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Applications of supramolecular capsules derived from resorcin[4]arenes, calix[n]arenes and metallo-ligands: from biology to catalysis

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Chiara M. A. Gangemi,^a Andrea Pappalardo*^{a,b} and Giuseppe Trusso Sfrassetto*^a

Supramolecular architectures developed after the initial studies of Cram, Lehn and Pedersen have become structurally complex but fascinating. In this context, supramolecular capsules based on resorcin[4]arenes, calix[n]arenes or metallo-ligand structures are dynamic assemblies inspired to biological systems. The reversible formation of these assemblies combined with the possibility to modify their dimensions and shapes in the presence of a guest (concepts of reversibility and adaptivity) make them similar to biological macromolecules, such as proteins and enzymes. The small space inside a supramolecular capsule is characterized by different properties compared to the bulk solution. This review describes concrete applications of capsular supramolecular self-assemblies in biomedical field, in catalysis and in material science.

Introduction

The enhancements in the noncovalent synthesis of macrocyclic molecules have led to the development of Supramolecular Chemistry, a field that has attracted increasing attention in the last decades.¹⁻⁷ Many important aspects have been investigated by supramolecular chemistry including molecular self-assembly,⁸ folding,⁹ molecular recognition, host-guest chemistry,¹⁰ mechanically-interlocked molecular architectures,¹¹ and dynamic covalent chemistry.² Researchers have explored the host-guest interactions by employing several classical macrocyclic hosts, comprising crown ethers, cyclodextrins, calixarenes, cavitands and cucurbiturils. Since the pioneering studies of Donald J. Cram, Jean-Marie Lehn and Charles J. Pedersen (Nobel Prizes for Chemistry in 1987), researchers started to survey exciting areas of material chemistry and nanoscience, with many potential applications in polymer science,¹² organic photovoltaics,¹³ as well as in vitro and in vivo biological imaging.¹⁴ In particular, supramolecular chemistry built on weak and reversible non-covalent interactions has emerged as a powerful and versatile strategy for the fabrication of new materials, due to its facile accessibility, extraordinary reversibility and adaptivity. Supramolecular capsules represent a branch of these new materials: the inner space inside them shows unique properties, different from the bulk solution, making them new attractive and useful “supramolecular tools” in different fields. Cram’s work was concerned with the formation of molecular

capsules (carcerands or hemicarcerands), by covalently linking two resorcin[4]arene units.¹⁵ The high stability of these capsules associated with the covalent nature of their formation, represent a main advantage. However, the low yielding syntheses and the difficulty to encapsulate/release a specific guest have compelled the researchers to develop a different strategy to obtain containers, able to self-assemble in solution, thus leading to the “supramolecular capsules”. Hydrogen bonding is one of the strongest driving forces for a well-defined self-aggregation. Rebek et al. firstly reported the formation of a supramolecular capsule, exploiting the formation of several hydrogen bonds between two bis-glycoluril derivatives.¹⁶ A remarkable key aspect of the supramolecular strategy to generate a capsules is the dynamic nature of the self-assembly, which leads to the mutual modification of the molecular structures of host and guest.¹⁷⁻²¹ As a consequence, physical-chemical properties of guests included inside a container are altered with respect to the free molecules in solution. For these reasons, supramolecular cages have found applications in different fields, as alternative route to the classic chemistry in solution.

A fundamental contribute to the study and characterization of supramolecular capsules was provided by the development of sophisticated NMR techniques, particularly diffusion NMR.²² Diffusion ordered spectroscopy (DOSY)²⁸ was used to characterize and determine dimensions and structure of several host-guest systems,²⁹⁻³⁹ organometallic complexes,⁴⁰⁻⁴³ supramolecular systems,⁴⁵⁻⁴⁹ and supramolecular polymers.⁵⁰⁻⁵³ Recently, Cohen and Avram reported on the applications of the diffusion NMR to study cages and container molecules describing some methodological and practical aspects.⁵⁴ In general, three strategies for the self-assembly of supramolecular capsules are employed: hydrogen bonding, metal coordination and hydrophobic effect. The success of

^a Department of Chemical Sciences, University of Catania, Viale A. Doria 6, 95125 Catania, Italy.

^b I.N.S.T.M. UdR of Catania, Viale A. Doria 6, 95125 Catania, Italy.
E-mail: andrea.pappalardo@unict.it; giuseppe.trusso@unict.it

REVIEW

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these approaches is warranted by the strong and highly directional non-covalent interactions that lead to the product formation. However, the inclusion of a guest inside the capsule facilitates the self-assembly process. As a result of the formation of supramolecular complex, encapsulated guests should diffuse as a single entity with the capsule, causing a clear change of the diffusion coefficient of the included guest. An additional significant contribute for the understanding of supramolecular systems was also given by Dynamic Light Scattering techniques (DLS).⁵⁵

This review collects the applications of supramolecular capsules assembled from calixarenes, resorcinarenes and metallo-cage building blocks. In particular, the applications of these capsular supramolecular assemblies as nanoreactors for specific organic reactions are analyzed and discussed, without neglecting the applications of some hosts as new materials in AFM analysis and in the biomedical field as drug delivery systems.

Biomedical Applications

Calix[n]arenes and cavitands have been used for biomedical applications,⁵⁶ albeit they are macrocyclic hosts that show hydrophobic properties and poor water solubility. To overcome this drawback, researchers have spent considerable effort to prepare hydrophilic and water-soluble hosts. For example in calix[n]arene derivatives, sulfonation,⁵⁷ the introduction of carboxylic acid groups at the lower rim,⁵⁸ and the functionalization with polar groups at the upper rim⁵⁹ are the most common strategies to prepare water-soluble hosts. Furthermore, by using click chemistry, cationic, anionic, and non-ionic hydrophilic calixarene macrocycles have been efficiently synthesized.⁶⁰ In terms of biocompatibility, water-soluble calixarene derivatives exhibit low toxicity, and the in vivo dosage can reach up to 100 mg kg⁻¹ without any toxic effect in mice.⁶¹ On the basis of these considerations, the formation of supramolecular structures capable of encapsulating guest molecules into the host cavities has become an attractive topic. Although biomedical applications of cyclodextrins are widely diffused,⁶² no reports have so far appeared in the literature concerning concrete applications of cyclodextrin capsules. Furthermore, the binding constants of calix[n]arenes and resorcin[4]arene cavitands toward guest molecules are usually higher than those with cyclodextrins. In this context, Nau and co-workers reported on the possibility to encapsulate guest drugs into calixarene derivatives.⁶³

Supramolecular approach has been used in drug delivery, mainly to solve the problems associated with the low solubility of hydrophobic drugs in aqueous solution, and the difficulty of anticancer drugs to penetrate the cancer cell membranes.⁶⁴⁻⁶⁶ Chemical activity of drugs might be improved by their inclusion into the inner space of a capsule and, upon external stimuli, (i.e. thermal change, pH variation, or competitive binding) the encapsulated drugs can be released from the cavity, leading to prolonged therapeutic effects.⁶⁷

Drug Delivery

Menon and co-workers prepared a *para*-sulfonatocalix[4]resorcinarene **1** able to encapsulate several drugs including the poorly soluble mycophenolate mofetil - an immunosuppressant drug used to prevent rejection in organ transplantation - by forming the 2:1 host-guest complexes (Figure 1).⁶⁸⁻⁷⁰

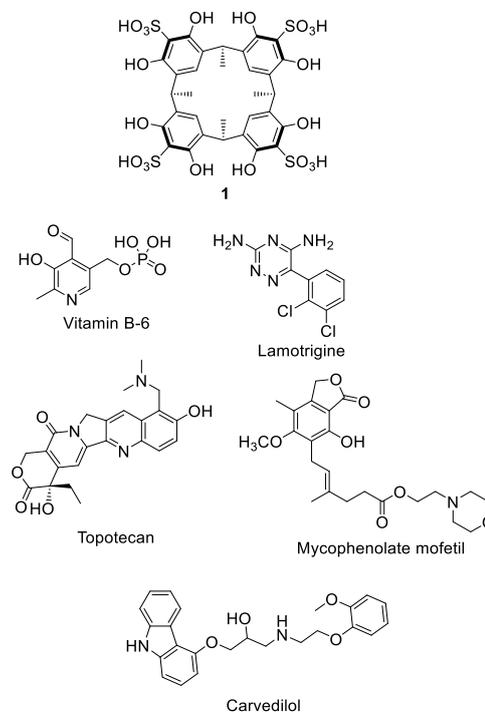
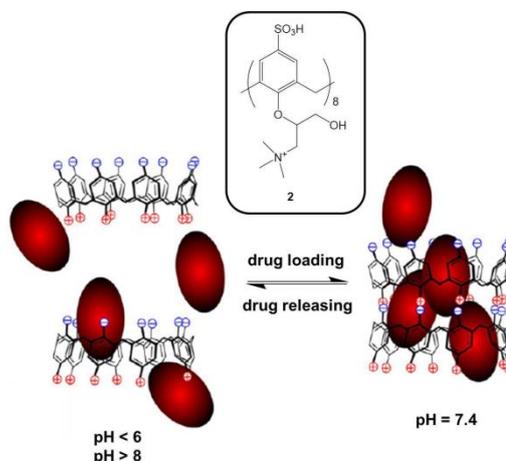


Figure 1. Drugs used by Menon and co-workers to form the host-guest complexes with *para*-sulfonatocalix[4]resorcinarene **1**.

Xiao reported on a new amphoteric calix[8]arene **2** that displays a pH-triggered drug releasing behavior (Scheme 1).⁷¹ The upper rim of the calix[8]arene is functionalized with sulfonate groups, while the lower rim presents positive charges due to the presence of quaternary ammonium groups.



Scheme 1. Model of pH-triggered drug loading and releasing procedure developed by Xiao. Adapted from Y. Xue, Y. Guan, A. Zheng and H. Xiao, *Colloids Surf., B*, 2013, **101**, 55–60, with permission from Elsevier.

Hydrophobic model drug, ciprofloxacin, was included into the calixarene cavity at neutral pH, self-assembling into superstructures through electrostatic interactions between the upper and lower rims (Scheme 1). At higher or lower pH values, the capsule disassembles releasing the ciprofloxacin. Such pH-responsive drug delivery system shows great potential for future theranostic applications.

Very recently, Lippard et al. reported on an innovative application of the tetrahedral metal-cage **3** (M = Pt) as nanocontainer of a cis-platinum prodrug able to exhibit high cellular uptake (Figure 2 and Scheme 3).⁷²

The metallo-cage **3**, reported by Fujita in 1995, is one of the first capsular systems based on the metal coordination, assembled from four tridentate nitrogen-based ligands, six metal (palladium or platinum) ions, and six ethylenediamine ligands.⁷³ This cage can accommodate several guests, including tripeptides via a series of π - π and CH- π interactions and intramolecular guest-guest interactions.⁷⁴⁻⁷⁷

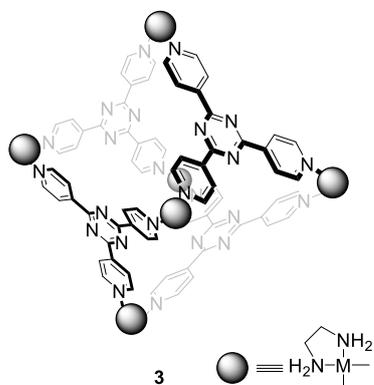
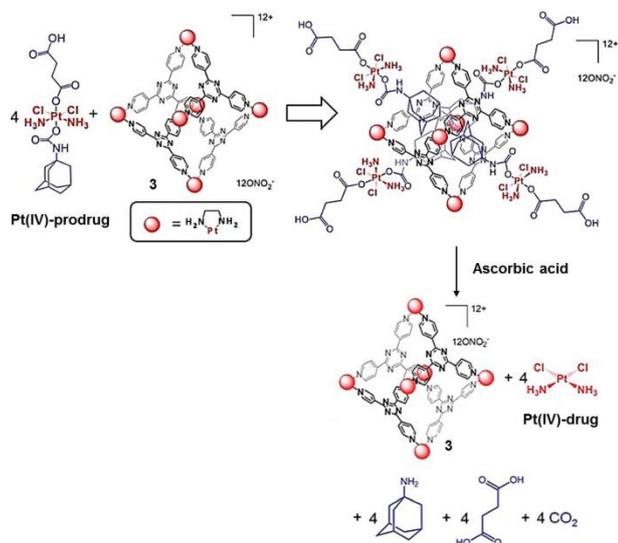


Figure 2. Tetrahedral cage **3**.



Scheme 2. Assembly of supramolecular complex **3** and release of Pt(IV)-drug in presence of ascorbic acid. Adapted from Y. Zheng, K. Suntharalingam, T. C. Johnstone and S. J. Lippard, *Chem. Sci.*, 2015, 6, 1189. Published by The Royal Society of Chemistry.

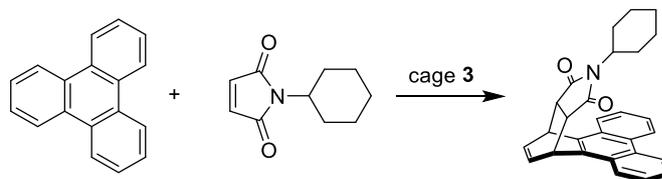
In particular, the delivery systems constituted by cytotoxic Pt(IV)-prodrugs and the hexanuclear Pt(II) cage **3** possess low toxicity, and an excellent cellular uptake due to the presence of twelve positive charges (Scheme 2).

To explicate anticancer activity, cisplatin must be released from this host-guest system upon reduction with ascorbic acid. The supramolecular cage **3** displays micromolar potency, comparable to cisplatin, against several cancer cell lines (lung carcinoma, ovarian carcinoma, and ovarian carcinoma).

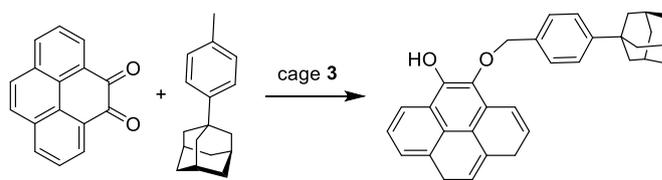
Applications in catalysis

Metallo-cage capsules

The inclusion of two molecules within such a small volume leads to a high concentration of the guests and, consequently, to an increased likelihood of reaction between them. Fujita and co-workers used metallo-cage **3** to catalyze reactions of normally unreactive species, or to induce asymmetric reactions into the cavity of the cage, which possesses a chiral element attached to the metal center.⁷⁸ The enhancement of "activity" of the guests inside a similar supramolecular cage is demonstrated by the Diels-Alder reaction between the triphenylene and maleimides shown in Scheme 4,⁷⁹ and by the photocatalytic reaction between o-quinone and 4-(1-adamantyl)-toluene reported in Scheme 5.⁸⁰



Scheme 4. Diels-Alder reaction catalyzed by supramolecular cage **3**.



Scheme 5. Photocatalytic reaction catalyzed by supramolecular cage **3**.

Ramamurthy et al. reported also on the reaction of photodimerization of trans-cinnamic acid esters inside the capsular system **3**, leading to both the monomeric cis-isomer, in considerably reduced yield with respect to the reaction in absence of the cage **3**, and dimeric products in a range of 21–63% yield.⁸¹ The same research group has also examined how host **3** can afford the exclusive formation of syn head-head dimers of several coumarin derivatives, while in free aqueous solution syn head-head, syn head-tail, and anti head-head dimers are obtained.⁸² Photodimerization was also investigated using acenaphthylene as guest.⁸³

Raymond's group developed a new tetrahedral metallocage **4**, consisting of a series of metal ions (e.g. Ga(III), Al(III), In(III), Ti(IV) and Ge(IV)) and six catecholamide-based ligands (Figure

3). The metal cation determines the kinetic stability of the capsule, which can include a wide range of guests.⁸⁴⁻⁸⁷

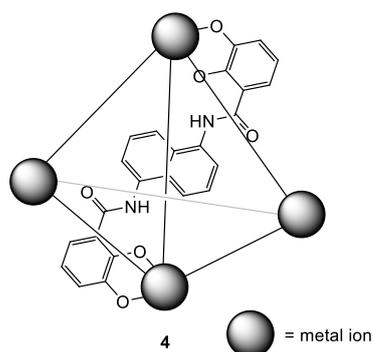
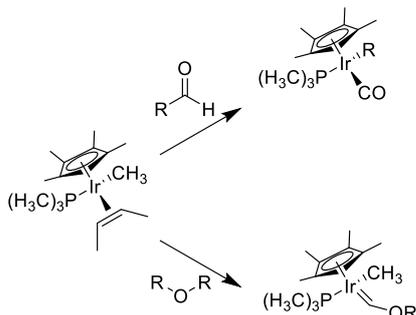


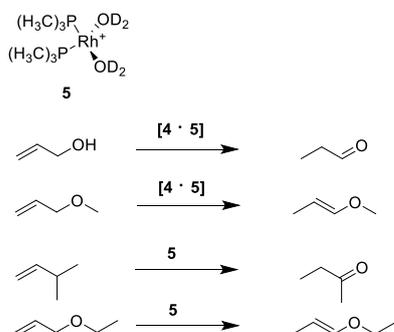
Figure 3. Raymond's tetrahedral capsule 4.

The gallium complex **4** is able to encapsulate in water media the (CpRuCl(cod)) (Cp = cyclopentadiene, cod = 1,5-cyclooctadiene), a catalyst used for the formation of C-C bonds.⁸⁸ Raymond and co-workers studied the applications of tetrahedral metallocage **4** as nanoscale reactor. In particular, the reactivity of encapsulated mono-cationic half-sandwich iridium guests was analyzed (Scheme 6).⁸⁹ The reactivity of this complex into **4** shows highly specific size and shape selectivities in the C-H bond activation of aldehydes and ethers.



Scheme 6. Reactions of iridium complex inside the cage 4.

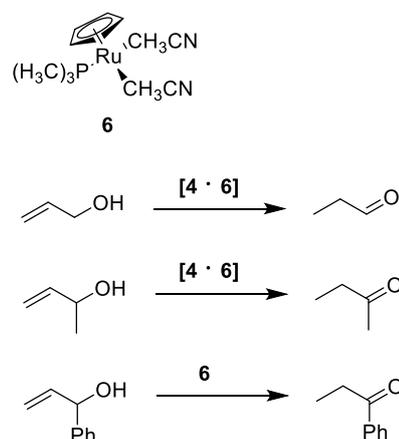
The catalytic properties of other metal transition complexes inside the supramolecular cage **4** were further examined. In particular, a series of bisphosphine rhodium-diene cations were encapsulated, affording the hydrated active catalyst (Rh(PMe₃)₂(D₂O)₂ **5** (Scheme 7).⁹⁰



Scheme 7. Isomerization of allylic substrates with supramolecular catalyst [4 • 5].

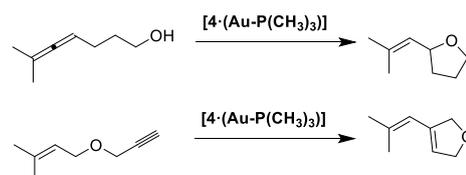
This host-guest complex [4 • 5] is stable within 12 hours, and catalyzes the isomerization of allylic substrates exhibiting substrate selectivity depending on the steric hindrance (Scheme 7): only prop-2-en-1-ol and its methyl ether were isomerized, while larger substrates are isomerized only by the non-encapsulated catalyst.

Also [RuCp(PMe₃)(MeCN)₂]⁺ **6** was encapsulated by **4**, leading to the supramolecular catalyst [4 • 6] capable to isomerize allylic alcohols to the corresponding aldehydes or ketones showing a similar substrates selectivity. In fact, the larger 1-phenylprop-2-en-1-ol does not react with the encapsulated catalyst (Scheme 8).⁹¹ Notably, the supramolecular catalyst [4 • 6] shows a TON higher than those obtained for the non-encapsulated catalyst. The same supramolecular catalyst was used in association with enzymes, like esterases, lipases and alcohol dehydrogenases, to perform cascade reactions. In a one-pot reaction, the aliphatic alcohol was obtained starting from the corresponding allylic alcohol.⁹² This result demonstrates that metal complex encapsulation can prevent the degradation of the catalyst.



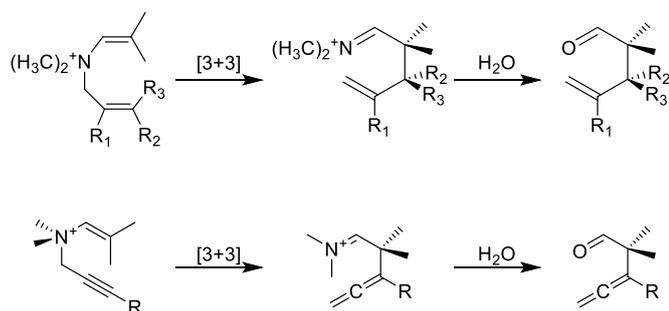
Scheme 8. Isomerization of allylic substrates with supramolecular catalyst [4 • 6].

Furthermore, supramolecular complex [4 • (Au-P(CH₃)₃)], assembled by the tetrahedral cage **4** and monophosphine gold ion, is able to catalyze the intramolecular cyclization of an allen-ol and of an en-yne (Scheme 9).^{93,94} The use of the bromide salt of the gold complex in the reaction with allen-ol results in an acceleration rate of eight times, and an increase of TON value of 67. Whereas, in the case of cyclization of en-yne, the formation of the product is selective only in the presence of the supramolecular catalyst, the tetrahedral cage around the gold complex controls the coordination sphere of the gold, acting as a phase transfer reagent, enhancing the reaction rate and tuning the regioselectivity of the reaction.



Scheme 9. Intramolecular cyclizations of an allen-ol and of an en-yne, catalyzed by supramolecular catalyst [4 • (Au-P(CH₃)₃)].

In addition, Raymond's group reported on the ability of cage **4** to catalyze the 3-aza Cope rearrangements showed in Scheme 10, observing an acceleration of the reaction into the range 5-854 times with respect to the normal conditions.^{95,96}



Scheme 10. The 3-aza Cope rearrangements inside the cage **4**.

Capsule **4** can also accommodate basic amines, phosphines, and (super basic) azaphosphatranes, since these guests are internalized in the protonated state.⁹⁷ This phenomenon is ascribed to a shift of the pK_a values of the guests into the host environment. Searching on a plausible explanation of how host **4** can shift the pK_a of an encapsulated guest, Raymond reported on an acid catalysis in basic solution. The formate esters, normally stable in neutral and basic conditions, were rapidly hydrolyzed at pH 11, with a catalytic amount of host **4**, showing an acceleration rate of ca. 650-890 times with respect to the non-catalyzed reaction.⁹⁸ Furthermore, cage **4** has been used as catalyst for the hydrolysis of acetals and ketals at pH 10, with an acceleration rate higher than 1000 times.^{99,100}

Supramolecular capsules assembled *via* hydrophobic effect

In addition to metal coordination, also hydrophobic effect can induce the formation of supramolecular capsules, exploiting the desolvation of hydrophobic surfaces of the single molecules.^{101,102} Few examples of self-assembled capsules driven by the hydrophobic effect have been described (compounds **7-10**, Figure 4).¹⁰³⁻¹⁰⁶

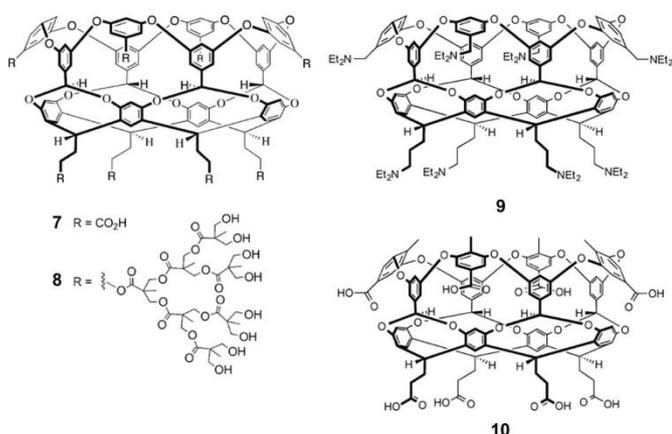
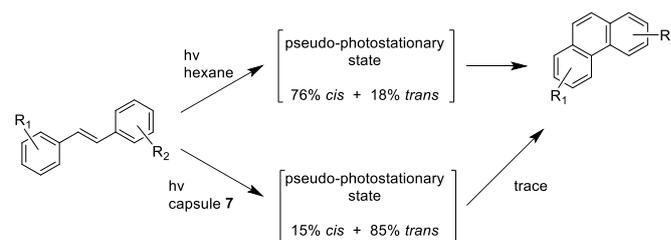


Figure 4. Water soluble cavitands **7-10**. Adapted from Z. Laughrey and B. C. Gibb, *Chem. Soc. Rev.*, 2011, **40**, 363, with permission of The Royal Society of Chemistry.

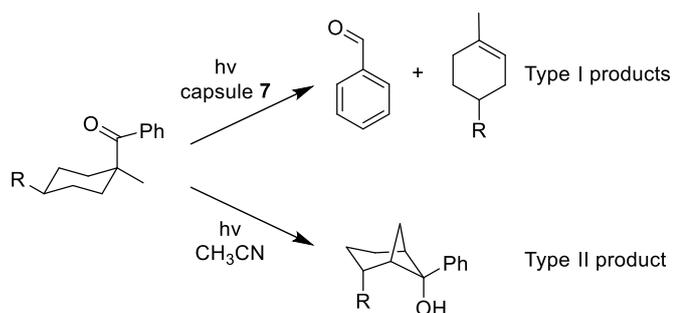
The octa acid (OA) derivative **7** is the first example of water soluble deep cavitands based on a resorcin[4]arene scaffold, able to provide supramolecular dimeric capsules in presence of several guests.¹⁰⁷ Octa acid cavitands **7-10** differ from similar opened containers (such as micelles, open cavitands, cyclodextrins, cucurbiturils and Pd nanocages) because they are closed containers. Unlike micelles and open cavitands, the entire guest molecule is enveloped within a hydrophobic container. Interestingly, **7** can include propane and butane with a 2:2 stoichiometry from the gas phase and the aqueous phase.¹⁰⁸ Due to the high difference of binding constant values between propane and butane, capsule **7** can selectively extract butane from a propane/butane mixture. Ramamurthy and co-workers used the OA capsule **7** as chemical reactor in aqueous solution,¹⁰⁹ for the generation of singlet oxygen,^{110,111} the photodimerization of acenaphthylene,¹¹² and the photo-induced rearrangement of dibenzylketone.^{109,113} Furthermore, this nano-capsule can affect the photochemistry of α -(*n*-alkyl) dibenzyl ketones depending on the dimension of the guests:¹¹⁴ different kinds of packing motif lead to diverse photochemical behaviors. With the smallest guests a simple decarbonylation is observed, whereas, rearrangement products became prominent with the guests that possess bulkier alkyl groups. To clarify the mechanism of this rearrangement, optically pure *cis*-deoxybenzoin was used as guests contained into OA capsule.¹¹⁵ In addition, analysis with stilbene derivatives as substrate demonstrated that photophysical and photochemical properties of the encapsulated guests are strongly influenced by the formation of the capsule.^{116,117} In particular, as shown in Scheme 11, the inner space of the capsule mainly leads to the formation of the *trans* pseudo-photostationary state of the stilbenes, which precludes the cyclization into the final product. The general ability of the capsule to control photo-dimerization reactions has been also studied with methyl cinnamates, *p*-methyl styrene, indene, and 4,4-dimethylcyclohex-2-enone.¹¹⁸



Scheme 11. Photochemical products obtained by the photolysis of stilbene derivatives in free solution and inside the OA capsule **7**.

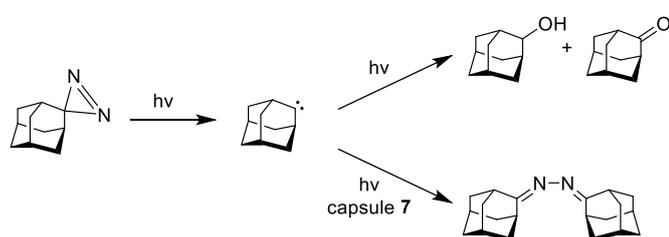
Ramamurthy reported on another example of how the inner space of octa acid capsule alters the outcome of some photochemical reactions. By photochemical reaction, cyclohexyl-phenyl ketones can afford Type I and Type II Norrish products. Cyclobutanol, the Type II Norrish product, is formed in free solution of acetonitrile, while only the Type I products are obtained with octa acid capsule (Scheme 12).¹¹⁹

The inner space of octa acid container **7** can also influence the chemical behavior of incarcerated carbenes generated by photolysis of adamantanediazirines.¹²⁰



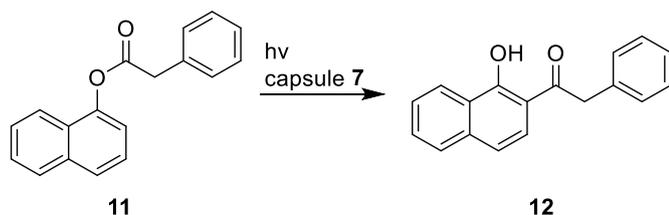
Scheme 12. Type I and Type II Norrish photochemical reaction of cyclohexyl-phenyl ketone.

In free solution, formation of alcohol and ketone was observed, while carbene generated into OA capsule furnished the azine derivative in high yield (Scheme 13).



Scheme 13. Reactivity of carbenes generated within the OA capsule.

Gibb has also reported that OA **7** controls the product distribution during photo-Fries rearrangement of naphthyl esters in water by restricting the mobility of primary singlet radical pair.¹²¹ In normal condition, ester **11** in hexane upon irradiation affords eight products, while, after inclusion into the cavity of **7**, only compound **12** is formed in 99% yield (Scheme 14).



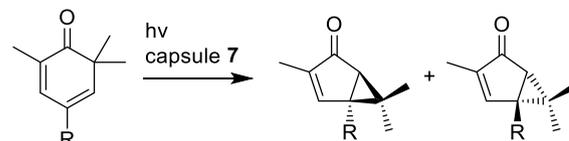
Scheme 14. Photo-Fries reactions within the capsule **7**.

The same ortho-rearrangement was observed with other ester compounds. The high selectivity was attributed to the limited movement of the guest inside the capsular assembly, and the rapid recombination of the radicals.

Gibb's group described the kinetic resolution of pairs of constitutional isomers of long chain esters using the octa acid capsule **7**, that cannot be resolved since they react at similar rates.¹²² Their strategy was based on the higher affinity of one guest to be preferentially encapsulated into the capsule **7**, leaving the other molecule to undergo hydrolysis in solution. The resolution is determined by a competitive binding equilibrium in which the stronger binder mainly occupies the

inner space of the capsule, whereas the weaker binding ester mostly resides in the bulk hydrolytic medium.

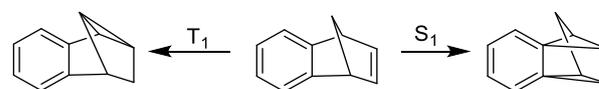
Supramolecular cage **7** has been used to carry out diastereoselective photoreactions. In particular, photocyclization of tropolone ethers and the oxa-dimethane rearrangement of cyclohexadienones within the capsule revealed good diastereoselectivities inside the capsule (17%) in comparison with the bulk solution (3%) (Scheme 15).¹²³



Scheme 15. Diastereoselective rearrangement photoinduced inside **7**.

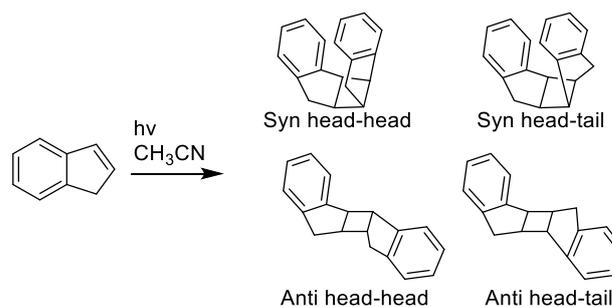
A higher enhancement of diastereoselectivity inside the capsule **7** (73%) with respect to the free solution (4%) was obtained by Gibb and co-workers, while studying the photoelectrocyclization of pyridones.¹²⁴

Recent studies highlighted how these water soluble capsules can act as active species in some photochemical reactions.¹²⁵ In fact, combining octa acid cavitand **7** with a resorcinol-capped octa acid cavitand (devoid of carboxylic groups at the upper rim and with four resorcinol groups at the lower rim), a hetero-capsule was formed and able to act as triplet sensitizers towards aromatic guests, leading to different products depending on the type of excitation (Scheme 16).



Scheme 16. Photochemistry of benzonorbornadiene in solution.

Recently, Ramamurthy emphasized how the guests inside OA **7** capsule undergo a pre-orientation effect, because all parts of the enclosed guest molecules are exposed only to a hydrophobic inner space, thus excluding any orientation from hydrophobic-hydrophilic interactions, characteristics of other opened molecular reactors. This feature is particularly important in the regio- and stereo-selectivity of the reaction catalyzed inside the capsule.¹²⁶ In the photodimerization of indene in acetonitrile (Scheme 17), four possible reaction products are possible. However, in the presence of OA **7**, anti-head-tail dimer is exclusively formed inside the cavity.

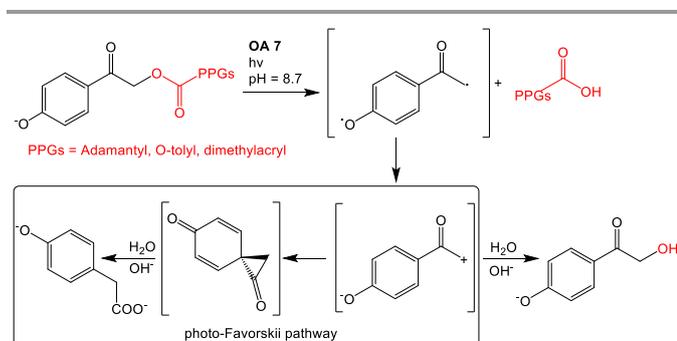


Scheme 17. Photodimerization of indene and possible reaction products.

An interesting application of capsule **7** was recently reported by Ramamurthy's research group. They explored the feasibility of opening the capsule in order to release its contents in an aqueous media.¹²⁷ In particular, *p*-methoxyphenacyl esters were photo-hydrolyzed in ca. 90 minutes leading to the corresponding acid derivatives as main products, and the disassembly of the capsule, hence releasing the products in solution. This system presents potential applications in the selective photo-release of molecules for pharmaceutical purposes.

Ramamurthy's group have explored the properties of the OA **7** as photo-reactor on the silica surface.¹²⁸ They demonstrated that the properties of photo-reactor are maintained in the heterogeneous system, and that capsular assemblies are stable on silica surface.

Very recently, Ramamurthy and co-workers reported on the photorelease of different carboxylic acids hosted into the OA capsule **7**, after a rapid photo-Favorskii rearrangement of *p*-hydroxyphenacyl esters (Scheme 18).¹²⁹

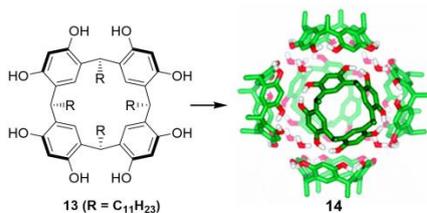


Scheme 18. Mechanism for the photorelease of carboxylic acids into OA capsule **7**.

In particular, the acids were esterified with photoremovable protecting groups (PPGs), which upon irradiation > 300 nm for 50 minutes undergo to the hydrolysis of the ester bonds. The absence of radical attack on the OA capsule **7** by *p*-hydroxyphenacyl ester photolysis is a clear evidence that the photorelease mechanism for OA encapsulated *p*-hydroxyphenacyl esters differs from that of the *p*-methoxyphenacyl esters.

Hexameric supramolecular capsules

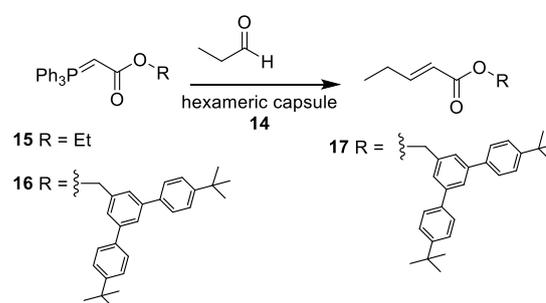
By the formation of multiple hydrogen bonds, in apolar solvents, the resorcin[4]arene **13** can self-assemble to the hexameric capsule **14** (Scheme 19), which was reported for the first time by Atwood in 1997.^{130,131}



Scheme 19. Resorcin[4]arene **13** and relative hexameric capsule **14**. Adapted with permission from *J. Am. Chem. Soc.* 2008, **130**, 2344–2350. Copyright 2008 American Chemical Society

With an internal volume of ca. 1400 Å³, hexameric capsule **14** represents one of the largest hydrogen-bonded molecular capsules. The presence of eight water molecules is essential to the formation of this assembly.¹³² The formation of the capsule and the encapsulation of different guests have been extensively investigated in solution.¹³³⁻¹⁴²

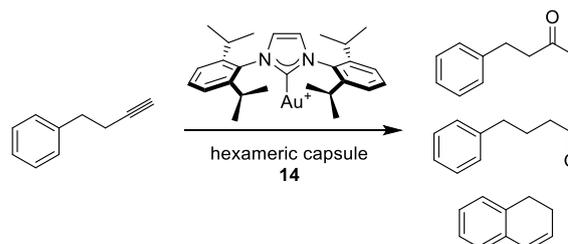
Tiefenbacher and Zhang reported on the first catalytic application of capsule **14**: due to the value of pK_a (approximately 5.5-6), the capsule acts as a strong Brønsted acid.¹⁴³ The authors explored the possibility to protonate a stabilized Wittig ylide inside the capsule **14** (Scheme 20). Ylide **15** is included inside the hexameric capsule **14**, as confirmed by NMR spectroscopy. Even the addition of an excess of propanal (10 equiv.) did not produce any alkene product, although the uptake of propanal into the capsule is demonstrated by the appearance of characteristic signals in the NMR spectra.



Scheme 20. Wittig reaction catalyzed by hexameric capsule **14**.

With the larger Wittig ester **16**, which is not able to fit the inner space of the capsule, the formation of alkene **17** occurred, indicating that the protonation of the Wittig ylide outside the capsule is reversible and does not prevent conversion to the alkene. Furthermore, the authors explored the potential use of the hexameric capsule as a selective enzyme-like catalyst, investigating the hydrolysis of acetals. They proved that a catalytic conversion is indeed possible with the capsule and that the reaction takes place inside the cavity. In addition, comparing the results obtained by using different substrates, they concluded that hexameric capsule **14**, due to the stabilization of cationic intermediates and transition states in the hydrolysis process, enables reactions under mild conditions that are not possible in the solution phase.

Reek and co-workers used hexameric capsule **14** to include gold complexes, obtaining a supramolecular catalyst for the hydration of 4-phenyl-butyne (Scheme 21).¹⁴⁴



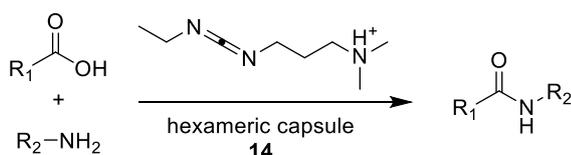
Scheme 21. Hydration of 4-phenyl-butyne catalyzed by hexameric capsule **14** containing gold complex.

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This reaction normally occurs with Markovnikov addition of water, leading to the corresponding ketone, or 1,2 dihydronaphthalene in absence of water. In the presence of hexameric capsule **14** the formation of aldehyde is observed, as well as the ketone and 1,2 dihydronaphthalene with different ratio respect to the normal reaction in solution. Afterward, the same research group evaluated the impact of steric hindrance and structural rigidity of the guests on the rate of reaction.¹⁴⁵ Interestingly, the reaction rates of the Au-catalyst in absence of the hexameric capsule show an opposite trend respect to the supramolecular catalyst.

Very recently, Scarso and co-workers reported on the use of **14** as a nanoreactor in the synthesis of several amide derivatives, differing for the length of substituent R_1 and R_2 (Scheme 22).¹⁴⁶



Scheme 22. Synthesis of amide derivatives encapsulated into hexameric capsule **14**.

The capsule acts as nanoreactor that imparts steric restriction to the encapsulated reagent. In particular, the capsule includes the cationic carbodiimide activator, and preferentially select the shorter acidic and amine reagents leading to the shorter amide derivatives. In absence of the supramolecular cage, scarce product selectivities were detected, thus demonstrating the active role of the hexameric capsule.

AFM Applications

AFM (Atomic Force Microscopy) is a powerful technique, applied mainly to the material science, with several applications in imaging and manipulation of the surfaces at nanoscale level.^{147,148} The basic principle is based on a small force sensor (cantilever) and a piezo scan tube positioned onto the sample. The sharp tip of the cantilever, which has a radius of ca. 10 nm, interacts with the substrate via a wide range of weak forces, and this phenomenon leads to a minimal deflection of the sensor (Figure 5). Furthermore, nano-scale objects can be precisely manipulated with the cantilever tip by applying very low forces (in the range of pN=10-12 N), which is the magnitude of weak intermolecular bonds. A typical AFM-SMFS (AFM-single molecule force spectroscopy) mechanochemistry experiment consists in the monitoring of interactions between two molecules, i.e. a host and a guest, using this technique. The tip of the cantilever is functionalized with a flexible linker (typically a PEG spacer) bearing one of the molecules object of the study. At the same time, the surface is covered by the other "partner" molecule.¹⁴⁹⁻¹⁵¹

A precise determination of the forces between host and guest occurs, following the deflection on the cantilever. For this reason, the development of new synthetic receptors able to exploit non-covalent interactions using different weak forces is

of primary importance in this technique. The first problem to solve is the covalent anchoring of host.

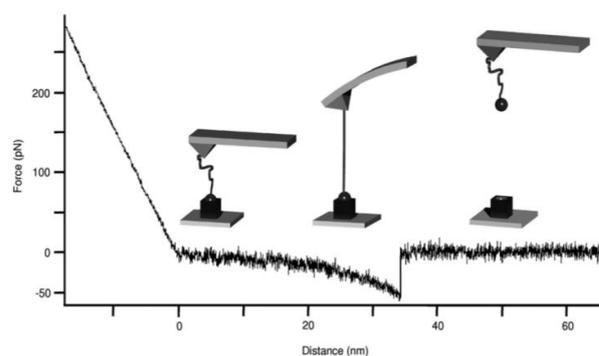


Figure 5. Scheme of the single-molecule force spectroscopy experiment and typical force-distance curve. Reproduced with permission of T. Schröder, S. N. Sahu, D. Anselmetti and J. Mattay, *Isr. J. Chem.*, 2011, **51**, 725–742.

One of the most common strategies is the functionalization of the lower rim with sulfur-containing groups for its attachment onto a gold surface.^{152,153} For SMFS experiments, Schindler's research group immobilized a tetra-(carboxyl)cavitand with a PEG linker to the cantilever, to add steric freedom to the system and allowing the complex formation to take place (Figure 6).¹⁵⁴

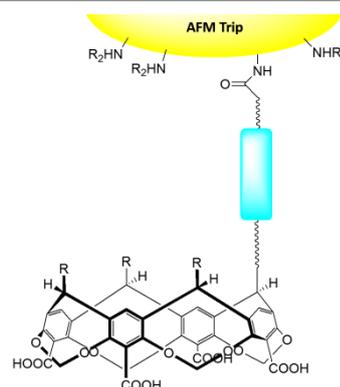


Figure 6. Tetra-(carboxyl)cavitand immobilized with a PEG linker to the cantilever.

The spacer was further modified introducing a new type of linker via "click chemistry".¹⁵⁵ The first set of experiments were carried out using a tetra-(pyridyl)cavitand covalently attached on the gold surface, and a tetra-(carboxyl)cavitand immobilized on the cantilever. All measurements were carried out in *p*-xylene, which is encapsulated during the assembly process. Because of the high concentration of the tetra-(pyridyl)cavitand in the surface, multiple interactions due to simultaneous formation of several supramolecular capsules were detected.

Moreover, mixed self-assembled monolayers (SAMs) containing alkyl sulfides without functional groups can be used to realize a functionalized surface at low density, thus ensuring single-molecule recognition.^{156,157} The force-distance curve observed contains only one distinct force jump, associated to the dissociation of a supramolecular capsule formed between

the two hosts and *p*-xylene. Plotting the detected dissociation forces in a force histogram, a narrow distribution of forces characteristic for single-molecule force spectroscopy experiments was observed, allowing for a precise determination of the dissociation force, along with the mechanical stability and the dynamics of the dissociation process of this supramolecular capsule in a quantitative manner.

Recently, AFM measurements were employed to quantitatively evaluate drug-receptor interactions,¹⁵⁸ and drug-cell interactions¹⁵⁹ for analytical applications. Furthermore, these studies had led to the development of new drugs with higher efficiency and also give fundamental insight into the mechanism of molecular level interactions in biological systems.

Conclusion and Outlook

In this review we detailed supramolecular capsules based on resorcin[4]arenes, calix[n]arenes and metal-ligands, having concrete applications in biomedical field, catalysis and material science. The inner space of these self-assembled structures represents a unique environment, with chemical-physical properties different with respect to the bulk solution. For this reason, one (or more) guest molecule encapsulated in this nanospace can undergo a different "chemistry" relative to the normal conditions. This feature is of particular interest in catalysis, leading to nanoreactors able to catalyze reactions not allowed in normal solution, or with the classical organo-metallic catalysts, or in biomedical applications, obtaining efficient drug-delivery system with potential theranostic properties. Although these supramolecular systems are known since '80, the research interest to design new and efficient (supra)molecular architectures, with practical uses in medicinal and materials, is still today an important and active field.

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