Molecular Capsule Catalysis: Ready to Address Current Challenges in Synthetic Organic Chemistry?

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Abstract: Self-assembled molecular capsules, host structures that form spontaneously when their building blocks are mixed, have been known since the 1990s. They share some basic similarities with enzyme pockets, as they feature defined hydrophobic binding pockets that are able to bind molecules of appropriate size and shape. The potential to utilize such host structures for catalysis has been explored since their discovery; however, applications that solve current challenges in synthetic organic chemistry have remained limited. In this short article, we discuss the challenges associated with the use of molecular capsules as catalysts, and highlight some recent applications of supramolecular capsules to overcome challenges in synthetic organic chemistry.

Keywords: Catalysis · Cyclization · Host–guest chemistry · Molecular capsule · Supramolecular chemistry

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1. Introduction

Self-assembled molecular capsules are homogenous molecular host structures that form spontaneously when their building blocks are mixed under suitable conditions. They enclose a specific volume of space in which they are able to reversibly bind guest molecules. Ever since self-assembled molecular capsules were reported in the early 1990s,[1] they have attracted the interest of chemists working in the broad field of catalysis due to their apparent similarities to enzyme pockets. Much like an enzyme pocket, they are able to selectively isolate suitable substrates from the solvent inside their hydrophobic reaction pocket. Depending on the specific host–guest interactions, they are able to adjust the substrates’ orientation towards each other, and/or their conformation, and in some cases alter or enhance the substrate’s reactivity by non-covalent interactions. The first example of a reaction
mediated by a self-assembled supramolecular capsule was reported by Rebek’s group. In 1997 they reported the 200-fold acceleration of the Diels-Alder reaction between p-quinone and cyclohexadiene inside the dimeric ‘softball’ capsule.[2] Several other examples followed, and nowadays hundreds of examples for reactions taking place, or even being catalyzed, inside molecular capsules have been described.[3,4] In many cases, interesting substrate and/or product selectivities have been observed. However, most of these examples up to this day still represent proof-of-principle studies with little connection to current challenges in synthetic organic chemistry. To become a useful and widely applied tool in organic chemistry, molecular capsule catalysis has to provide solutions for current synthetic challenges that are difficult to address with other tools available. Therefore, in this short, non-comprehensive article, we want to highlight some recent examples which demonstrate that molecular capsules are able to overcome real challenges in synthetic organic chemistry. We are very optimistic that more examples will become available in the near future.

2. Fujita’s Site-selective Functionalization of Linear Diterpenoids

In 2019, Fujita and coworkers disclosed a remarkable site-selective functionalization of linear diterpenoids by using the self-assembled supramolecular coordination cage I in aqueous media.[5] Cage I (Fig. 1a) is a positively charged assembly of six Pd(II)-ions and four tritopic organic ligands, and is soluble and stable in aqueous solutions. It features a tetrahedral shape, encloses a volume of approx. 460 Å³,[6] and provides four portals of approx. 8 Å in diameter for guest uptake. It can encapsulate various guests, ranging from small aromatic compounds to large hydrophobic molecules, by forming inclusion complexes of different guest/host ratios depending on the size of the guest molecules.[7] Besides the hydrophobic effect, interactions with the electron-deficient tritopic ligands drive the encapsulation. For the large flexible polyunsaturated terpenoids 1a–d, the group observed the formation of 1:1 inclusion complexes in which the substrates were conformationally frozen in U-shaped conformations (Fig. 1b). This was indicated by NMR spectroscopy, and

![Diagram of Fujita’s cage I and examples of functionalization](image_url)
confirmed by solid-state X-ray studies. Stacking of the internal alkenes onto the panels of I and carbonyl-π interactions stabilize the conformation.

The folded binding mode stands in contrast to earlier findings by the authors about the binding of linear hydrocarbons which lack strong specific guest–host interactions. The restricted binding mode shielded several reactive sites of the substrates 1a–d, which enabled the site-selective functionalization of the unshielded protruding terminal prenyl moiety (Fig. 1b, in blue) either via mCPBA or NBS. A related mono functionalization of less complex dialkenes was recently reported by the Rebek group utilizing a water-soluble cavitand.[8] The oxidation of the complex 1c:1a with 1 equiv. of mCPBA cleanly yielded the terminal epoxide 2a in 95% NMR yield as the only observed product. The control experiment in solution delivered bromohydrins – with NBS, interestingly, did not provide the usual bromohydrin opening. For instance, compound 4a, in a 3:1 ratio of products 2a and 3a. Furthermore, experiments with the separate cage components (ligand or Pd-salt) led to more complex mixtures, highlighting the directing role of cage I in the selective epoxidation. The functionalization of the encapsulated substrates 1a–d with NBS, interestingly, did not provide the usual bromohydrin 5 but the nitratobrominated product 4 (Fig. 1b). Its formation likely stems from the high local concentration of NO₃⁻ ions that intercept the bromonium intermediate. For instance, compound 4a was formed selectively and was isolated in 82% yield. The control experiment in solution delivered bromohydrins 5a and 6a in a 3:1 ratio. The experiments with the separate cage components (ligand or Pd-salt) also led to bromohydrin product mixtures, again highlighting the directing role of cage I in these functionalizations.

2.1 Fujita’s Demethylenation of Cyclopropanes

When irradiated, the Pd-coordinated triazine ligands of cage I can accept an electron from an encapsulated guest molecule, oxidizing it to the corresponding radical cation.[9] Making use of this reactivity, the group previously demonstrated the oxidation of adamantane[10] and triquinacene,[11] as well as the anti-Markovnikov hydration of alkynes.[12] Following these reports, the group showed that irradiation of cyclopropanes 7 encapsulated in cage I results in demethylenation to produce the corresponding alkene (Scheme 1a).[13] Photomediated demethylenation reactions of cyclopropanes are known.[14] However, these are mechanistically different from Fujita’s study as they do not involve an electron transfer process, but rather a cycloelimination to generate an alkene and a carbene; in these cases the demethylenation process often competes with alternative pathways such as ring opening.

Substrates 9 and 11 react to give the corresponding alkenes in good yields (85% and 82%, respectively, Scheme 1b). Mixtures of cis and trans isomers were formed in these cases (1:1:3 cis/trans for 10, 1:3 cis/trans for 12). The authors present evidence that these mixtures are due to light-mediated isomerization of the alkene product. Substrates that do not contain an alkene or a phenyl group adjacent to the cyclopropane represent a potential limitation

![Scheme 1. a) Photomediated demethylenation reaction of cyclopropanes inside cage I, and b) specific examples.](image)
of the method: the use of thujone (13) as the substrate was found to form the alkene product 14 in only low yield.

The authors propose that the reaction proceeds via a light-mediated host-to-guest electron transfer[9] to give a cyclopropyl radical cation together with the radical anion of the cage (I⊂18, Scheme 2). This is followed by opening of the cyclopropane radical cation by a nucleophile attack by the nitrate counterion of cage I. Fragmentation of the resulting radical 19 gives the alkene product 8, formaldehyde, and a nitrite radical. The latter is finally reduced to nitrite anion by accepting an electron from the cage radical anion.

An interesting application of this methodology is presented by the reaction of the steroid drosopirenone (16), which reacts selectively to give the mono-demethylenated product 17 in 86% isolated yield (Scheme 1b). Control experiments without cage I, or in the presence of only its subcomponents (ligand or Pd-salt) did not lead to the formation of 8. Furthermore, a modified cage, in which the triazine part of the ligand was replaced by a benzene, also failed to produce the demethylenated product 8. The high yield and selectivity obtained within cage I is certainly remarkable, and indicates its applicability for the late-stage modification of complex molecules.

Scheme 2. Proposed mechanism for the photomediated demethylation reaction of cyclopropanes inside cage I.

2.2 Bergman-Raymond-Toste’s Site-selective Hydrogenation

In the example discussed in the beginning of this article, encapsulation resulted in the site-selective functionalization of the alkene exposed to the solvent. In contrast, Bergman-Raymond-Toste’s selective catalytic hydrogenation of alkynes takes place inside the cage II (Fig. 2a).

Inspired by the Reek group’s selective supramolecular and Rh-catalyzed photochemistry,[15] this self-assembled system consists of four Ga(III) ions and four naphthalene-based catecholate ligands forming a negatively charged tetrahedral host.[16] It has excellent water solubility and provides a hydrophobic cavity of up to 450 Å³ capable of encapsulating various neutral or cationic guest molecules.[14,17] Since the host does not feature large portals like cage I, guest exchange has to take place via deformation of the host.[16b,18] Moreover, a larger version of this cage, assembly III, featuring pyrene ligands has also been reported (Fig. 2a).[19]

The high yield and selectivity obtained within cage I is certainly remarkable, and indicates its applicability for the late-stage modification of complex molecules.

2.3 Our Four-step Biomimetic Synthesis of Preislerpiperfolan-1β-ol and Unnatural Derivatives

Our group has demonstrated the remarkable capacity of the hexameric resorcinate capsule IV (Scheme 3a) to act as an artificial terpene synthase by catalyzing the tail-to-head terpene (THT) cyclization.[5,6,a,22,23] The hydrogen-bonded capsule IV is formed by the self-assembly of the monomer 30 in apolar solvents, encompassing a cavity of approximately 1400 Å³.[24–26] The aromatic walls of this cavity interact with cationic guests via cation-π interactions. In this way, the capsule is capable of complexing cationic guests (for instance, tetraalkylammonium ions),[26,27] and presumably stabilizing cationic intermediates and transition states involved in the terpene cyclization cascade. Guest encapsulation is believed to occur via the dissociation of one unit from the assembly.[28] The potential for catalysis of capsule IV was first reported by the Scarso group,[29,30] and has been explored by our group[31] and the Gaeta-Neri group.[32]
We applied the capsule IV to the THT cyclization of monoterpenes and sesquiterpenes, in the latter case achieving the selective synthesis of isolongifolene. While IV is a mild Brønsted acid, the use of HCl as a cocatalyst is necessary to initiate the cascade. The THT cyclization has been very hard to achieve in solution due to premature quenching of reactive intermediates; therefore these reports represented significant advances. However, isolongifolene is a commercially available compound, and it is not known to display any interesting biological activity. Applications of this capsule catalyst to the synthesis of valuable natural products, difficult to access by other means, is certainly a desirable next step.

The recent report of the biomimetic synthesis of presilphiperfolan-1β-ol (31, Scheme 3b) represents the first such example. Presilphiperfolan-1β-ol (31) is a tricyclic sesquiterpene that displays antimycobacterial properties; other members of the family act as insect antifeedants. Its complex structure makes it a challenging target for total synthesis: the only previous total synthesis consisted of 13 steps.

The biosynthesis of presilphiperfolan-1β-ol (31) involves cyclization of farnesyl pyrophosphate into caryophyllenyl cation 33 via humulenyl cation 32 (Scheme 3b). Cation 33 undergoes an 1,2-alkyl shift/cyclization cascade to form the presilphiperfolanol skeleton as cation 34; a hydride shift and capture by water then gives the natural product 31.

We demonstrated that it is possible to mimic this process by generating the key caryophyllenyl cation intermediate 33 within the confines of the capsule. Alcohol 28, prepared in three steps from commercially available caryophyllene oxide 38 using a literature procedure, was used as the substrate. Reaction of this compound.
with 10 mol% of capsule IV and 3 mol% HCl at 30 °C in CDCl₃, gave presilphipecolan-1β-ol (31) along with rearranged alkene 37 (Scheme 3b). Under the reaction conditions presilphipecol-1β-ol was slowly converted into 37, but it was found that this reaction could be suppressed by using water-saturated chloroform as the solvent. Employing optimized conditions (2.5 mol% HCl, water-saturated chloroform), the reaction was carried out in large scale to give the natural product in 35% isolated yield, thus accomplishing its total synthesis from commercial starting materials in four steps and 26.6% overall yield.

Control experiments in the absence of capsule or HCl failed to form products 31 or 37. The same was true for reactions with the capsule blocked by a strongly binding tetrabutylammonium guest, providing evidence that the reaction takes place within the capsule’s cavity. The unique capacity of the catalyst to accomplish this transformation was further demonstrated by assaying a number of Lewis and Brønsted acids, all of which failed to provide 31. This is in line with previous literature reports on acidic treatment of caryophyllene or its derivatives, all of which failed to produce a natural presilphiperfolanol. [41–43]

Furthermore, the formation of unnatural derivatives of presilphiperforlan-1β-ol (31) in the C4 position was achieved using this approach, starting from appropriately substituted precursors 40–44. Derivatives bearing Et-, n-Bu, i-Bu and n-Hex substituents provided the corresponding presilphiperforlan-1β-ol derivatives 46–49 in 20–27% yield. n-Oct-substituted substrate 44 provided a significantly reduced yield, while n-Dec-substituted substrate 45 failed to react, likely due to the size limit for the reaction inside the capsule’s cavity. These results, as well as the preparation of the novel rearranged alkene 37, are important as they demonstrate a potential advantage of supramolecular catalysts over enzymes. The natural cyclase enzyme, which has not been isolated and char-

Scheme 3. a) Structure of the hydrogen-bonded capsule IV that self-assembles from six resorcinarene units 30 in apolar solvents. b) Proposed biosynthesis of the natural product presilphipecol-1β-ol (31) and formation of rearranged alkene 37.

Scheme 4. Four-step total synthesis of the natural product presilphipecolan-1β-ol (31), utilizing the capsule IV-catalyzed cyclization of 39 as key step. Furthermore, access to novel derivatives 46–50, which cannot be formed by natural enzymes, was achieved.

Scheme 4. Four-step total synthesis of the natural product presilphipecolan-1β-ol (31), utilizing the capsule IV-catalyzed cyclization of 39 as key step.
acted yet, would most likely not be able to provide access to these products.

3. Discussion and Outlook

The examples presented highlight the applicability of molecular capsules in overcoming some first limitations in synthetic organic chemistry. Nevertheless, the examples are still scarce. What are the limitations of the applicability of molecular capsules? We believe that several points are noteworthy. First, the number of molecular capsules is still limited, especially when considering the volume required to encapsulate small- to medium-sized organic molecules containing approx. ten carbon atoms (approx. $\geq 400$ Å$^2$). Second, the guest uptake ability of novel hosts is not fully predictable, especially in organic solvents that lack the strong hydrophobic effect that drives encapsulation in aqueous solutions. Understanding and being able to predict the encapsulation behavior of novel hosts will be important for streamlining future work. Third, and even more importantly, many capsule structures turn out to be catalytically inactive. Whether a given host exhibits catalytic activity remains very hard to predict a priori. Fourth, most host structures are of very high symmetry. This is not surprising since they are formed by a self-assembly process of smaller building blocks, but it certainly limits their applicability. For illustration, less symmetric hosts would allow better control over the conformation of flexible substrates, for instance terpenes, and potentially increase the selectivities obtained in their conversion. Therefore, the development of less symmetric, heterocompounds will be important in driving the applicability to current challenges in synthetic organic chemistry. Ideally such hosts would be modifiable concerning size and shape; certainly a very challenging demand for a self-assembly process. Fifth, product inhibition, observed since the first capsule catalyzed reaction, is still challenging for many capsular catalysts; this is especially the case when working in aqueous media, and when performing bimolecular fusion reactions such as intermolecular Diels-Alder reactions. Very clearly, many challenges remain to be solved in the future work. Third, and even more importantly, many capsular assemblies will be important in driving the applicability to current challenges in synthetic organic chemistry. We are convinced that the growing interest in molecular capsule applicability to current challenges in synthetic organic chemistry, and potentially increase the selectivities obtained in their conversion, will catalyze a surge in useful applications.

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