performed in the bulk solvent leads to the formamide derivative together with anhydride, while, on the contrary, when run within the cylindrical capsule the main species detected in the cavity is a rearrangement product *N*-butyl-*N*-formyl-2-(4-methylphenyl)acetamide (Figure 12b) as a consequence of the reciprocal orientation of the substrates

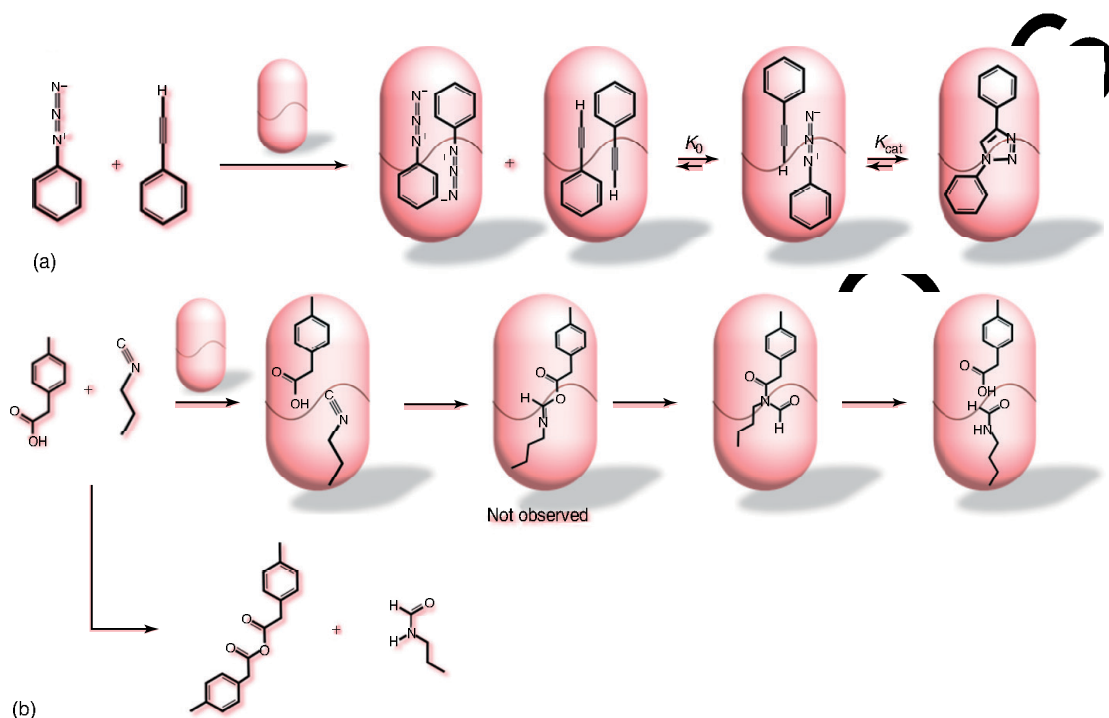


Figure 12 Examples of product selectivity driven by the dimeric cylindrical capsule: (a) reaction between phenylazide and phenylacetylene; (b) reaction between carboxylic acid and imidazole.

in the cavity with polar residues allocated toward the middle of the capsule where the seam of the hydrogen bond donor and acceptor can stabilize polar transition state.

2.2 Multimeric capsules

2.2.1 Tetrameric capsule

Tetrameric capsules are much less common; one known example is characterized by a unique head-to-tail orientation of the hydrogen-bonding monomers forming a barrel-like capsule with a pseudo-spherical cavity of about 160–184 Å.³ The monomers are based on a rigid aromatic spacer with a sulfamidic moiety (a typical good hydrogen bond donor) on one side and a pycoluril residue (a typical good hydrogen bond acceptor) on the other, while positions 1 and 4 present a hydrogen atom,⁶⁵ OH⁶⁶ (Figure 13) or H, OCH₃⁶⁷ residues when the spacer is a naphthyl residue. The monomers are scarcely soluble in noncompetitive solvents and, only upon addition of a suitable guest, they arrange in a tetrameric capsular form surrounding the guest that can make good CH– π and van der Waals contacts with the aromatic surfaces of the aggregate. In particular, the smaller subunit binds pseudospherical guests like adamantane in dichloromethane-*d*₂ with a remarkable entropic loss due to the multimeric nature of

the capsule that is overcome by good fitting of the cavity and positive attractive contacts between the surfaces of the host and the guest. Even better binding was possible with 2-adamantanone and 2,6-adamantanedione where the carbonyl residue offers extra attractive interactions via hydrogen bonding with polar ends of the capsule, giving rise to extremely good fitting of the cavity and high PC up to 72%. The longer representative of this family of capsules showed impressive differences in binding affinity as a function of the functional groups present on the central aromatic core. The methoxy-substituted monomer self-assembles in the presence of suitable guests like polycyclic molecules such as 1,3,5,7-tetramethyladamantane, camphor, or congressane, while the H-substituted analog does not, even if it seems to be less sterically hindered. Explanation for such behavior arises from more intense hydrogen bonding in the former system caused by the electronic effect of the methoxy group that can also make favorable van der Waals contacts with the neighboring aromatic rings. If the monomer is substituted with only one OH group in the aromatic central core, the molecule is chiral, and if used in the enantiopure form it provides an enantiopure tetrameric capsule displaying diastereoselection in the encapsulation of racemic guests.⁶⁸ In particular, ketone molecules showed the highest affinity and chiral recognition depending more on the positioning of functional groups

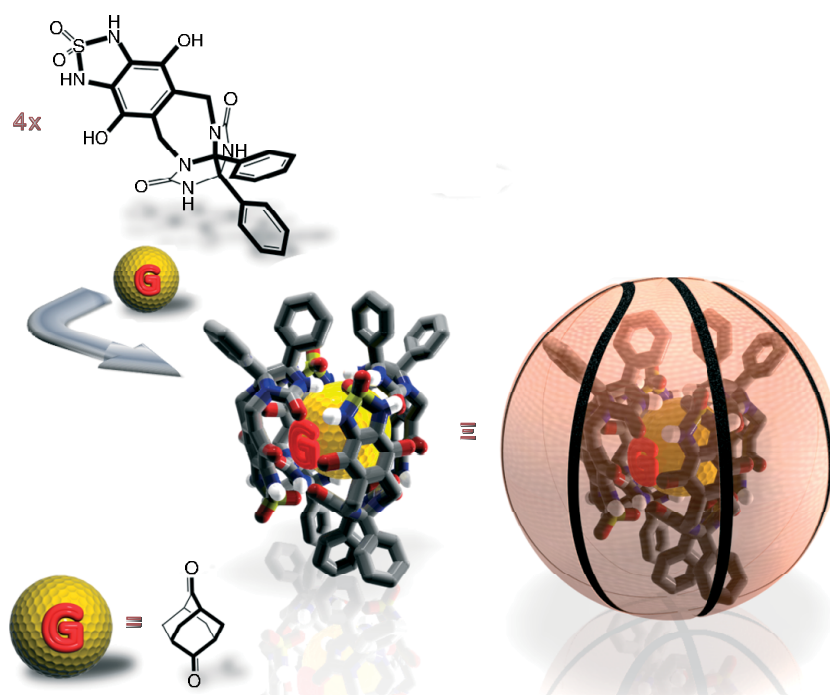


Figure 13 Tetrameric capsule showing binding of suitable guests that make multipoint hydrogen bonding with the top and bottom of the capsule.

in the capsule rather than the size of the guest as observed for (\pm)-norbornadione and (\pm)-3-methylcyclohexanone that has almost the same molecular volume but shows *d*_e of 23 and 60% respectively.

2.2.2 Hexameric resorcin[4]arene and pyrogallo[4]arene

The largest known hydrogen-bonded supramolecular capsule is based on self-assembly of one of the most used and easy to prepare scaffold: resorcin[4]arene. This molecule is characterized by a cup-like shape imparted by the four aromatic residues and it presents eight hydroxyl residues that adorn the rim of the shallow cavity. In 1997, Atwood first reported the resorcin[4]arene self-assembly behavior both in the solid state and in the solution in benzene-*d*₆, evidencing the formation of pseudospherical capsule comprising six units held together through a seam of about 60 hydrogen bonds between phenol groups and water molecules (Figure 14).⁶⁹ Interestingly, the hexameric capsule is chiral because of the twisted positioning of the calix[4]arenes with respect to the eight water molecules arranged in a cubic fashion. The assembly exists in organic solvents like chloroform-*d* or benzene-*d*₆ even at concentrations as low as nanomolar,^{70,71} but only if the solvent is saturated with

water. The cavity is about 1375 Å³ and such a space is usually filled by six to eight solvent molecules. Suitable guests are usually cationic species⁷² like tetraalkylammonium and phosphonium cations that, depending on their size, are coencapsulated with residual solvent molecules. Trapped guests show upfield NMR signals separated from those of the free guests in the bulk because in-out exchange is a slow process on the NMR as ingress and egress of guests occurs likely via temporary dissociation of one subunit from the hexameric structure.⁷³ Other common guests are Bu₄SbBr coencapsulated with various aromatic neutral species,⁷⁴ or cobaltocenium and ferrocenium cations that show high affinity, the latter allowing reversible assembly and disassembly of the capsule driven by electrochemical stimulus.⁷⁵ The large cavity is roomy enough to host an entire host-guest complex composed of a calix[4]arene and tetramethylammonium cation in a kind of nanometric Russian doll.⁷⁶ Some neutral polar guests showed affinity for the hexameric capsule, in particular, using diffusion-ordered NMR spectroscopy it was eventually demonstrated that six molecules of glutaric acid⁷⁷ or three molecules of β -methyl-D-glucopyranoside are hosted by the supramolecular aggregate,⁷⁸ conversely to what was assumed at the end of 1980s when 1:1 host-guest interactions were described.

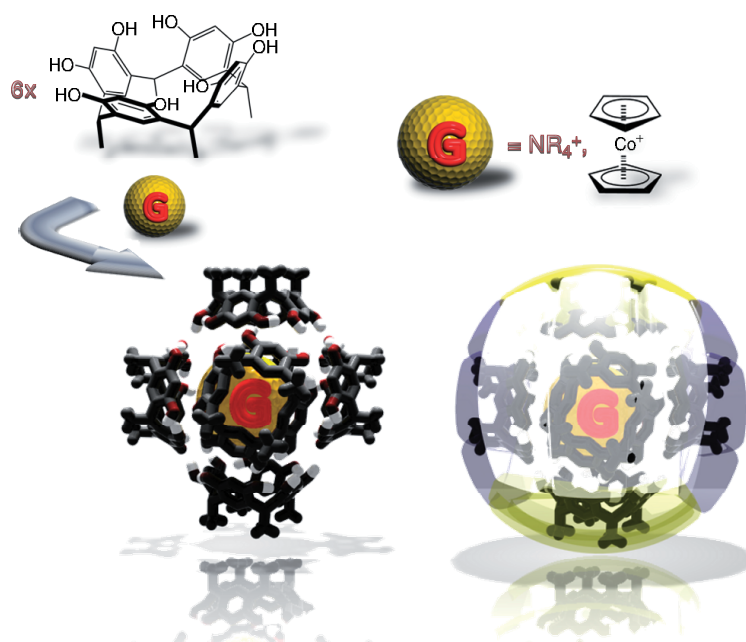


Figure 14 A large hexameric capsule that can accommodate several solvent molecules or cationic guests.

Pyrogallo[4]arene is a very similar structure compared to resorcin[4]arene bearing an extra phenol residue in-between the other two. Such subunits self-assemble, forming hexameric assemblies, but here the presence of water is not necessarily required⁷⁹ as extra hydrogen-bonding residues are intrinsically present in the monomer forming the hexamer with 72 hydrogen bonds. The self-assembly behavior is dependent on the synthetic procedure adopted, in particular, crystallization from acetone or methanol with little amounts of nitrobenzene or dichlorobenzene, and subsequent dissolution in even polar organic solvents ensures the formation of the hexameric capsule.⁸⁰ The large stability imparted by the numerous hydrogen bonds maintains the hexameric structure of the capsule even in 50% v/v mixture of acetone-*d*₆ and D₂O. Typical apolar organic solvents are chloroform-*d* or benzene-*d*₆ and, in these cases, the capsule contains several molecules of solvent characterized by different resonances probably because slightly different environments exist in the cavity.⁸¹

On mixing equal amounts of pyrogallo[4]arene and resorcin[4]arene the evidence of hetero-hexameric capsules was found as a consequence of the extremely high self-recognition process that caused the formation of only capsules constructed from the same macrocycle. Guest affinity is also different between the two capsules, with pyrogallo[4]arene that do not provide binding for alkylammonium cations but prefer encapsulation of tertiary amines⁸² or alkanes.⁸³ Large aromatic polycyclic molecules such as

pyrene butyric acid (PBA) are suitable guests as evidenced in solution by means of spectrophotometric studies. PBA was employed as a fluorescence probe showing double coencapsulation within the hexameric capsule with the two guests kept well separated owing to the specific interactions with the capsule walls.⁸⁴

3 HYDROGEN-BONDING HETEROMERIC CAPSULES

3.1 Dimeric capsules

3.1.1 Tetraacid-resorcin[4]arene with tetrapyrrolic-resorcin[4]arene

A hydrogen bond in noncompetitive solvents between a carboxylic acid and pyridine is a common synthon for the construction of supramolecular aggregates. The presence of cavitands based on the resorcin[4]arene scaffold rigidified by methylene connections between adjacent oxygen atoms, one endowed with four COOH and one with four 3-pyridil moieties form unidentified aggregates in chloroform-*d* but give rise to clear heterodimeric capsules if a solvent of correct volume and shape to be encapsulated is provided, like *p*-xylene-*d*₁₀ or CDCl₂CDCl₂, once again confirming the principle that cavities cannot remain empty but require the presence of molecules

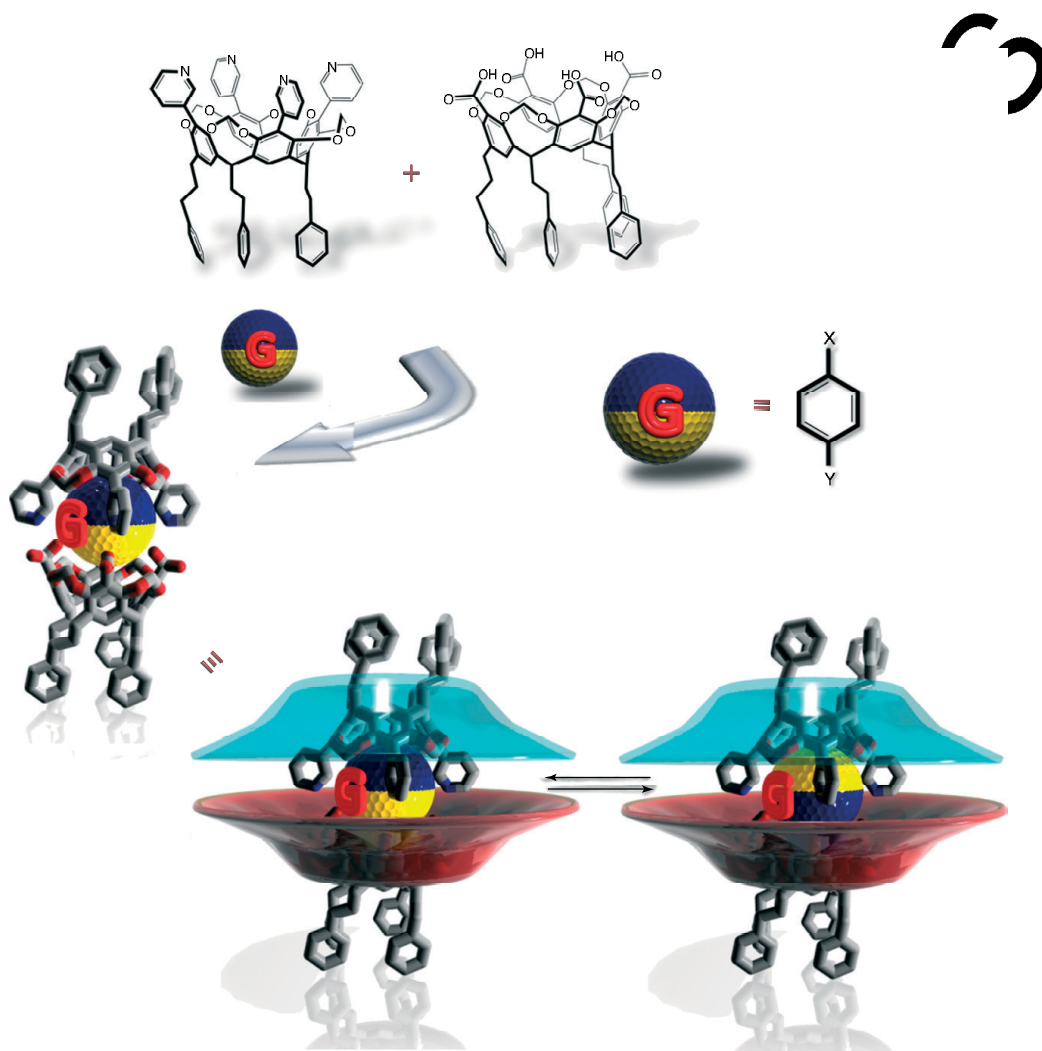


Figure 15 Hydrogen-bonded heterodimeric capsule featuring orientational isomerism for encapsulated guests.

for salvation of internal surfaces. Elongated molecules like *p*-disubstituted benzene systems have the right shape and average volume to fill a cavity of this kind of dimeric heterocapsule, with increased capsule formation in the order *p*-ethyltoluene < 1-ethyl-4-iodobenzene < 1-iodo-4-methoxybenzene < 1,4-dimethoxybenzene < 1,4-diiodobenzene, suggesting that CH-halogen and CH- π interactions between the guest with the methylene groups of the resorcinane play a pivotal role in the guest-induced assembly of the capsule.⁸⁵ In particular, guests with different substituents in position 1 and 4, when encapsulated, provide two possible isomeric assemblies as a function of the orientation of the substituents of the guest either toward the tetracarboxylic or toward the tetra-3-pyridyl pole of the capsule as the resulting balance of

weak attractive and repulsive interactions of the groups with the two halves of the capsule. Extensive investigation with a series of different substrates allowed to demonstrate the preferential allocation of iodo and methoxy groups preferentially oriented toward the pyridyl pole in the first one and toward the carboxyl pole in the methoxy group (Figure 15).⁸⁶

A smaller capsule with a semispherical shape based on the same combination of hydrogen bonds was obtained using the tetracarboxylic cavitand paired with *meso*-tetra(2-pyridyl)porphyrin with a rather small cavity suitable for encapsulation of gases and small molecules as guests.⁸⁷ The binding affinity for gases was in the order $\text{CH}_4 < \text{HC}\equiv\text{CH} < \text{H}_2\text{C}=\text{CH}_2$ in 1,1,2,2-tetrachloroethane- d_2 as a noncompetitive solvent with separate signals for bound and

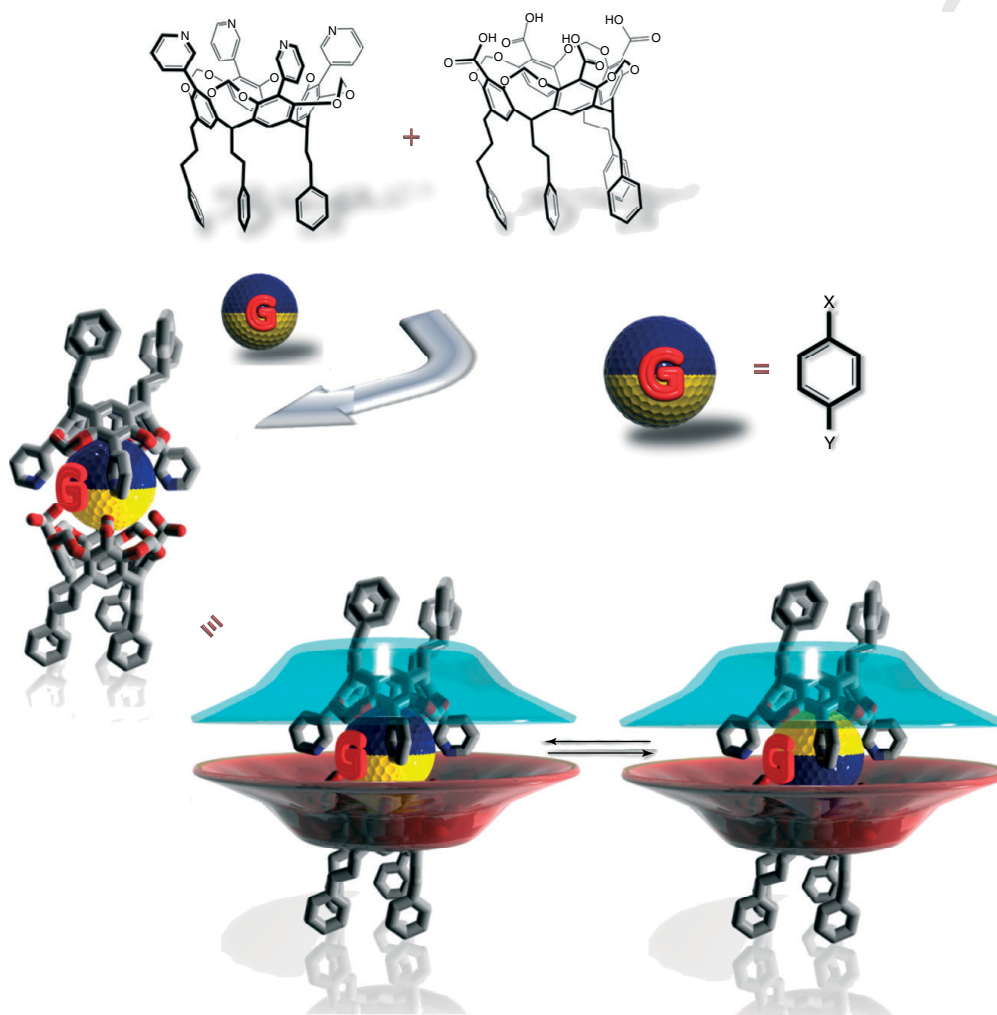


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free gaseous guest in solution even at room temperature as the slowest guest exchange rate so far reported for gaseous guests in self-assembled hosts.

3.1.2 Tetraphenol-resorcin[4]arene with tetrapyrrolyl-resorcin[4]arene

Phenol groups are less acidic compared to carboxylic groups but with pyridine they provide sufficiently strong hydrogen bonds. The research group of Kobayashi investigated the reversible self-assembly of hetero capsules between tetrakis(4-hydroxyphenyl) cavitand and tetra(4-pyridyl)-cavitand with resorcin[4]arene scaffold (Figure 16).⁸⁸ As observed for the above-mentioned capsule from the same research group, *p*-disubstituted aromatic or 2,6-disubstituted naphthyl substrates enable sufficient assembly of the ternary structure composed of the dimeric capsule and the guest. An extensive study of a wide range of substrates⁸⁹ demonstrated that the capsule discriminates guests on the basis of sizes that should be in the range

12.1–15.2 Å with strong differences even for one extra carbon atom; deuterated guests were worse compared to their protio counterparts because of the higher polarizability of C–H compared to that of C–D that favors CH– π contacts with the aromatic concave surfaces of the cavity. Orientational isomerism of the hetero capsule with the bound guest confirmed the preference of halogen substituents for the electron-poor tetrapyrrolyl-cavitand pole owing to favorable halogen–CH and halogen– π attractive interactions derived by the polarization of the I atom that presents $\delta+$ character in the polar region and $\delta-$ in the equatorial area of the C–I bond.

1,4-Diacetoxybenzene derivatives are another class of good guests that show restricted tumbling inside the capsule owing to their particular size, shape, and attractive CH– π contacts with the internal aromatic surfaces. If such guests are substituted in positions 2,5 with alkoxy residues, the spinning rate for rotation of the guest along the vertical axis decreases with increase in the length of

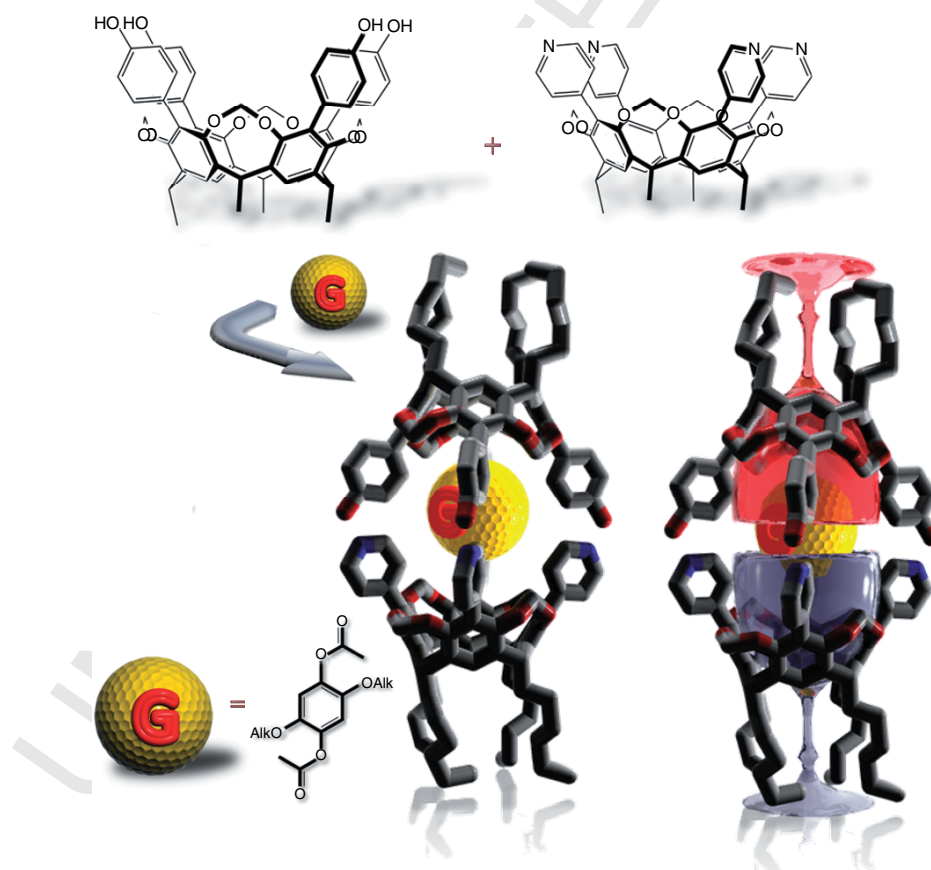


Figure 16 Hydrogen-bonded heterodimeric capsule featuring slow spinning for encapsulated tetrasubstituted aromatic guests.

18 Self-processes

the alkoxy group because of increased frictions with the capsule. The guests resemble the rotator that spins in the capsule as stator of the self-assembled supramolecular gyroscope.⁹⁰

3.1.3 Tetraimide-resorcin[4]arene cavitand and resorcin[4]arene

In the former capsules, the formation of heterodimers is driven by the presence of a strong hydrogen bond donor in one cavitand and a strong hydrogen bond acceptor like pyridine residues in the other, thus making the homodimerization process highly disfavored. Rebek and collaborators demonstrated that formation of hetero dimeric capsules can be driven by the size and shape of the guest as in the case of resorcinarene monomer and tetraimide-cavitand. The two units in chloroform-*d* give rise to three capsule, the hexameric resorcinarene filled with six molecules of solvent, the dimeric cylindrical capsule with three chloroform guests, and a new hybrid capsule⁹¹ (Figure 17) containing two molecules of chloroform derived by hydrogen bonding between resorcinarene and tetraimide cavitand. The amount of the hybrid capsule is dependent on the guest. In fact, in mesitylene-*d*₁₂ as a noncompetitive solvent, midsize guests, such as 1,4-diethylbenzene or *p*-cyclophane that are not singularly encapsulated either in the hexamer or in the cylindrical capsule, drive the exclusive formation of the new heterocapsule where

orientational stereoisomerism is observed with *p*-cymene depending on the position of the methyl and isopropyl group with respect to the deep or shallow pole of the capsule.

3.1.4 Tetraimide-resorcin[4]arene cavitand and monomer of tennis ball

A second different hybrid capsule was obtained by mixing tetraimide-cavitand with the glycoluril unit of the well-known tennis ball with complete disappearance of the dimeric homocapsules indicating that in chloroform-*d* the hybrid dimer is preferred owing to the good match between the imido hydrogen bond donor and ureido carbonyls as good hydrogen bond acceptors (Figure 18).⁹² Suitable guests for the present hybrid capsule are the same as the previous one, in particular, 2,2-*p*-cyclophane snug fit in the cavity giving rise to slow rotation along the vertical axis on the NMR timescale with an activation barrier of about 15.3 kcal mol⁻¹ between the two enantiomeric complexes. Other elongated guests such as 2-methyl heptane, 2,2-dimethylhexane, *p*-ethyltoluene, and *p*-cymene are easily encapsulated but are too long to freely tumble in the cavity showing two orientations in the capsule in slow exchange with increasing preference to allocate the small end toward the tapered end of the cavitand pole for strong CH- π contacts.

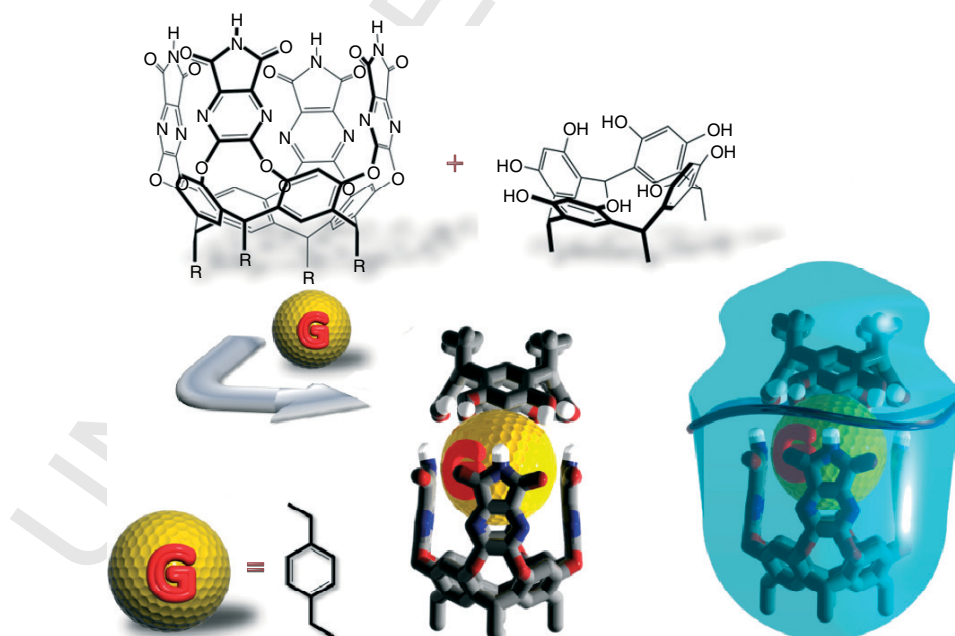


Figure 17 Heterodimeric capsule between a cavitand and resorcin[4]arene templated by the presence of suitable guests.

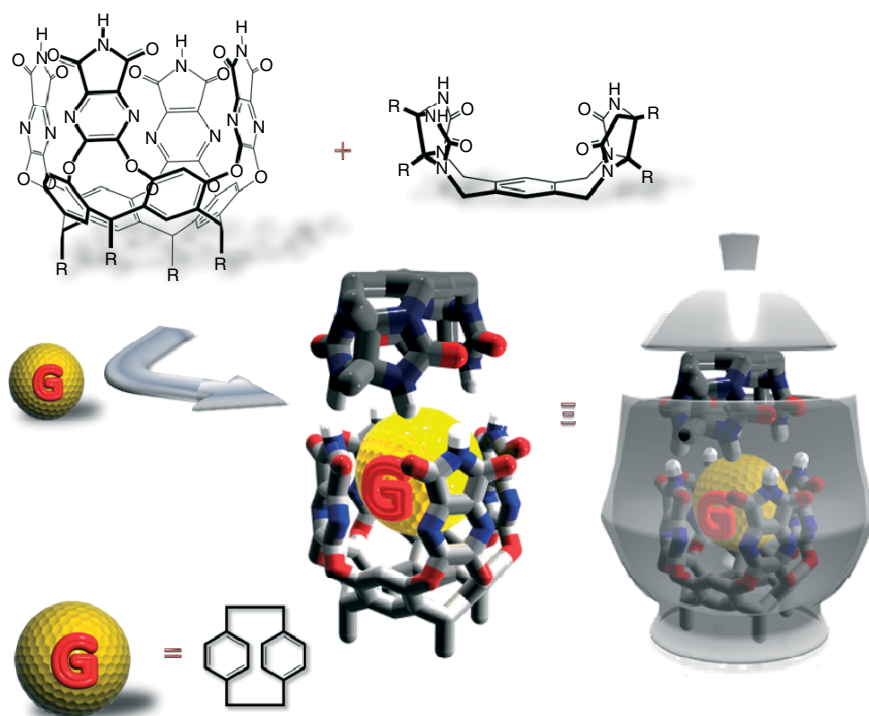


Figure 18 Heterodimeric capsule between a cavitant and a tennis ball monomer templated by the presence of suitable guests.

3.2 Multimeric capsules

3.2.1 Tetraacid-resorcin[4]arene with 2-amino-pyridine or tetrahydro-2-pyrimidinone

Large capsules are possible via interaction of several units using small organic molecules bearing functional groups that are able to both provide hydrogen bond donors and acceptors like 2-aminopyridine (2-AP)^{93,94} or tetrahydro-2-pyrimidinone (THP).⁹⁴ Overall six components self-assemble into an elongated capsule through the formation of 16 hydrogen bonds between two cavitants held together in a rim-to-rim fashion involving four molecules of 2-AP or THP. The structure was confirmed in solution by NMR analysis in chloroform-*d* and encapsulation of medium-sized guests like 2,6-dimethoxynaphthalene and 2,6-dibromonaphthalene, and *p*-diiodobenzene was possible when using a shorter tetracarboxyl-resorcin[4]arene, while very large guests like hexakis(4-methoxyphenyl)benzene or hexakis(4-iodophenyl)benzene were encapsulated using an extended tetracarboxyl-resorcin[4]arene as illustrated in Figure 19. In particular, guest selectivity was fine-tuned using the same tetraanionic cavitant as that with 2-AP, which

led to the encapsulation of hexakis(4-iodophenyl)benzene, while with THP the capsule selectively hosted hexakis(4-methoxyphenyl)benzene.

3.2.2 Tetraimide-resorcin[4]arene with glycoluril

Adequate matching of different subunits to form hybrid capsules depends strongly on the templating effect of the guest. Its size and shape can be used to select the one that provides the best cavity among several possible stoichiometry. As observed before, tetraimide cavitant and glycoluril not only form dimeric heterocapsules with mid-size guests but also enable the formation of new, even larger capsules when using long alkanes as templating guests. A dimeric cylindrical capsule was described to bind tetradecane in a helical conformation but pentadecane was too long to fit the cavity. Addition of excess of glycoluril to the tetraimide cavitant in the presence of alkanes from C₁₅H₃₂ to C₁₉H₄₀ led to the formation of new extended cylindrical capsules with increased length of ~7 Å and volume of ~200 Å³ (Figure 20) where four molecules of glycoluril intercalate in the polar belt of the imide moieties.⁹⁵ The new capsule can adopt two enantiomeric arrangements of the intercalating glycoluril residues, and methylene residues of the alkyl guests become diastereotopic in the nanometric

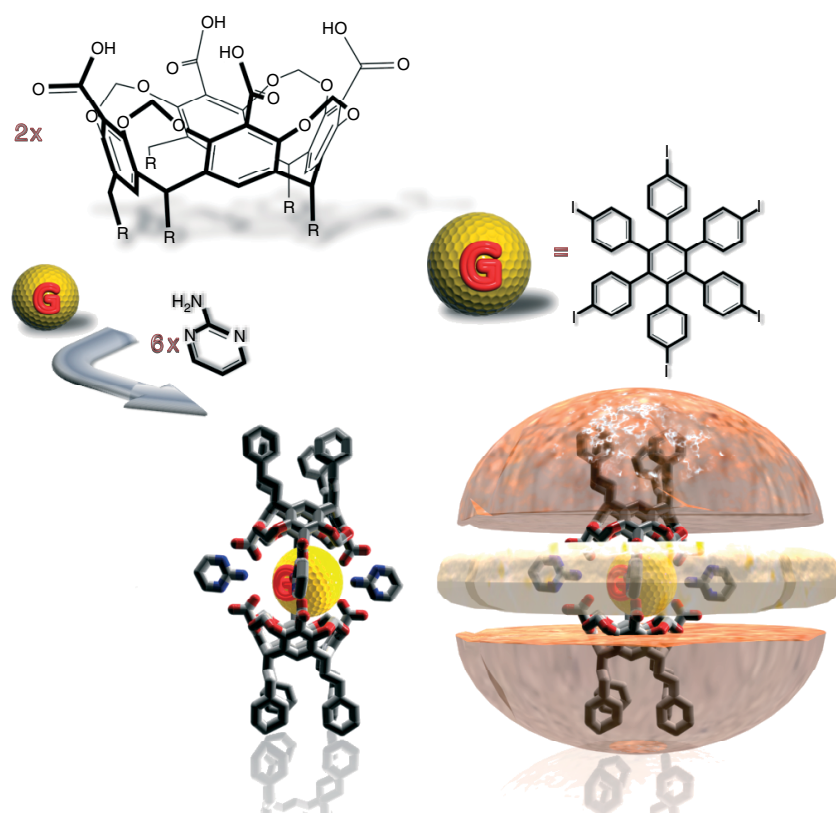


Figure 19 Multimeric hydrogen-bonded capsule showing encapsulation of large flat aromatic guests.

chiral environment. Interconversion of the two enantiomeric extended capsules is dependent on the size and coiling of the guest: in fact, the more the guest fills the cavity and the more it exerts pressure on the glycoluril belt, the more it favors interconversion of the enantiomers that occur at higher rates.⁹⁶ Using glycoluril endowed with amino residues in the side chains, it was possible to prepare a reversible spring-loaded device where tetradecane is encapsulated in its extended conformation and, upon addition of HCl, which protonates the amino groups and causes precipitation of the glycoluril, the capsule become shorter and the guest is forced to assume a helical conformation.⁹⁷ Even longer capsules, hyper-extended self-assembled containers, with two and three belts each composed of four glycoluril molecules can self-assemble, reaching the maximum internal length of 35 Å in the presence of alkanes up to C₂₆H₅₄ basically driven by optimization of CH- π contacts between the guest and the inner surfaces of the capsule that cannot efficiently be solvated by the bulky mesitylene-*d*₁₂ used as solvent.⁹⁸ Extended capsules with one belt of glycoluril can accommodate more than one guest like two molecules of *p*-xylene or four molecules of cyclopropane.⁹⁹

and even xenon coencapsulated with a longer guest such as nonane through dodecane.¹⁰⁰ When 1,4-disubstituted aromatic guests such as *p*-ethyltoluene were studied, three isomeric capsules were present, depending on the reciprocal orientation of the social isomers in the capsule that could be with both methyl groups in the middle (28%), both ethyl groups in the middle (68%), and only 4% of head-tail isomer even though the latter is statistically the more favorable but overall permits worse CH- π contacts with the walls of the cavity.¹⁰¹

3.2.3 Rosettes

Rosettes are beautiful supramolecular aggregates that form spontaneously when three calix[4]arene dimelamines units and six barbiturates or cyanurate are mixed in a 1:2 ratio in apolar solvents.¹⁰² These assemblies, made of nine achiral components, are held together by 36 hydrogen bonds that provide the driving force for the assembly, and can adopt up to three diastereoisomeric forms with *D*₃ (chiral), *C*_{3h}, and *C*_s symmetry due to the reciprocal staggering or aligning of the dimelamine units. Rosettes have been thoroughly studied for their unique features

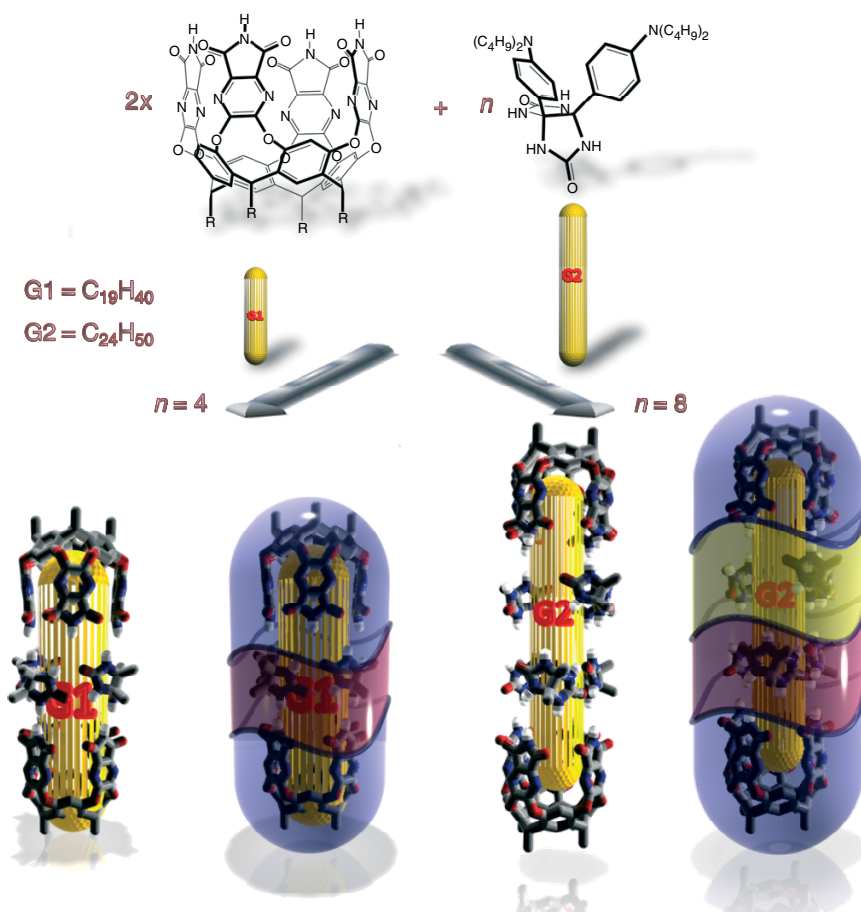


Figure 20 Guest templated formation of elongated cylindrical capsules between cavitand and glycoluril monomer.

in terms of supramolecular chirality and chiral memory effect,⁹ but intriguing encapsulation phenomena are also possible with these heteromeric capsules characterized by a dislike cavity. Anthraquinone derivatives¹⁰³ are electron-rich flat guests that, if adorned with hydroxy groups in certain positions like for alizarin, can be encapsulated in the rosettes forming a network of interguest hydrogen bonds and embarking in host–guest attractive π – π contacts (Figure 21).¹⁰⁴ Binding of this class of guests to rosettes is favorable, with $K_a \sim 10^{10} \text{ M}^{-3}$ observing a remarkable adaptation of the host, which switches symmetry from staggered to eclipsed and increases the distance between the floors of the assembly to fit the triplet of guests as a good example of a guest-induced fit.

The system has been further elaborated preparing rosettes bearing pyridyl residues attached to the external periphery of the assembly¹⁰⁵ and able to make hydrogen bonding with dicarboxylic acids.¹⁰⁶ This class of rosettes enabled exclusive *endo* binding of anthraquinone guests

allocated within the cavity and *exo* binding of up to three dibenzoyl-D-tartaric acid molecules on the outer of the capsule.

4 ION-PAIRING HETEROMERIC CAPSULES

Ionic interactions between positively and negatively charged residues have been much less investigated compared to hydrogen bonds and have rarely been implemented into supramolecular assemblies. In fact, due to solubility concerns, the construction of supramolecular aggregates held together by ionic couples is a more challenging task because often charge pairing could cause a net decrease in solubility of the aggregate, resulting in precipitation. Because of the difficulty in mastering ionic interactions that are less directional compared to hydrogen bonding, rare examples of multimeric capsules are known; basically,

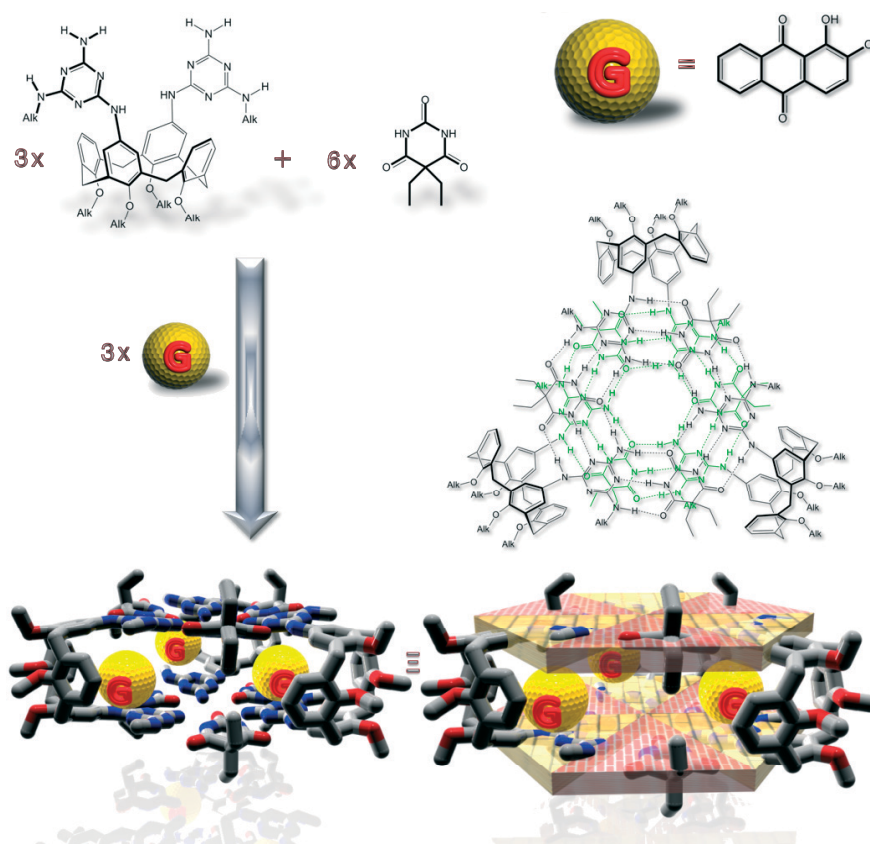


Figure 21 Encapsulation of triplets of alizarin neutral guests within the cavity of self-assembled rosettes.

only heterodimeric capsules where one subunit is positively and the other negatively charged.

4.1 Dimeric capsules

The construction of self-assembled capsules based on ionic interactions to be tested as supramolecular hosts in polar solvents such as alcohols or water is a timely goal that, compared to hydrogen-bonded capsules, is still in its infancy even though important steps have been taken. Few examples have been reported regarding ionic capsules between cationic flat tetrapyrrolium-Zn(II)-porphyrinate and anionic tetrasulfonate-calix[4]arenes¹⁰⁷ that form a hemispherical entropy-driven capsule that displayed high stability in the presence of water or competing salts. Apart from solvent molecules, such capsules showed encapsulation of small guests like 1-methylimidazole or 4-methylpyridine via coordination to the Zn(II) metal center, while bulkier caffeine was bound outside on the opposite side of the porphyrin plane.¹⁰⁸

All the other dimeric ionic capsules are based on two oppositely charged calix[4]arene scaffolds that dimerize in solution owing to the presence of one subunit of typical hydrophilic anionic groups such as sulfonate, phosphate, and carboxylate that make ion pairing with cationic groups such as ammonium and anilinium present in the second subunit. The binding affinity is, as expected, dependent on the pK_a of the functional groups involved, with stronger associations observed for dimers characterized by larger differences in pK_a between anionic and cationic counterparts, with values on the order 10^4 – 10^7 M^{-1} , for example, tetrabenzylphosphonate-calix[4]arene prefers tetraammonium-calix[4]arene compared to tetraanilinium-calix[4]arene for about 2 order of magnitude.^{109,110} In most of the cases, thermodynamic investigation showed that the association process in methanol-water media is strongly entropy driven, most likely due to the release of highly ordered solvent molecules in the bulk solvent.¹¹¹ Weaker interactions are therefore present for dimeric capsules based on ammonium and carboxylate functional groups

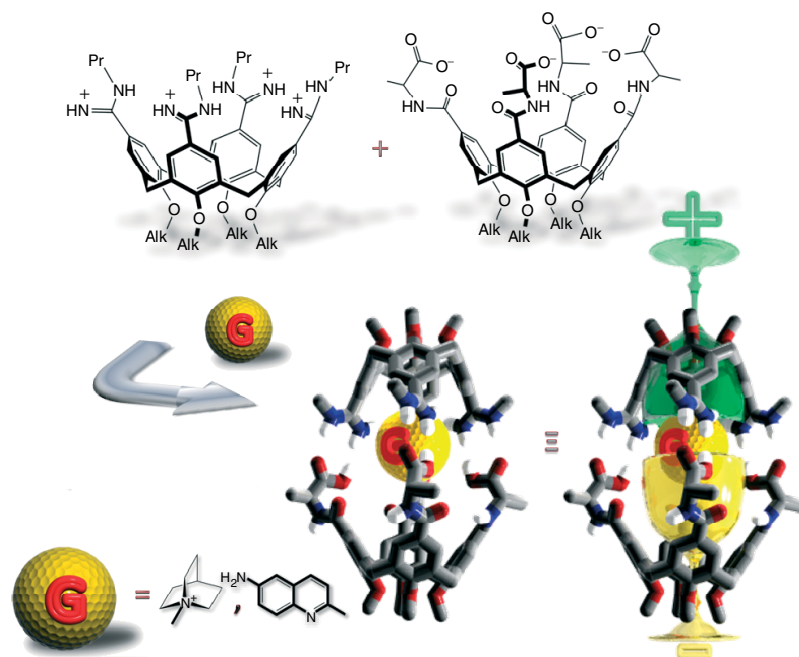


Figure 22 Ionic heterodimeric capsule based on tetraalkylamidinium-calix[4]arene with a tetracarboxylate-calix[4]arene as host for cationic and neutral guests.

that provide calix[4]arene-based capsules with association constants of about 10^3 M^{-1} in $\text{dmsO}-d_6$ with 5% of buffer at pH 6.5.¹¹² None of the above-mentioned ionic capsules displayed clear-cut examples of guest binding, albeit it is likely that the cavity of such capsules is occupied by solvent.

4.1.1 Tetraamidinium-calix[4]arene and tetraanionic-calix[4]arenes

A step forward was accomplished using tetraalkylamidinium-calix[4]arenes as cationic subunits that showed easy dimerization with tetrasulfonate-calix[4]arene¹¹³ under fast exchange on the NMR timescale. Dimerization was proved via NMR analysis that showed an upfield shift for the protons of the propyl amidinium chains compared to the simple tetracationic scaffold in solution, as an indication of dimer formation via inclusion of the alkyl chain inside the cavity. Upon addition of the guest, the alkyl chains are displaced by the incoming molecule indicating that a certain degree of hydrophobic effect contributes to the binding ability of the guests in the apolar and weakly solvated core of the capsule. A suitable guest was *N*-methylquinuclidinium and also tetramethylammonium or acetylcholine with good association constants in the range $20\text{--}170 \text{ M}^{-1}$.

Pairing of the tetraalkylamidinium-calix[4]arene with a calix[4]arene scaffold bearing *N*-coupled *L*-alanine carboxylate anionic groups on the wider rim led to the formation of another heterodimeric ionic capsule (Figure 22)¹¹⁴

that not only showed similar encapsulation behavior compared to the former one toward cationic guests but also enabled encapsulation of neutral guests. A wide range of possible candidates was computationally investigated concluding that 6-amino-2-methylquinoline was a good guest with a binding constant for the capsule of $2 \times 10^3 \text{ M}^{-1}$.¹¹⁵ The presence of the *L*-alanine residues imparts chirality to the capsular assembly but thus far examples of enantioselective binding have not been observed, even though the ionic interactions that hold together the capsule provide an association constant as high as 10^5 M^{-1} in pure water.

4.2 Multimeric capsules

Multimeric capsules are rare; one example in water is based on ion pairing between two tris(imidazoline) scaffold with two tartaric acid, leading to a capsular assembly with no cavity. In this system, proton exchange between the acid and the base provide strong multiply charged interactions with hydrogen bond contacts strong enough to enable aggregation in pure water with $\text{p}K_a \sim 6$.¹¹⁶

A more complex multimeric ionic capsule has been reported few years ago and is based on the interaction between two tetracationic molecules of tetrakis(pyridiniummethyl)teramethyl cavitands that do not reject as expected but face each other owing to the insertion

of four anionic species between two different pyridyl moieties thus forming a capsular structure in methanol- d_4 with a cavity where one or two anions, depending their size, can be accommodated.¹¹⁷ The driving force for the aggregation comes from the formation of four pyridinium–anion–pyridinium attractive interactions, and this capsule exists in equilibrium with the analogous comprising only three triple-ion interactions. The latter aggregate presents one available binding site formed by two relatively closed pyridinium moieties that can form pyridinium–guest–pyridinium interactions with neutral electron-rich aromatic guests like *p*-iodophenol or *p*-iodoaniline. In the latter case, interaction of the guest does not occur within the cavity of the capsule but binding takes place on the equatorial area of the capsule.

5 HYDROPHOBIC CAPSULES

While formation of capsular self-assembled systems based on hydrogen bonding or ion pairing can be, in some way, predicted on the basis of the distribution of functional groups, shape, and the form of subunits, the same is not valid and serendipity takes the lead when the self-assembly process is driven by the hydrophobic effect. The latter, in its more common version, is based on the entropic gain that arises when apolar surfaces are forced to interact, liberating water molecules in the bulk. Conversely, hydrogen bonding, ion pairing, and metal–ligand coordination are usually enthalpically driven. While it is relatively easy to select combinations of functional groups that are able to strongly interact by means of weak noncovalent intermolecular

forces, it is not easy to predict for a given molecule how it will aggregate and which final supramolecular aggregate will form once it is placed in water. This explains why the number of well-defined aggregates and capsules assembled via the hydrophobic effect is largely smaller compared to hydrogen-bonded capsules, even though mastering of the hydrophobic effect for molecular recognition and supramolecular chemistry in general have great potential applications for a series of disciplines related to pharmaceutical chemistry and drug delivery.

5.1 Dimeric capsule

5.1.1 Resorcinarene cavitand

One of the most studied hydrophobically assembled dimeric capsule has been developed by Gibb and collaborators and is based on a deep partially water-soluble cavitand bearing eight carboxylic moieties and comprising a resorcin[4]arene scaffold with a second belt consisting of four aromatic rings to rigidify the structure. A third row of four aromatic residues is present to provide a hydrophobic rim that is involved in the dimerization process.¹¹⁸ Such octa-acid cavitand is soluble at millimolar concentration in pH 8.9 buffered solutions in water and in the presence of suitable apolar guests of opportune size and shape undergo dimerization forming a hydrophobic cavity with volume of about 500–800 Å³ that, depending on the size of the guest, can accommodate one or two guest molecules (Figure 23).¹¹⁹ It is the guest that, on the basis of its size and shape, acts as a template steering the formation of the assembly toward

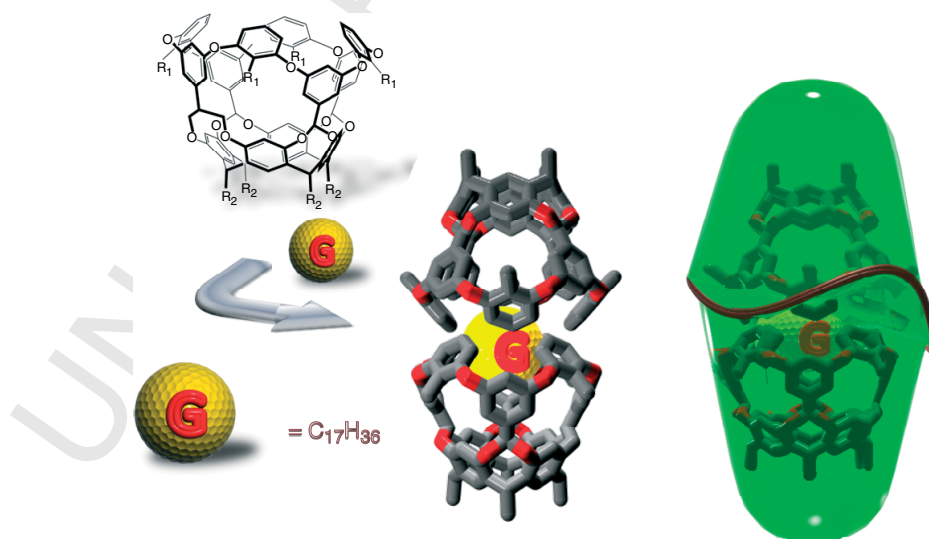


Figure 23 Hydrophobically driven dimerization of water-soluble octa-acid cavitand encapsulating apolar templating guests.

dimeric capsules and decides the overall stoichiometry of the hydrophobic assembly.

Guest exchange is a rather slow process that takes place on the order of $0.1-1 \text{ s}^{-1}$ and is governed by the assembly and disassembly process. There are many suitable guests, ranging from steroids, hydrocarbons from pentane through octadecane displaying high binding affinity $>10^8 \text{ M}^{-1}$ and PCs between 48 and 73%, but also smaller molecules such as gases like propane and butane with very high affinity for the latter, enabling the separation of mixtures of the two, simply equilibrating the gas with an aqueous solution of the hydrophobic cavitation.¹²⁰

If the guest bound via the hydrophobic effect is also the substrate for a photocatalytic reaction, the dimeric capsule, owing to its high kinetic stability and the extremely short time frame of this kind of reactions, acts as a nanometric reaction chamber that is able to impart unique product selectivities. The system has been largely investigated for a series of reactions; selected examples are reported in

the following, while a more exhaustive description can be found in the literature.^{119, 121}

Dibenzoyl ketones are suitable guests for this dimeric capsule and they undergo exclusive formation of decarboxylation products in the absence of the hosting dimer, while in the presence of the capsule unusual massive formation of rearrangement products derived by recombination of radical residues and minor amounts of decarboxylation products is observed (Figure 24a).¹²² Moreover, as far as the decarboxylation products are concerned, photolysis within the capsule provided only mixed products and no homodimers, confirming that the recombination of radicals occurs in the capsule faster than in the in-out exchange.

Photocatalytic reactions of α -alkyl dibenzoyl ketones were investigated along with the effect of the alkyl chain length that dictates the particular arrangement of the guest within the capsule and the subsequent product distribution as depicted in Figure 24(b), while in the absence of the capsule all the substrate led to the same pattern of products.

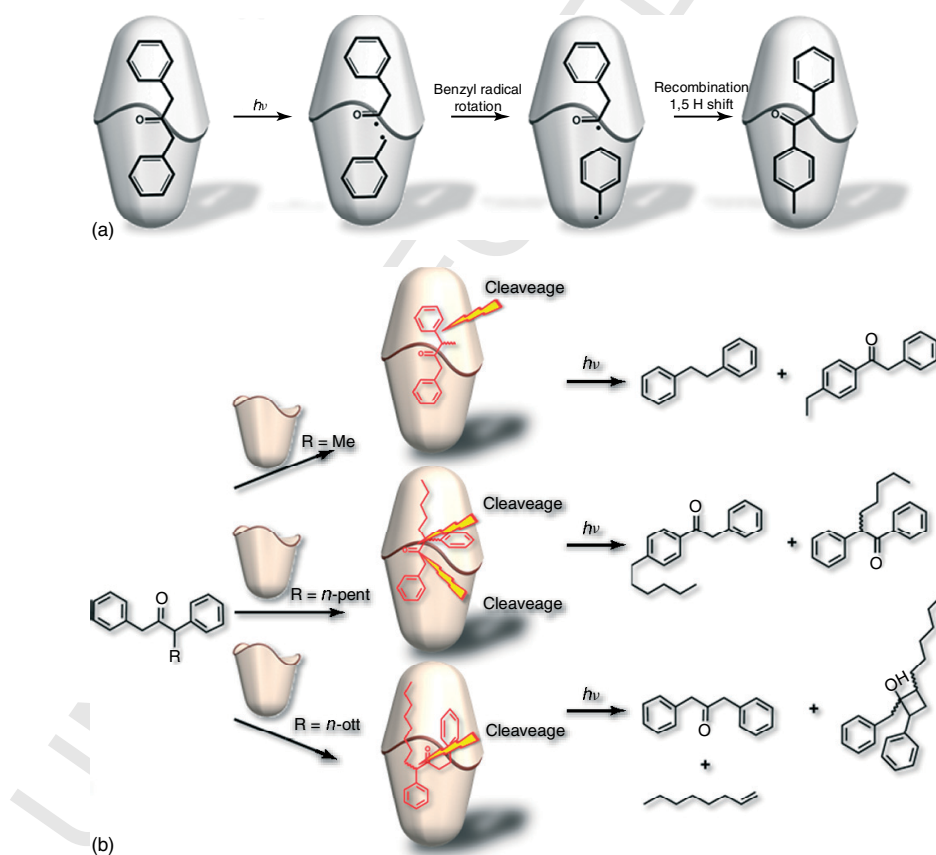


Figure 24 (a) Hydrophobic dimeric capsule leads to selective formation of 1-(4-methylphenyl)-2-phenylethanone with no decarboxylation side products in the photolysis of the encapsulated dibenzoyl ketone. (b) Photocatalytic cleavage of the encapsulated α -alkyl dibenzoyl ketones undergo with different product distributions as a consequence of the length of the alkyl chain and the relative positioning within the capsule.

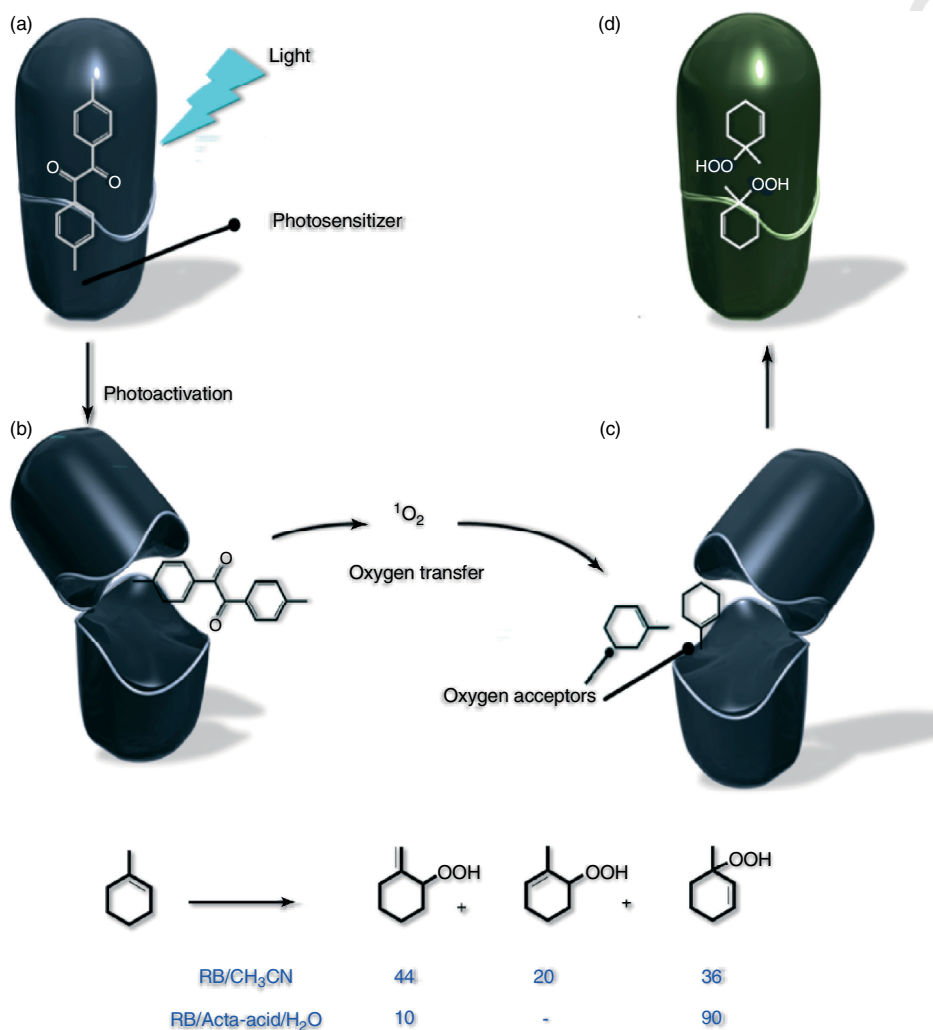


Figure 25 An encapsulated sensitizer is excited with light and it releases the energy to molecular oxygen that oxidizes a second hydrophobic guest selectively to the corresponding hydroperoxide.

For the encapsulated guests, with the methyl-substituted substrate, the aryl residues were placed on the tapered end of the capsule, while with the longer *n*-pentyl residue the alkyl group was placed toward the end of the cavity. Even longer *n*-octyl residues led to an even different substrate positioning with consequent different product distribution.¹²³

It was also possible to set up a photocatalytic reaction where singlet oxygen oxidation of cyclic alkenes was controlled by the capsule via interaction with a sensitizer like water-soluble Rose Bengal (RB) or insoluble dimethylbenzil (DMB) as sensitizers.¹²⁴ All the alkenes provided quaternary 2:2 capsular self-assembled structures with the oxidation product distribution related to

the position assumed in the cavity. The same reaction in acetonitrile without host led to a complex mixture of hydroperoxides (Figure 25).

5.2 Hexameric and tetrameric capsules

5.2.1 Hexagram-shaped amphiphile

The hydrophobic effect is very difficult to predict; in fact, even though it is rather simple to prepare amphiphilic molecules, it is highly difficult to predict the formation of discrete assemblies and often serendipity takes part in the game. One example is reported in Figure 26 where

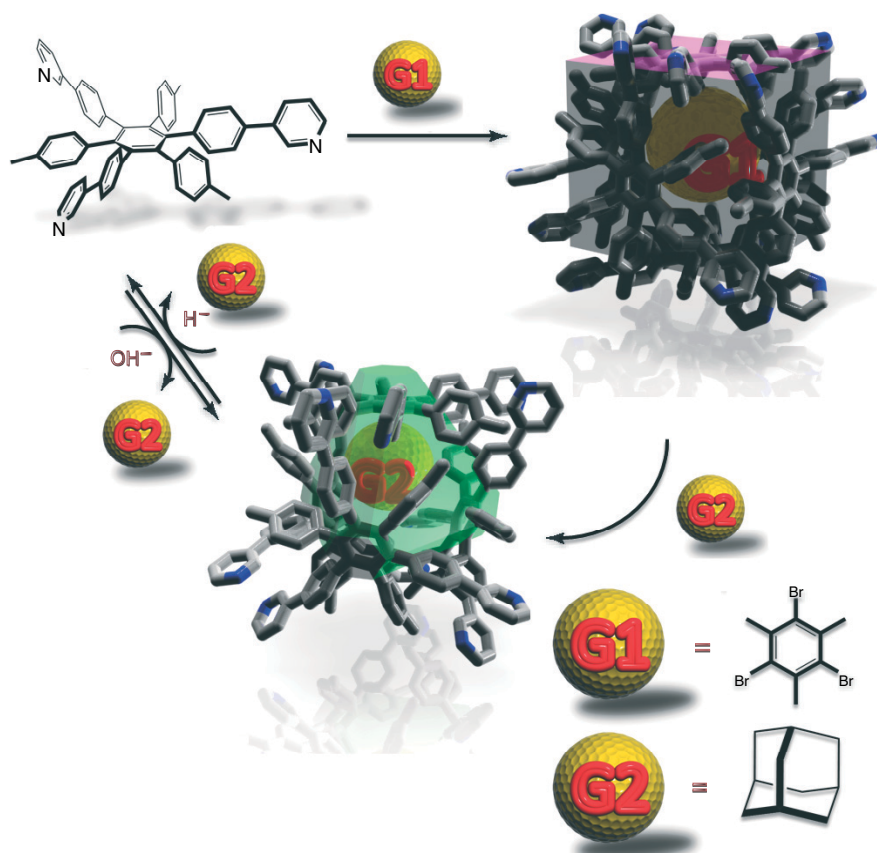


Figure 26 Amphiphilic hexagram-shaped molecules self-assemble via the hydrophobic effect, forming a hexameric box or a tetrameric tetrahedral-shaped capsule as a function of the templating hydrophobic guest.

the structure of the hexagram-shaped amphiphile molecule based on an aromatic apolar hexa-phenyl benzene core adorned with alternating pyridyl and methyl substituents is depicted.¹²⁵ Such a molecule is singularly solvated in CD_3OD providing signals on the NMR in accordance with its C_3 symmetry, but in the presence of increasing amounts of D_2O , new signals in the upfield region arise and, in $\text{CD}_3\text{OD}-\text{D}_2\text{O}$ 75:25, a hexameric boxlike aggregate is present that not only exists in solution but can also accommodate suitable guests like two molecules of tribromomesitylene that stack one another in the apolar core of the system (Figure 26 guest G1). It is worth noting that the presence of methyl residues on the monomer is crucial for the formation of the aggregate via the hydrophobic effect; in fact, without such residues the system does not provide the box aggregate but simply leads to multilayered structures. Van der Waals forces and $\text{CH}-\pi$ interactions between such methyl groups and the adjacent aromatic rings help stabilize the discrete capsule structure of the

hexameric aggregate to a great extent. As often described, the guest needs to complement the cavity provided by the hexameric supermolecule well, where hexamethylbenzene, mesitylene, and 1,3,5-tribromobenzene were suitable guests, while slightly larger hexabromobenzene or smaller 1,3,5-trichlorobenzene were not. Even more remarkable is the switch of the shape and nature of the self-assembled host induced by a more spherical guest such as adamantane, representing one of the most clear-cut examples of induced-fit assembly of the host to better complement the guest. Addition of 1.5 equivalents of adamantane with respect to the free hexameric assemble switches the aggregate toward a tetrahedral tetrameric new host that better complement the guest (Figure 26 guest G2). The structure of the new systems was unambiguously determined by X-ray analysis confirming its C_3 symmetry with the pyridine located between a cleft formed by other hexagram-shaped molecules and the guest not close enough to the host thus supporting the encapsulation via hydrophobic

effect rather than van der Waals interactions. The presence of the pyridine moieties allowed the reversible assembly and disassembly of the host–guest system by means of addition of 12 equivalents of DCl that protonate the nitrogen atoms, liberating adamantane and the monomer in solution as a tris-cationic species, while neutralization with NaOD returned the host–guest systems in its original tetrahedral form.¹²⁶ The thermodynamic properties of the aggregation process of the amphiphilic monomer described above has been investigated in detail, and it was observed that aggregation does not occur under the classical entropic hydrophobic effect where the driving force is the release of water molecules that are more free to move, but via a nonclassical enthalpic hydrophobic effect that is present when the systems have extended aromatic π surfaces that aggregate with enthalpically favorable π – π contacts.

6 CONCLUSIONS

Organic self-assembled capsules have become increasingly sophisticated nanometric self-assembled devices over the years that are able to display unique control levels on a single or a few encapsulated molecules. The latter experience restricted rotation, tumbling, single molecule-to-molecule orientation, influenced chemical equilibria, and reactivity: all properties that cannot be controlled at the same level of sophistication for molecules in the bulk. Owing to the development of synthons like certain hydrogen-bonding moieties or particular scaffolds, it is possible to design and create new and more sophisticated capsules.

One of the most common comparisons involves supramolecular capsules and enzymes because they share many behaviors, properties, and common features. Encapsulation phenomena reveal new concepts that clearly show interaction between substrates and enzymes in the formation of active complexes that subsequently lead to catalytic reactions and product formation. Encapsulation criteria, and the relative driving forces involved, teach about substrate selectivity typical of enzymatic reactions, therefore the future development of new self-assembled capsules and the study of their encapsulation phenomena represents a test bench to master molecular recognition. Supramolecular capsules have already acted as supramolecular catalysts that are able to accelerate chemical transformation and to steer product selectivity, but turnover ability is still the critical point that requires improvements.

Another natural application of self-assembled capsules is the storage of particular chemicals, gases, for instance, or the delivery of drugs under certain conditions. These properties need increasing effort to be practicable but this is mainly dictated by the will.

It is therefore likely that the study of supramolecular encapsulation phenomena will increase in the near future boosted by the creativity and driven by the experience of talented scientists toward new results that will allow to bridge the gap between man-made and nature-made systems.

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FURTHER READING

Reviews and book chapters on organic self-assembled capsules.^{127–129}

Reviews on supramolecular catalysis involving self-assembling organic capsules.^{121,130–132}

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ABSTRACT: The present contribution is aimed at illustrating to the reader the state of the art on the construction of artificial, finite supramolecular assemblies characterized in solution by capsular shape held together by means of weak intermolecular noncovalent forces in solution, except metal-ligand coordination. These supramolecular assemblies provide cavities of correct size and shape where molecules of guests present in solution can be hosted if the available space is appropriately filled. Guests within the cavity are held for lifetimes ranging from milliseconds to hours, depending on the number and quality of weak intermolecular forces and the number of subunits that compose the capsule.

The in-out process of exchange of guests influences their behavior profoundly, enabling a series of applications spanning from molecular recognition of one up to several guests at a time with creation of new forms of isomerism derived by guest-guest interactions to supramolecular catalysis, which is the ultimate goal of such kind of assemblies.

A further intriguing aspect of self-assembled capsules is chirality that can be implemented in the subunits, that forms the capsule, or that can be the result of a particular arrangement of achiral units. In the latter case, the presence of strong attractive forces between the subunits enables to template the formation of enantiomerically enriched capsules with enantiopure guests based on achiral units via the chiral memory effect.

KEYWORDS: self-assembled capsules, hydrogen bonding, ion pairing, hydrophobic effect, encapsulation, packing coefficient, supramolecular chirality, supramolecular catalysis, orientational isomerism, social isomerism



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