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HIGHLIGHT

Cyclizations catalyzed inside a hexameric resorcinarene capsule

Yujie Zhu,[a] Julius Rebek, Jr.,[a,b]* and Yang Yu[a]*

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The self-assembled, hydrogen-bonded hexameric resorcin[4]arene capsule represents one of the most readily accessible host systems for the study of container catalysis. This assembly can stabilize cationic intermediates and transition states through cation–π interactions with the aromatic walls and several reactions have been successfully performed in its cavity. This highlight focuses mainly on the application of this host system for the catalysis of cyclization reactions such as terpene cyclizations, intramolecular hydroalkoxylation and carbonyl–olefin metathesis.

Introduction

Catalysis plays an important role in science as it provides tools for preparing chemicals and materials efficiently and selectively.[1,2,3] In addition to the impressive developments of these fields in the past few decades, supramolecular chemistry applications in intermolecular reactions offer an alternative means of controlling chemical reactivity. Compared with traditional disciplines, the interdisciplinary science of supramolecular catalysis has received relatively little attention,[4] but is growing rapidly.

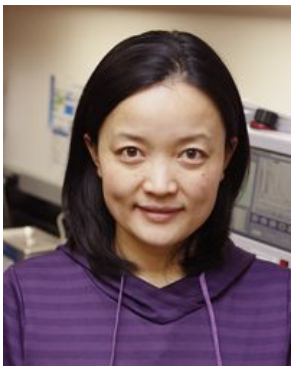
Nature's catalysts, enzymes, provide molecular-sized pockets with fixed shapes capable of accelerating reactions with remarkable regio- and stereo-control.[5,6,7] Therefore, they have served as an ultimate source of inspiration for chemists involved in the design of supramolecular catalyst. e catalysis with preorganized open or macrocyclic structures. As a consequence, many efforts have been made to mimic enzym[8,9] In the last two decades, chemists have increasingly turned to the structures of more closed supramolecular capsules bearing an internal cavity, where substrates can be isolated in analogy to the binding sites of enzymes.[10-21] Applications of these covalently linked hosts and non-covalently self-assembled structures to catalysis have been increasingly studied.[22-27] The advantage of self-assembled systems stems from their ease in preparation. Nevertheless, the use of hydrogen-bonded systems in catalysis is limited.[28-32] Tiefenbacher and co-workers have ingeniously exploited the resorcinarene hexamer **I** (Fig. 1) for the catalysis of a wide range of reactions. Capsule **I**, originally reported by the Atwood research group,[33] self-assembles from six resorcinarene units **1** and eight water molecules (Fig. 1) in apolar solvents.[34,35] The behavior of this system in solution was studied extensively and is well known to stabilize cationic transition states and intermediates via cation-π interactions with the aromatic cavity

[a] *Center for Supramolecular Chemistry & Catalytic Chemistry and Department of Chemistry, College of Science, Shanghai University, 99 Shang-Da Road, Shanghai 200444, China.*

E-mail: jrebek@scripps.edu; yangyu2017@shu.edu.cn

Yujie Zhu

Yujie Zhu received a B.S. degree from Xinyang Normal University in 2009. She studied organic chemistry at Nankai University (2013-2018) and finished her Ph.D. under the supervision of Professor Zhijin Fan. In 2018, she became a postdoctoral researcher with Professor Julius Rebek, Jr. and Professor Yang Yu at Shanghai University. Her current research is mainly in molecular recognition.



Yang Yu received her doctorate at Heidelberg University with Professor A. S. K. Hashmi in 2013 and continued as a postdoctoral researcher with Professor U. Tambar at UT Southwestern Medical Center. In 2015, she joined Professor Julius Rebek, Jr. at The Scripps Research Institute as a research associate. In 2017, she started her independent career as a professor in Shanghai University. Her current research interests lie in supramolecular chemistry and catalysis.

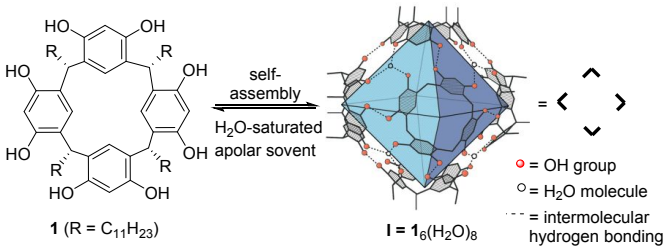
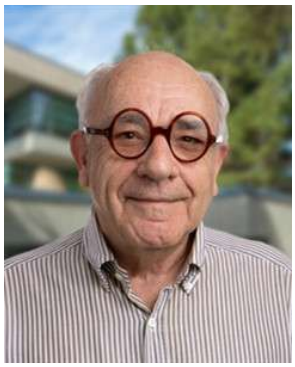


Fig. 1 Structure of the hexameric resorcin[4]arene capsule **I**.

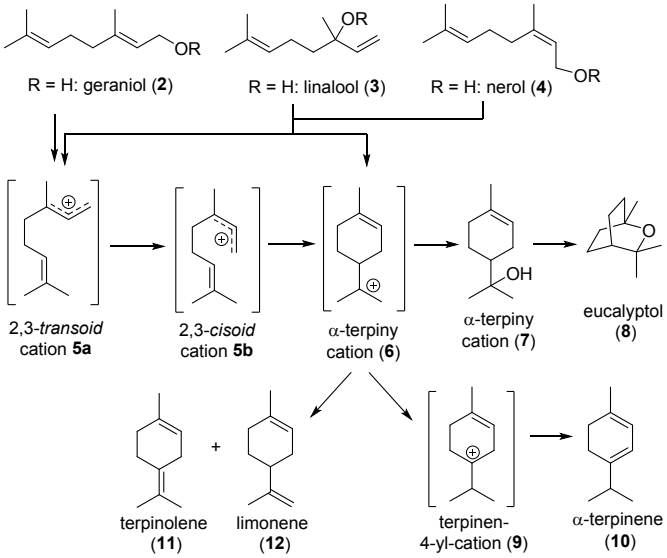
walls.[36] A survey of the literature revealed that the hexameric resorcinarene capsule **I** behaved as a mild Brønsted acid (pK_a = 5.5–6.0)[37-38] and served as an efficient catalyst for a variety of cationic reactions.[39-44] Subsequently, Tiefenbacher and co-workers gave an detailed elucidation of the differences between capsule **I** and its structurally closely related pyrogallolarene hexamer[45] to clarify its catalytic activity.[46] Here we mainly highlights recent important examples of the catalytic potential of capsule **I** for cyclizations involving such intermediates and transition states.

Aromatic residues play a significant role in stabilizing cationic intermediates and transition states via cation-π interactions.[47,48,49] In 2015, Tiefenbacher group reported the first example of a successful tail-to-head (THT) cyclization inside capsule **I**.[50] In nature, tail-to-head terpene (THT) cyclization forms most of the complex terpene natural products from just a few simple acyclic terpenes. In contrast to the head-to-tail terpene cyclization,[51] the tail-to-head (THT) reaction is difficult to control in solution, mainly due to the side reactions of cationic intermediates. Since capsule **I** can function as a Brønsted acid and stabilize cationic species, investigation of this reaction in the confinement of the container is a good choice. It was demonstrated that capsule **I** is sufficiently acidic to cyclize the commercially available terpenes geraniol **2**, linalool **3** and nerol **4** (Scheme 1). The cyclization of nerol **4** resulted, for instance, the formation of eucalyptol **8** as the main product (39%). In this reaction system, acetate turned out to be a suitable leaving group, and **1** can suppresses the interception of the cationic intermediate **6** by water molecules.



Julius Rebek, Jr.

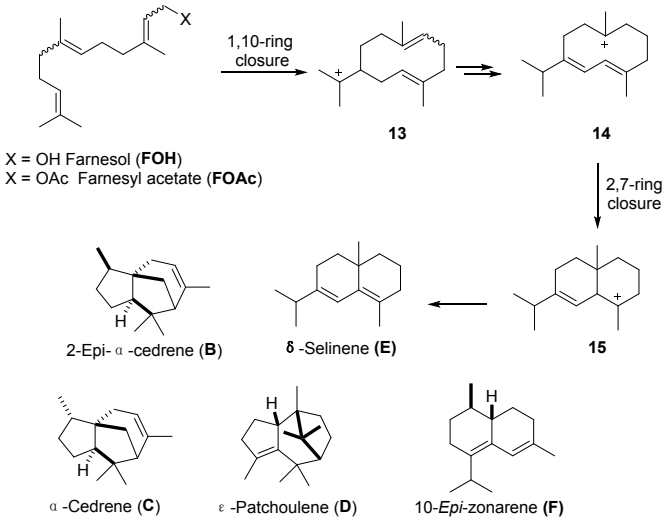
Julius Rebek, Jr. is the Director of the Skaggs Institute for Chemical Biology and Professor of Chemistry at The Scripps Research Institute and a visiting professor at Shanghai University from 2016. He obtained the Ph.D. from MIT and has held professorships at UCLA, the University of Pittsburgh, and MIT. He is a member of the U.S. National Academy of Sciences, the American Academy of Arts and Sciences, and the Royal Swedish Academy. His current research interests include self-assembling systems and molecular behavior in small spaces.



Scheme 1 Catalytic application of hexamer **I** in tail-to-head cyclizations.

The cyclization of geranyl acetate inside capsule **I** yielded mainly α-terpinene **10** in a process that seems to be a "nonstop" cyclization since no intermediate products were observed during the reaction. Control experiments showed that compounds **11** and **12** were formed mainly via direct cyclization processes. Further detailed investigations of product selectivity demonstrated that the selectivity of the reaction can be achieved by changing the nature of the leaving group.[52] Additionally, mechanistic studies were also presented, and it was revealed that the observed catalytic activity depends on the synergistic interplay between capsule **I** and HCl formed by the photodegradation of the solvent employed. A series of control experiments were also performed to prove that the reaction indeed occurs inside the cavity of capsule **I**.

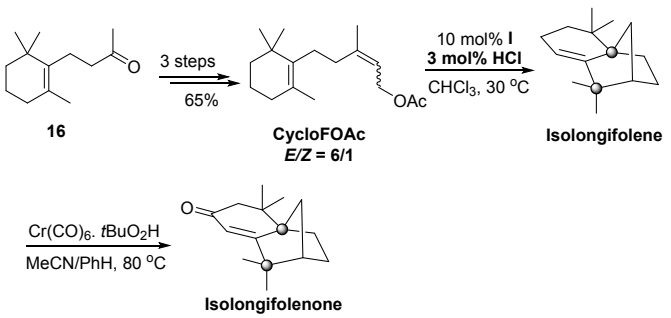
In addition, this group also reported that the resorcinarene capsule **I** can serve as an efficient catalyst for biomimetic tail-to-head cyclization of sesquiterpenes.[53] It was revealed that the linear sesquiterpene (2*E*,6*Z*)-farnesyl acetate isomer exhibited a markedly improved product selectivity with δ-selinene (**E**) (18%) and 10-*epi*-zonarene (**F**) (10%) as the main products in the presence of 10 mol% capsule **I** and 3 mol% HCl (Scheme 2). Mechanistically, the selective formation of δ-selinene (**E**) taking place inside the capsule arises from 1,10-cyclization followed by a reaction cascade.[54] However, when (2*E*, 6*E*)-farnesyl acetate was used as cyclization precursor, the selectivity for δ-selinene was significantly attenuated and intriguingly, no traces of δ-selinene could be observed in the cyclization reactions of (2*Z*, 6*E*)- and (2*Z*, 6*Z*)-farnesyl acetate. These results together demonstrate that the conformational control of the substrate and intermediates plays an important role in the selectivity of the cyclization reaction. Additionally, the cyclization of monocyclic sesquiterpenes was also studied.[53] Indeed, the cyclization of the cyclofarnesyl acetate displayed a further improved selectivity than the corresponding cyclofarnesyl alcohol and afforded the tricyclic sesquiterpene isolongifolene as a single major species in the presence of capsule **I** and HCl.



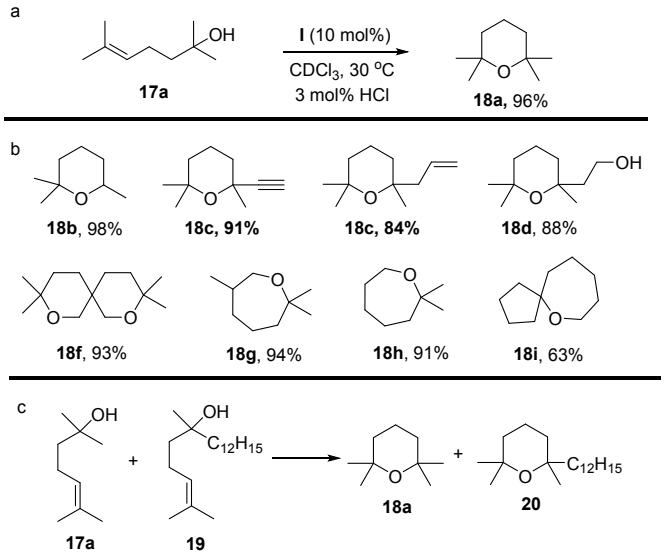
Scheme 2 Structures of the cyclization precursors, main cyclization products and proposed mechanism.

This strategy was successfully applied to the total synthesis of complex tricyclic sesquiterpene natural products isolongifolene[55] and isolongifolenone[56] via the selective cyclization of cyclofarnesyl acetates (Scheme 3).[53] The inexpensive dihydro-β-ionone **16** was used as starting material and was smoothly transformed into **cycloFOAc** in a scalable three-step sequence. Then the capsule-catalysed tail-to-head terpene cyclization was used as the key step to complicate the total synthesis of isolongifolene in preparatively useful yields. Isolongifolenone could be obtained by subsequent allylic oxidation.

Based on the study of terpene cyclization, the Tiefenbacher group further explored the potential use of capsule **I** as an acid catalyst in the intramolecular hydroalkoxylation reaction of unsaturated alcohols (Scheme 4).[57] It was found that hydroxy olefin **17a** can be converted into the corresponding cyclic ether **18a** (Scheme 4a). The amount of water was essential for reaction rates and trace amounts of HCl/DCl served as cocatalyst. The scope of capsule-catalyzed intramolecular hydroalkoxylation was evaluated and different tetrahydropyrans **18a-f** and oxepanes **18g-i** were obtained with generally excellent yields (scheme 4b). Additional control experiments showed that the reactions take place inside the capsule. In the presence of catalytic amounts of **I** (10 mol%), the



Scheme 3 Short total synthesis of natural products isolongifolene and isolongifolene.

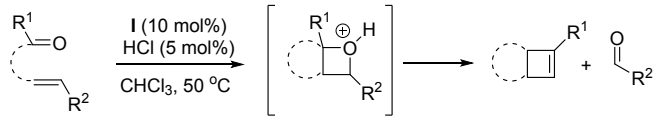


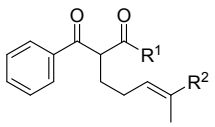
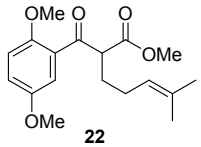
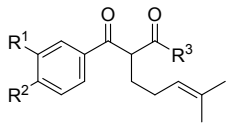
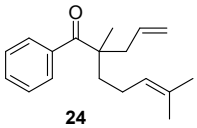
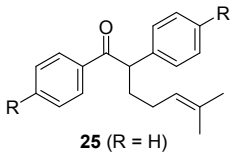
cat.	conversion	ratio **18a** : **20**
10 mol% TfOH	67%	46 : 54
10 mol% + 3 mol% HCl	53%	92 : 8

Scheme 4 Intramolecular hydroalkoxylation catalyzed by **I**. (a) Hydroalkoxylation under optimized reaction conditions. (b) Investigation of the scope of **I**-catalyzed intramolecular hydroalkoxylation. (c) Size selective intramolecular hydroalkoxylation catalyzed by **I.**

cyclization of small unsaturated alcohols like **17a** was rapid, while the larger derivatives like alcohol **19** cyclized much more slowly. No such selectivity exists in solution with strong Brønsted acids (Scheme 4c).

Very recently, Tiefenbacher and co-workers applied the co-catalytic system of capsule **I** and HCl to carbonyl-olefin metathesis (Scheme 5).[58] It is the first example of realizing Brønsted acid-catalyzed carbonyl-olefin metathesis in the presence of supramolecular host. The author demonstrated that the supramolecular host and the Brønsted acid are indispensable and work in a synergistic fashion to catalyze the metathesis reaction. Again, a series of control experiments confirmed the reactions take place inside the cavity of capsule. For example, when the cavity was occupied by the strongly binding tetrabutylammonium bromide (a competitive inhibitor), the reaction was inhibited. Notably, when a mixture of different size substrates was subjected to the solution, the smaller substrate exhibited an obviously faster conversion than the larger counterpart due to its more efficient encapsulation. Comparisons between the performance of this supramolecular catalytic system with the current Lewis acid benchmark catalyst $FeCl_3$[59] in terms of substrate scope and product yield were made, and revealed that the newly-developed catalytic system provides comparable or even better yields than the benchmark catalyst $FeCl_3$. When substrates bearing δ,ε-unsaturated aryl ketones like **24, 25** (Scheme 5) were used, the yields obtained were significantly improved over the values reported in the literature. Additionally, a mechanistic probe indicated that the formation of oxetane intermediates is likely a stepwise process.



entry	substrate	ratio of DB isomers	yield
1	 **21** (R^1 = OEt; R^2 = Ph)	8.9 :1	71% ($FeCl_3$: 49%)
2	 **22**	3.4 : 1	91% ($FeCl_3$: 64%)
3	 **23** (R^1 = OMe; R^3 = OEt)	1 : 0	76% ($FeCl_3$: 66%)
4	 **24**	1 : 0	90% ($FeCl_3$: 44%)
5	 **25** (R = H)	7.5 : 1	78% (FeCl3: 43%)

Scheme 5 Carbonyl-olefin metathesis inside **I**.

Conclusions

Supramolecular catalysis has increasingly attracted the interest of chemists, since the confined spaces offer the possibility of performing reactions with different reactivities and selectivities compared to those in bulk solution. Resorcin[4]arene hexamer **I**, a hydrogen bonded, self-assembled capsule, has been studied in detail by Tiefenbacher and co-workers. The capsule is readily accessible (a one-step synthesis), although its application in catalysis is limited to molecules that fit inside. Since many larger systems are available,[60,61] supramolecular capsules are promising catalysts. At present, most supramolecular capsules have no synthetic relevance, but the isolation from solvent has emerged as a prerequisite for control of catalytic activity. Such information should help in the development of next-generation supramolecular hosts for recognition and catalysis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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