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## Graphical abstract

### Binding and Reactivity in Deep Cavitands

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This review provides an overview on deep-cavitands as synthetic receptors in organic and aqueous solution. Relation between binding orientation and reactivity in the host-guest complex is deeply discussed, pointing out the importance of intermolecular interactions and similarities with the action of biological enzymes.

# Binding and reactivity in deep cavitands based on resorcin[4]arene

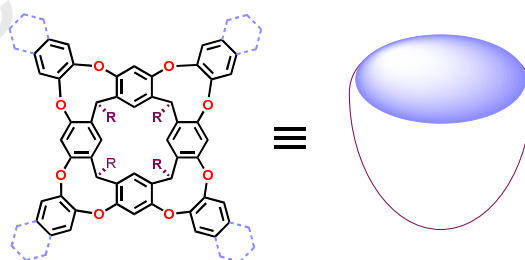
Manuel Petroselli<sup>a</sup>, Yong-Qing Chen<sup>a</sup>, Julius Jr. Rebek<sup>b</sup>, Yang Yu<sup>a</sup>✉

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## 1. Introduction

Nature has always inspired science, and in the last decades, many synthetic container molecules have been created to mimic enzymes and receptors [1]. The biological compounds use binding forces such as hydrogen bonds, hydrophobic interactions or van der Waals forces to stabilize reactive intermediates and transition states of small molecules held inside. The stabilization occurs in a confined space that makes otherwise unfavorable reactions accessible under mild conditions. The space where reactions take place is often hydrophobic and isolated from the aqueous medium. The synthetic chemists have sought such “active sites” in practically concave platform, comprising cyclodextrins [2], cyclophanes [3], cucurbiturils [4], pillararenes [4], calix[n]pyrroles [4] and calix[n]arenes [4]. Here we summarize applications of cavitands based on resorcin[4]arene. In 1983, Cram et al. reported the first synthesis of resorcin[4]arene cavitands [5], where binding properties and potential uses in organic solvents were expressed in detail. Since then, resorcin[4]arenes have been widely studied, initially in organic-solvent and in the last decade in water, as organic molecules able to mimic the actions of biological enzymes. Resorcin[4]arenes having “extended” aromatic walls offered relatively large lipophilic cavities, leading them to be called deep cavitands. The vase conformation is the “active form” of the host in which a “cavity” is generated and where suitable guests can be included (Fig. 1). Furthermore, due to these cavities, the deep cavitands often work well as reaction vessels [5], but rarely as supramolecular catalysts [6].



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solubility in aqueous medium. The upper rim (blue part in Fig. 1) has two functions: a) to increase the solubility of the host adding hydrophobic or hydrophilic groups; b) to provide functional groups that modify the binding properties of the host or guest's reactivity. We report here a collection of the most representative studies on binding and reactivity for organic- and water-soluble deep cavitands.

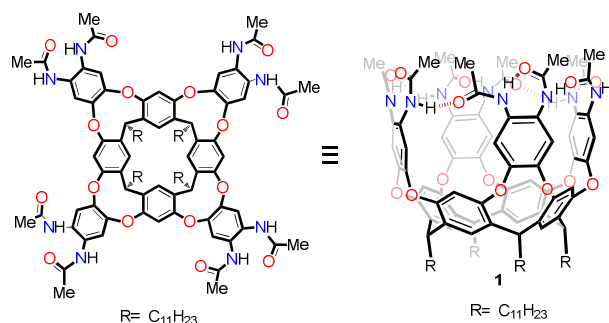
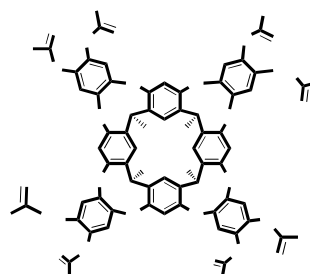
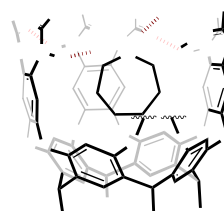
## 2. Organic-soluble hosts

Intermolecular forces as hydrogen bonds (HB) or electrostatic interactions are extremely sensitive to the environment [9]. Their contributions to binding energetics are maximum in apolar organic solvents and they can drastically change in presence of polar co-solvents [10,11]. Hydrogen bonds also play an important role in molecular recognition [12-14], binding selectivity and molecular stabilization [15-17]. The unusual reactivities and behaviors of guests in confined spaces initially were examined in organic media. Mesitylene- $d_{12}$  is often used as solvent and it is preferred to other organic solvents (i.e.,  $CDCl_3$  or THF- $d_8$ ) due to its unwieldy size. It shows low affinity to the cavity and its low polarity amplifies the polar interactions between the host and guest, making the interpretation of their interactions by NMR spectroscopy easier.

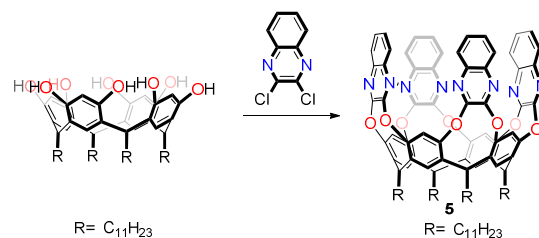
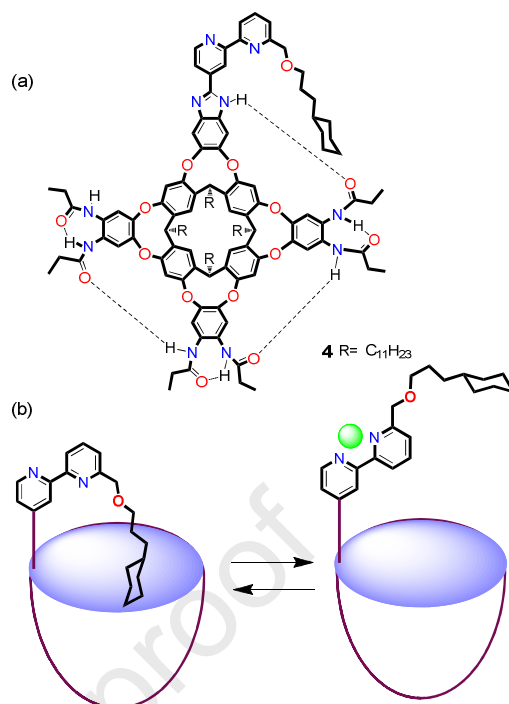
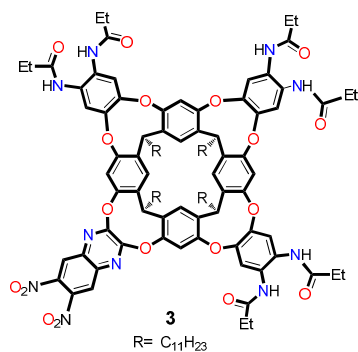
### 2.1. Binding in organic-soluble cavitands

Cavitands are concave hosts that are able to bind small molecules of complementary size, shape and chemical surface [18]. The dimerization to capsules is often possible but it can be avoided by the absence of self-complementary functional groups on the rim [9,19]. The shape and inner space of the cavitand affects the orientation and reactivity of the guest, leading to behaviors in cavitands completely different from those observed in bulk solution.

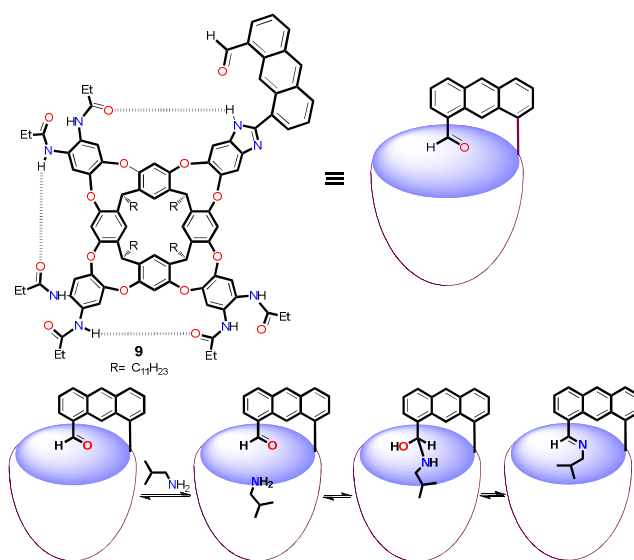
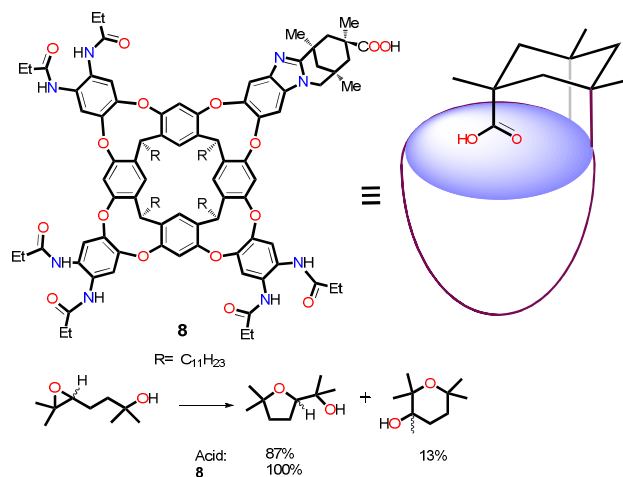
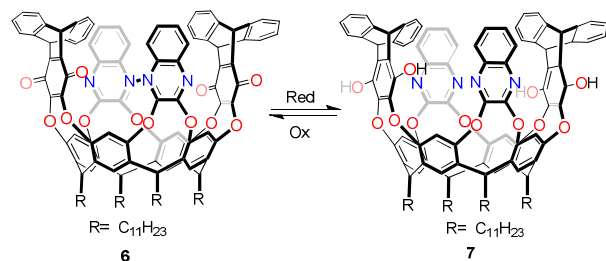
The orientation of the amide groups on host 1 prevents intermolecular interactions (HBs) and capsule formation with other host molecules but allows intramolecular HBs between adjacent amides (Fig. 2). The hydrogen bond network plays an important role in the stabilization of the host's vase form and the host-guest complex.



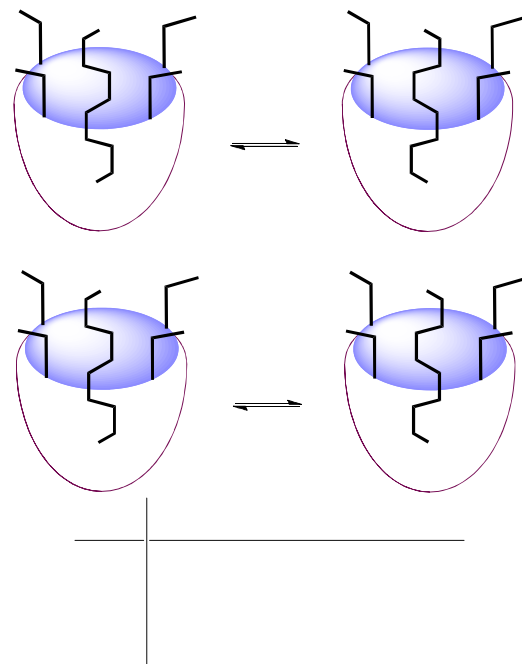
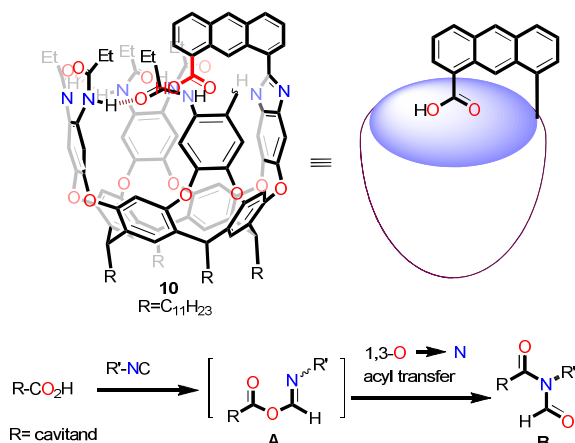
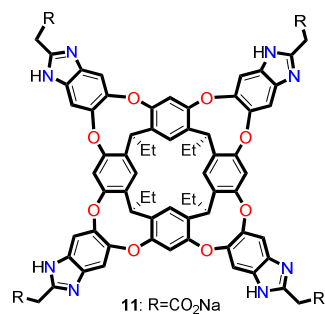
guests. One of the largest guests for resorcinarene-based cavitands is 2,2'-paracyclophane but it is readily bound by **3**, in which it tumbles and spins slowly. The higher mobility of the new wall in **3** does not affect the properties of the other three "amide walls" in comparison with **1** but it drastically lowers binding affinities and facilitates in/out exchange rates of the guest.



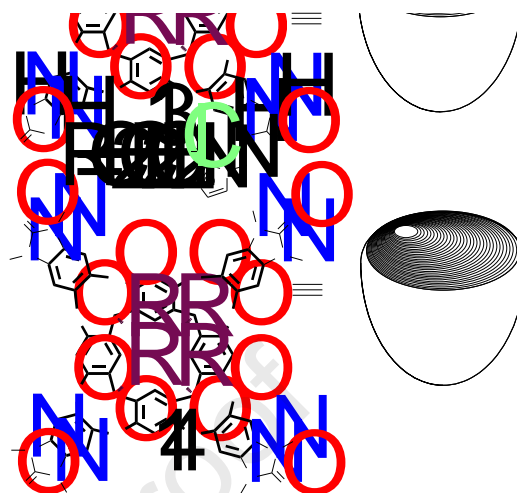
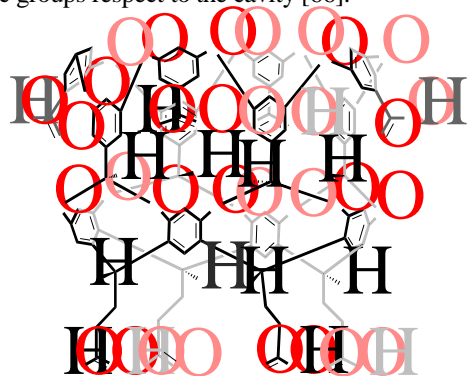
while vase form is predominant in THF-d<sub>8</sub>. In pure mesitylene-d<sub>12</sub> 6 and 7 are present in the kite conformation, due to the low affinity of mesitylene for the cavity (Fig. 8). Binding experiments in mesitylene-d<sub>12</sub> show a binding constant ( $K_d$ ) of 19.2 and 3.1 L/mol for bound cyclohexane in 6 and 7, respectively. The higher binding constant for 6 is attributed to the lower  $\Delta G$  for the kite  $\rightarrow$  vase switching respect to the one observed for 7.



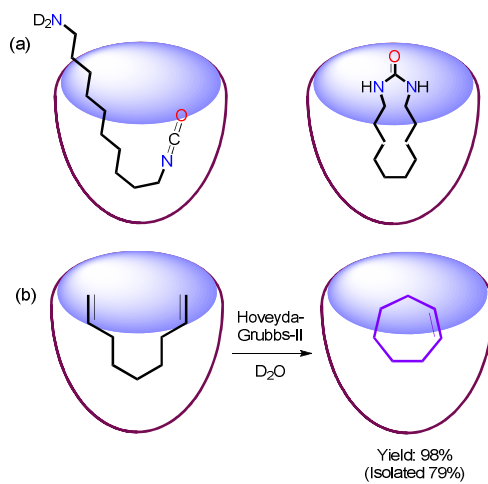
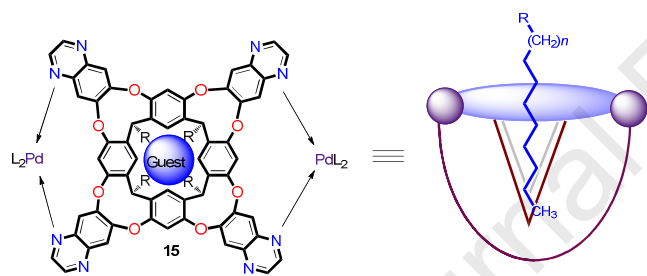
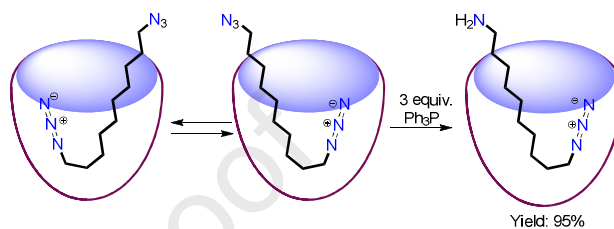
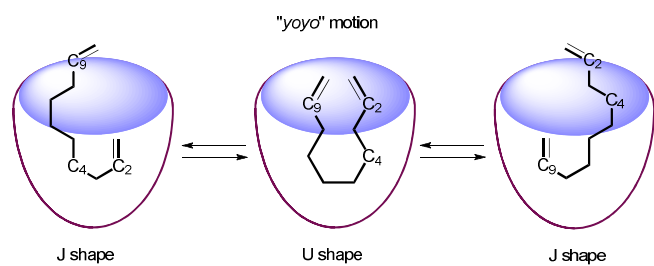
where O-acyl isoimide intermediate A rearranges to form N-acylformamide B by a 1,3-O  $\rightarrow$  N acyl transfer (Fig. 11). The transient intermediate A is hard to detect in bulk solution because of its low stability, but it is observed by NMR spectroscopy in 10. The relative higher concentration of the reacting species in 10 makes the reaction faster and accessible while the confined space affects the movements of the intermediate A, making the rearrangement slower. These features are specific for the cavity and create a unique environment not possible in bulk solution.



properties of the guest (i.e., fluorescence), due to the change of the environment around them [62]. This aspect is boosted when aromatic guests, having proper shape and size, are encapsulated in more confined systems such as capsules. In these systems, spectroscopic properties or reactivity are extremely different or even suppressed respects to the ones that are usually observed in solution [63-65]. Recently, modulation of the binding properties of 12 was reported by Gibb, showing the effect of the orientation of carboxylic groups respect to the cavity [66].







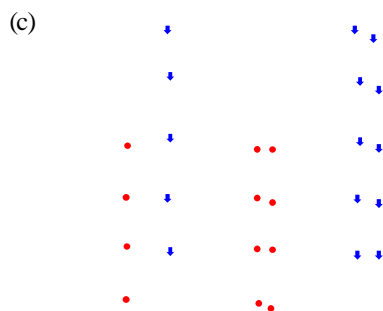


Fig 20. (a) Representation of the host-guest complex in 14 of asymmetric intermediate (right) and cyclic urea (left); (b) Cartoon for RCM reaction of cycloheptane@14. (c) Upfield  $^1\text{H}$  NMR spectra for RCM reaction catalyzed by Hoveyda-Grubbs-II for C<sub>7</sub>-diene@14 after treatment with HG-II for 1.5 h, 3.0 h, 4.0 h, 6.0 h, authentic cycloheptene in 14 (from bottom to top).

#### 4. Conclusion

In summary, host-guest complex formation occurs in organic and aqueous solutions in deep-cavitands through intermolecular forces such as halogen bonds, hydrogen bonds, electrostatic interactions or the hydrophobic effect. Binding and reactivity in deep open-ended containers show some similarities to the behavior observed in biological enzymes, making them interesting and promising model synthetic receptors. Confinement of guests in limited spaces (cavities) forces the guest to adopt unusual orientations, leading to unexpected reactivity or changes in their chemical and physical properties. Bi-functional guests such as dienes, diazides and dihalides show characteristic U-shaped conformation and “yo-yo” motions in water-soluble cavitands that are totally unknown in bulk solution. Mono-polar head guests show asymmetric binding (J-shaped conformation) and their “yo-yo” motion depends on the nature and polarity of the involved functional groups. Reactions such as mono-functionalization and macrocyclization are successfully reported in which hosts act as protecting groups, templates or reaction vessels. Stoichiometric amounts of host are still required when reactions are performed in deep cavitands, so development of catalytic systems based cavitands is currently of primary importance to further justify and extend their use in chemistry and biology. In fact, deep-cavitand chemistry is a relatively young research area, but it is playing an important role in better understanding the actions of enzymes in biological systems and developing tools for new medical applications such as drug delivery.

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#### Declaration of competing interest

The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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**Declaration of interests**

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

• The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: