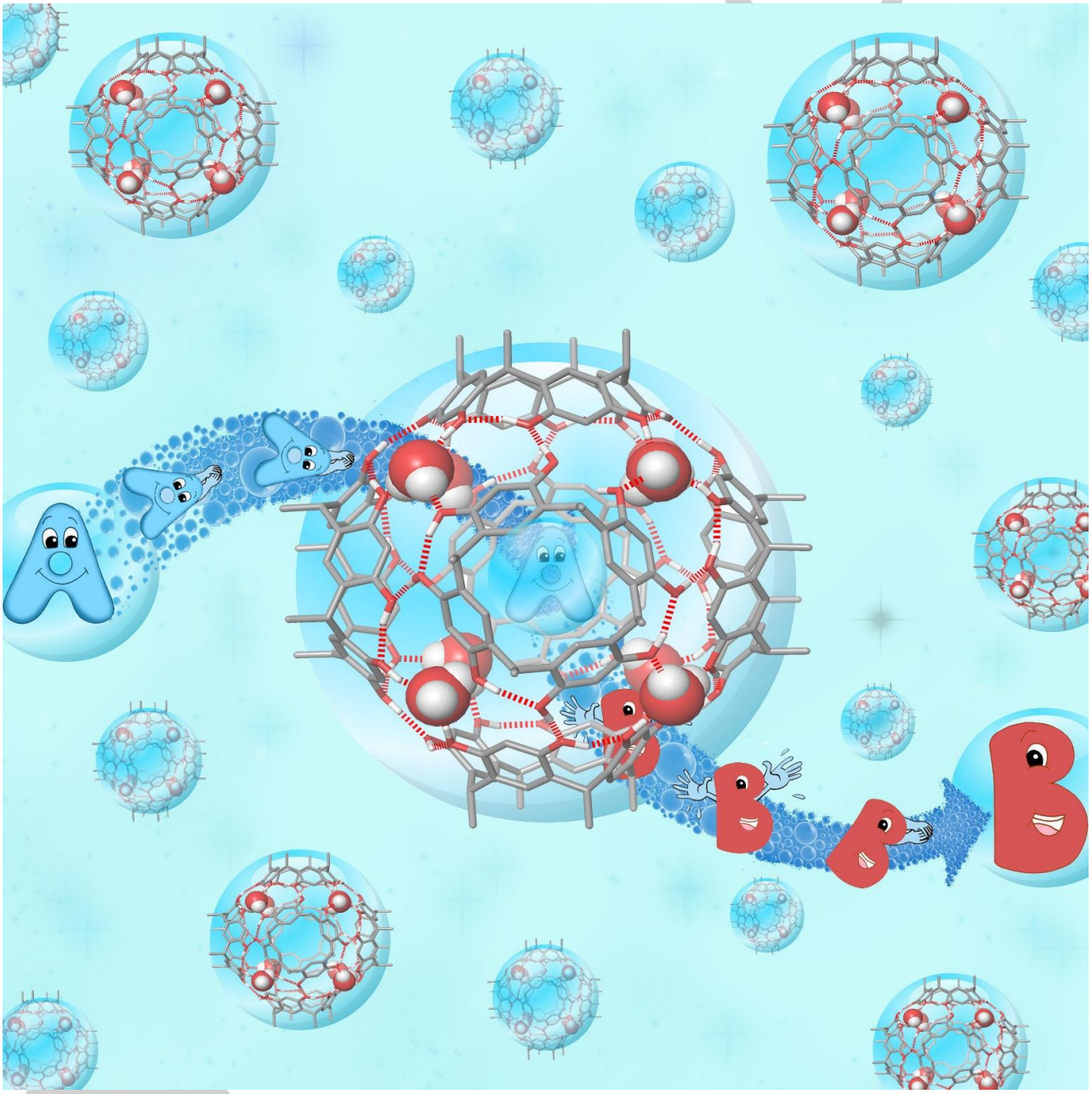
The Hexameric Resorcinarene Capsule at Work: Supramolecular Catalysis in Confined Spaces

Carmine Gaeta,* Carmen Talotta,* Margherita De Rosa, Pellegrino La Manna, Annunziata Soriente, and Placido Neri*



Abstract: The hexameric resorcinarene capsule reported by Atwood in 1997, is able to act as a supramolecular catalyst. Its inner cavity provides a unique environment in which organic reactions can be efficiently catalysed, thanks to the confinement effect of the substrates. In addition, different stereo- and regiochemical outcomes can be observed with respect to the reactions in the bulk solvent. The hexameric capsule shows some catalytic features reminiscent of natural enzymes. In particular, we highlighted here i) its ability to recognize the substrates (substrate selectivity), ii) the possibility of stabilizing the transition states and the intermediates by secondary interactions, iii) an inherent Brønsted acidity, and finally iv) the ability to act as a H-bond catalyst. In addition, it is also shown how the catalytic activity of the hexameric capsule can be modulated in the presence of competitive alkylammonium guests, which show high affinities for its internal cavity. These aspects will be discussed in this mini-review by a critical examination of the literature data reported in the last years.

1. Introduction

Nature is a continuous source of inspiration for scientists that, by mimicking the *modus operandi* of natural systems, have designed artificial systems with more and more advanced functions and properties. [1,2] Thus, by taking inspiration from the genetic evolution of living systems, researchers[2] have developed novel enzymes for specific reactions. Supramolecular catalysis [3] finds inspiration from natural enzymes, which show catalytic features, such as: selectivity toward the substrates and products, efficiency, geometric control, and velocity. When the reactants are confined in the restricted space inside an enzyme pocket, the proximity effect between them and the stabilization of the intermediates and transition states induce a reaction acceleration. Thus, learning the lesson from natural enzymes, novel supramolecular catalysts have been designed which show substrate selectivity, turnover, regio- and stereoselectivity.[3] At this regard, the self-assembled molecular capsules[4] constituted a significant milestone toward the design of supramolecular catalysts with advanced properties and functions.[5] In fact, the confined environment inside a self-assembled capsule is the ideal habitat to simulate the catalytic functions of an enzyme pocket.[5] Thus, self-assembled capsules were reported to be able to perform catalysis of organic reactions with efficient turnover, regio- and stereoselectivities.[6]

Self-assembled capsules are formed by a spontaneous and ordered aggregation of molecular components driven by secondary interactions. Among the examples reported in literature, the H-bonded self-assembled capsules have played a crucial role. [4] In a pioneering work, Rebek[6a] reported an example of self-assembled hydrogen-bonded system, the so called ‘‘soft-ball”, in which two glycoluril units were sealed by 16 H-bonds. The pseudo-spherical soft-ball showed catalytic activity toward the Diels-Alder reaction between *p*-quinone and cyclohexadiene.[6a] In this specific case, π-π stacking interactions stabilized the substrates inside the supramolecular architecture. Successively, in another fundamental report, the Rebek's cylindrical capsule, formed by self-assembly of two resorcinarene cavitands, showed catalytic activity in a click reaction between alkynes and azides with a good regioselectivity.[7]

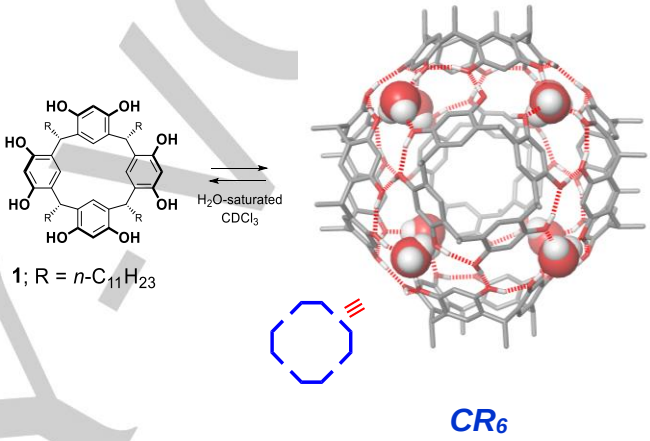


Figure 1. Self-assembling of *C*-undecylresorcin[4]arene **1** in the hexameric capsule **CR$_6$**. Tube model **CR$_6$**: undecyl chains and H-atoms have been removed for clarity, while bridging H_2O molecules are represented as CPK model.[8]

Among the examples of self-assembled capsule, the hexameric resorcinarene system reported by Atwood[8] has been particularly investigated. In his pioneering work,[8] Atwood showed that in the solid state the hexameric capsule **CR$_6$** (Figure 1) is formed by self-assembly of six resorcinarene **1** molecules with 8 water molecules, sealed by 60 (O-H···O) H-bonds. The X-ray structure[8] of the hexameric capsule resembles a cube with six resorcinarene molecules located on the sides and eight water molecules as the corners in a chiral structure. A close inspection of the X-ray structure of **CR$_6$** reported by Atwood,[8] reveals the presence of a hydrogen bond belt between the eight bridged water molecules and the six resorcinarene molecules. In details, the hexameric resorcinarene capsule bears 8 water molecules located to the corners of a cube (Figures 1 and 2), which establish three H-bonds each one (Figure 2). Four of these bridging-water molecules donate two H-bonds (Figure 2, H_2O drawing in blue), completing their H-bond donating valence and act as acceptor of a single H-bond. The other four bridging-water molecules donate a single H-bond (Figure 2, magenta) and act as a double H-bond acceptor, in this way, each one, remains with a *H-bond donating free valence.* Thus, an

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octahedral-shaped cavity was formed with an internal volume of 1375 Å^3 that can host about 6-8 molecules of chloroform or benzene. In 2001 Rebek,[9a] for the first time, reported NMR evidences of the encapsulation of ammonium guests inside the hexameric capsule in solution. In this work, the authors evidenced the crucial role played by cation-π interactions between the cationic guests and the π-electron rich cavity of **CR$_6$** for the stabilization of the complex $^+$NR$_4$@**CR$_6$**, in solution. In this report,[9a] it was clearly showed that the internal volume of **CR$_6$** is several times that of tetrabutylammonium cation, thus the simultaneous encapsulation of both cation and anion inside **CR$_6$** occurrs. In particular, while the ion pairs encapsulation was shown with I^- and BF_4^-, as counteranions of $^+$N(*n*-Bu)$_4$, no complexes of tetrabutylammonium cation were observed with large tosylate and $^-$B(Ph)$_4$ counteranions.[9a] Successively, in a fundamental work,[10] Cohen showed that the presence of the cationic guest is not essential for the formation of **CR$_6$** in solution. In fact, through diffusion NMR studies in solution, Cohen[10] showed that the capsule is also self-assembled in water-saturated $CHCl_3$ (or $CDCl_3$) or wet-benzene, and in these cases the empty space inside **CR$_6$** was filled with solvent molecules.

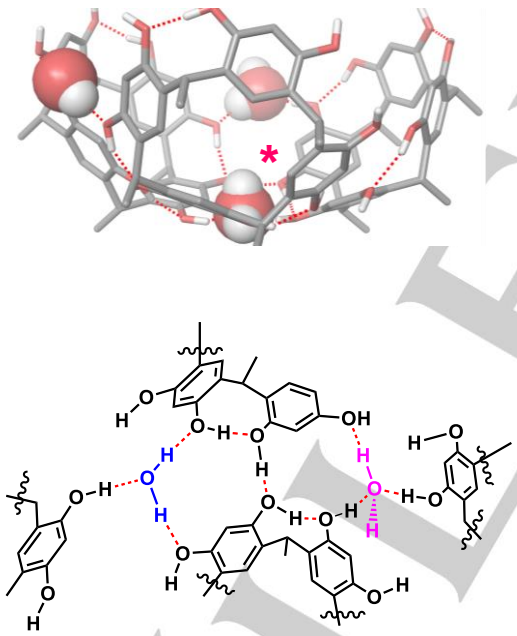
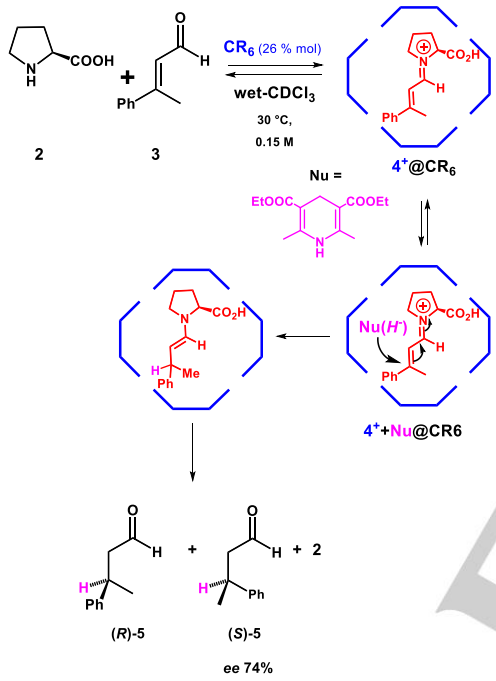


Figure 2. Detailed views of the H-bonding interactions between the bridging water molecule of **CR$_6$** and resorcinarene units. (Bottom) Chemical drawing of the model representing a bridging water molecule with one *H-bond donating free valence* (in magenta).

Surprisingly, the water molecules on the corner of the hexameric capsule can be replaced by alcohol molecules, which can be on the seam of the H-bonds.[11] Interestingly, it has been shown[12] that 6/8 H_2O molecules can be replaced by (±)-2-ethylhexanol in an hexameric structure sealed by 50 H-bonding interactions. Tiefenbacher's group reached another milestone when[13] they showed that **CR$_6$** behaves as a mild Brønsted acid with a p*K*$_a$ value of about 5.5–6.0. The authors calculated this range of values by studying the protonation equilibria of amines of decreasing basicity with the capsule **CR$_6$**, and measuring the percentage of protonated amine by integration of appropriate ^{1}H NMR signals. [13] Interestingly, when pyridine (*p*K$_a$ = 5.2) was added to the water-saturated solution of **CR$_6$** then the 53 % of protonation was measured. From this datum and considering the p*K*a of pyridine, a p*K*a value of 5.6 was calculated for the hexameric capsule **CR$_6$**. Using aniline (*p*K$_a$ = 4.6) the degree of protonation was decreased to 23 % ^{and} by this datum a p*K*a value of 5.9 was calculated for **CR$_6$**. Finally, *para*-substituted anilines of lower basicity were not protonated. The acidity of the hexameric capsule is justified by the stabilization of the resulting anion upon delocalization of the negative charge over the phenolic groups and water molecules of the assembly. Recently, we reported that QM calculations estimate a p*K*$_a$ of the four bridged-water molecules with *H-bond donating free valence* (blu in Figure 2) of ≈ 2.5, while the mean p*K*$_a$ value of all OH groups of **CR$_6$** is 6.1,[14] in excellent agreement with the experimental value.[13] In particular, **CR$_6$** is able to accommodate tertiary amines, which are protonated inside the capsule. The resulting ammonium guests are held inside by cation-π interactions, while the anionic charge is stabilized by delocalization on the entire whole of the capsule. The chemical-physical properties of **CR$_6$** have inspired the imagination of researchers attracted by the idea to mimic the catalytic features of an enzyme pocket. In fact, like in an enzymatic active site, the inner cavity of **CR$_6$** is able to host selectively the substrates; by virtue of the confinement effect, they can react, leading to the formation of intermediates and transition states stabilized by interactions with the capsule. Thus, in the last decade, many reports in the field of supramolecular catalysis have shown that the resorcinarene hexameric capsule **CR$_6$** is able to catalyze chemical reactions.[5a,c,e,h,l] Interestingly, examples have been reported in which **CR$_6$** works as a nano-reactor, in which, thanks to its large cavity, is able to host, both catalyst and substrates. In these cases, the nano-reactor[5e] **CR$_6$** is able to select the substrates and to accelerate the reaction thanks to the confinement effect of the catalyst and substrates. Finally, in many cases, an unusual reaction outcome was observed when the reaction occurs inside **CR$_6$**. In these cases, different regio- and stereochemistries were obtained with respect to the reaction in the absence of capsule. Significantly, capsule effects were also observed when the hexameric capsule **CR$_6$** works as a catalyst itself. In these instances, in the absence of any co-catalyst, the capsule is able to catalyze chemical reactions thanks to the stabilization of intermediates and transition states. In this particular case, very recently, [14] our group has highlighted the catalytic role of the water-bridged molecules with *H-bond donating free valence* as H-bond donating groups (*vide infra*).

1.1. The Hexameric Resorcinarene Capsule as a Nano-Reactor

Examples[5a,c,e,h,l] have been reported in which the hexameric capsule **CR$_6$** acts as a container[5e] for substrates and catalyst, showing a remarkable reaction acceleration. In these cases, the capsule confines the catalyst and the reagents in a restricted space where the proximity effect between them and their overconcentration, due to the confinement in a restricted space, induce a reaction acceleration: we can define this as the *capsule effect* on the reaction rate.[5a,c,e,h]



Scheme 1. The reductase-mimicking example reported by Tiefenbacher[15] in which **CR$_6$** works as a nanoreactor, confining the Hantzsch ester and the iminium **4**$^+$ inside the cavity.

Tiefenbacher and coworkers[15] have recently reported an interesting example of reductase-mimicking in which **CR$_6$** works as a nano-reactor in an iminium organocatalysis (Scheme 1). The authors showed that, when L–proline **2** and α,β-unsaturated aldehyde **3** were mixed in water-saturated $CDCl_3$ at 30 °C in the presence of 26 mol % of **CR$_6$**, then the iminium derivative **4**$^+$ was encapsulated inside the nano-reactor thanks to stabilizing cation···π interactions. First of all, the encapsulation of L-proline inside **CR$_6$** was demonstrated by NMR spectroscopy. In details, the ^{1}H NMR spectrum in $CDCl_3$, of a mixture of **CR$_6$** (26 mol %) and L-proline, evidenced the presence of signals in the up-field region, from –2 to 0 ppm, attributable to the L-proline shielded by the aromatic cavity of the capsule. When aldehyde **3** (Scheme 1) was added to this solution, new signals appeared in the up-field region of the ^{1}H NMR spectrum (from –2 to 0 ppm), due to the formation of an iminium specie. Finally, a DOSY experiment indicated a diffusion coefficient for the iminium signals very similar to that calculated for **CR$_6$**. When the encapsulated iminium **4**$^+$ was reduced in the presence of an NADH-like artificial-cofactor, as the Hantzsch ester, then the product **5** was obtained in 93 % yield, while a good enantioselectivity was observed in favor of the (*S*) enantiomer.

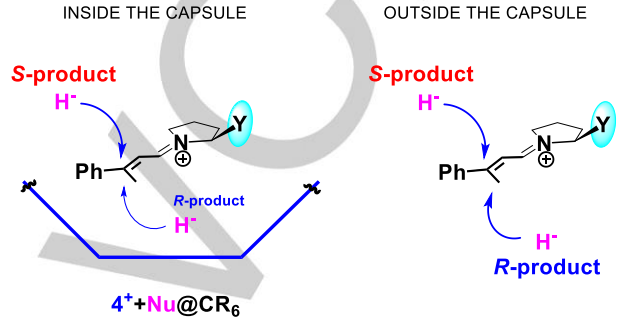
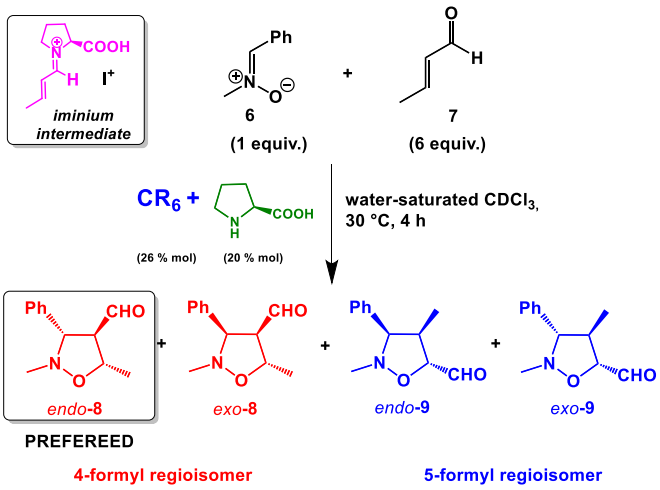


Figure 3. The model proposed by Tiefenbacher[15] to explain the *capsule effect* on the stereochemistry of the reaction in Scheme 2. Inside the capsule (left), the attack on the *Re* face is shielded by the capsule walls.

In detail, an enantiomeric excess of 74 % was measured for the (*S*) enantiomer of **5**, a value significantly higher than that observed in a regular solution experiment (9 % of *ee* for *S*, Δ*ee* = 65 %) in the absence of **CR$_6$** (27 % yield of **5**). In particular, the authors proposed [15] that inside the capsule iminium **4**$^+$ adopts the orientation reported in Figure 3 (left). In this way, **4**$^+$ establishes a more favorable cation···π interaction with the aromatic walls of **CR$_6$** from the less hindered face. Consequently, the attack of H$^-$ occurs from the face in *syn* with respect to the encumbering Y group. Naturally, when the reaction in Scheme 1 is performed in bulk solution, in the absence of **CR$_6$**, the attack from the face in *syn* to Y group is unfavored. Summarizing, in the example reported by Tiefenbacher and coworkers in Scheme 1, the *capsule effect* was observed both, on the reaction acceleration and on the enantioselectivity of the reaction.

Successively, [16] we reported an example of *capsule effect* on both regio- and stereochemistry of a 1,3-dipolar cycloaddition between nitrones and unsaturated aldehydes (Scheme 2) inside **CR$_6$**. In details, the cycloaddition between (*E*)-crotonaldehyde **7** and nitrone **6** (Scheme 2) can afford the two 4- and 5-formyl regioisomers, **8** and **9**, respectively, both as two *endo* and *exo* diastereomers, in two possible enantiomeric forms (Scheme 2). When the reaction was performed in the bulk medium in the absence of capsule and in the presence of L-proline as cocatalyst, no hint of products, **8** and/or **9**, was detected by NMR spectroscopy.



Scheme 2. Possible regio- and stereoisomers obtainable by 1,3-DC between nitrones **6** with α,β-unsaturated aldehydes **7**.[16]

Differently, a *capsule effect* was observed on the reaction acceleration when L-proline, (*E*)-crotonaldehyde **7**, and nitrone **6** were confined inside the nano-reactor **CR$_6$** (26 mol %) where a 90 % yield was observed after 4 h. Proofs of the encapsulation of the reagents inside **CR$_6$** were obtained by 1D- and 2D-NMR studies. In details, an ^{1}H NMR spectrum of **CR$_6$** and L-proline in water-saturated $CDCl_3$ solution showed the presence of signals in the up-field region, at negative values, indicative of the inclusion of the catalyst inside the hexameric capsule. [15] Analogous results were observed when the hexameric capsule was mixed with aldehyde **7** and nitrone **6.** 2D DOSY and NOESY/EXSY experiments [16] evidenced the formation of the iminium specie **I$^+$** (Scheme 2) inside the capsule. In details, when the aldehyde **7** was mixed with L-proline in the presence of **CR$_6$**, the signals at negative values of the included L-proline disappeared and a new set of signals emerged due to the formation of the iminium specie **I$^+$** stabilized by cation···π interactions inside the hexameric capsule.

A control experiment was performed repeating the reaction in Scheme 2 in the presence of hexamethonium iodide (HMI) as a competitive guest for the cavity. [15a] As it is known, [15a] the hexamethonium cation, by occupying the cavity of **CR$_6$,** acts as an inhibitor: in fact, no hint of the products **8** and **9** was detected in its presence, thus providing further evidence that the reaction took place inside **CR$_6$**. A *capsule effect* was also observed on the regio- and stereochemistry of the 1,3-DC in Scheme 2. In fact, the 4-formyl regioisomer **8** was preferentially formed with an **8**/**9** ratio of 98/2, while a diastereoisomeric *endo*-**8**/*exo*-**8** ratio of 84/14 was measured. An *ee* of 95 % was measured in favour of the 4R enantiomer of *endo*-**8**. Quantum mechanical calculations [16] suggested that inside **CR$_6$** the 1,3-DC (Scheme 2) takes place with a stepwise mechanism (Figure 4), while the formation of iminium intermediate **I$^+$** (Scheme 2) takes place inside the nano-reactor, catalyzed by the acidity of the capsule. The QM calculations also suggested that the carboxylic function of L-proline is H-bonded to a bridging water molecule (Figure 4) of **CR$_6$**. The formation of the iminium intermediate **I$^+$** (Scheme 2) caused a lowering of the LUMO of the aldehyde, which explains the very low activation free energy for the Michael-type addition (Figure 4, **II**) between nitrone **6** and iminium **I$^+$**. Calculations of the Mulliken atomic charges revealed a significant charge transfer (CT) flow from the capsule to the iminium **I$^+$**, which stabilizes the cationic intermediate inside **CR$_6$**. Summarizing, the results of the QM calculations confirm a *capsule effect* on the observed regio- and enantioselectivity for the 1,3-DC in Scheme 2.

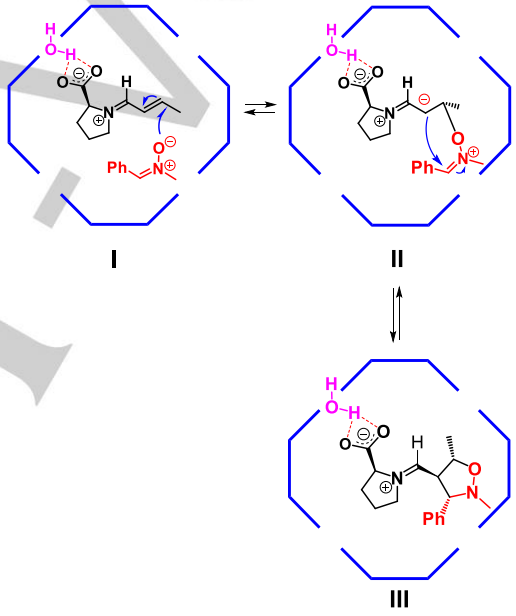
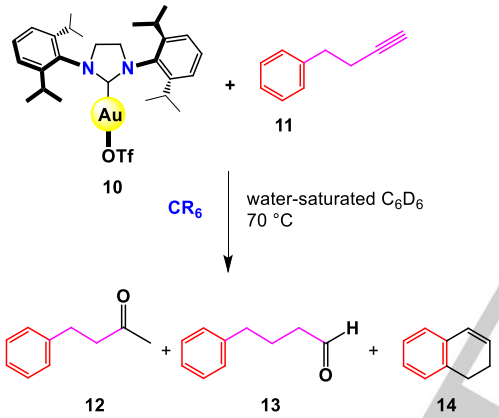


Figure 4. Calculated mechanism for the 1,3-DC between **6** and **7** inside **CR$_6$**.[16]

An interesting example of supramolecular catalysis in confined space has been reported by Scarso, [17] concerning the hydration of alkynes to methyl ketones. Aromatic alkynes were converted to methyl ketones in the presence of catalytic amounts of **CR$_6$** (36 mM respect to **1** and 60 mM respect to the alkynes) and sub-stoichiometric amounts of HBF_4, in water-saturated $CDCl_3$ at 60 °C, in few hours. The authors showed that the reaction takes place only when **CR$_6$** was combined with HBF_4, while no conversion was obtained in the absence of **CR$_6$** and/or HBF_4. The stabilization of the transition state leading to the cationic vinyl intermediate was proposed to justify the *capsule effect* on the reaction acceleration.

In a similar way, Tiefenbacher and Catti, showed that hexameric **CR$_6$** and co-catalyst HCl work in synergistic way to catalyze carbonyl–olefin metathesis reactions.[18]

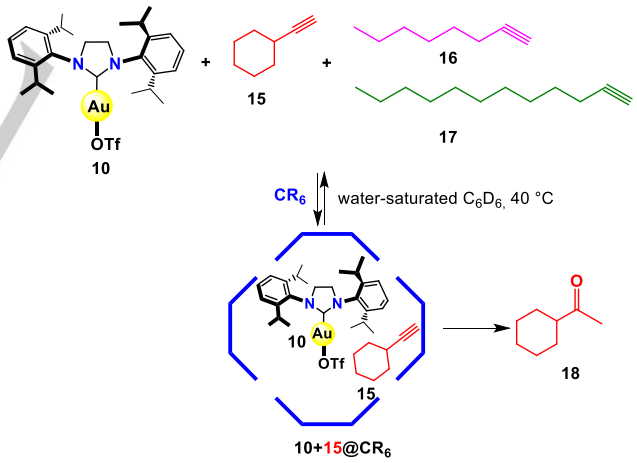
An example of capsule effect on the chemo- and regioselectivity of an organic reaction has been reported by Reek and Scarso (Scheme 3).[19] The authors, studied the hydration of the 4-phenyl-1-butyne **11** (66 mM) in the presence of **CR$_6$** as a nano-reactor (33 mM with respect to **1**) and (*i*-Pr-NHC)AuOTf complex **10** (3.3 mM) as catalyst (Scheme 3) in water saturated C_6D_6 at 70 °C.[19] First of all, they showed that in absence of **CR$_6$** the free (*i*-Pr-NHC)AuOTf catalyst was able to convert 4-phenyl-1-butyne **11** to **12** in quantitative yield after 30 minutes, in water saturated C_6D_6 at 70 °C (only traces of products **13** and **14** were detected under these conditions). When the (*i*-Pr-NHC)AuOTf catalyst was encapsulated inside **CR$_6$** then the 4-phenyl-1-butyne **11** was converted more slowly, and after 400 minutes only 28 % of **11** was converted.



Scheme 3. Regioselective hydration of 4-phenyl-1-butyne **11** in the presence of **CR$_6$** as nano-reactor and (*i*-Pr-NHC)Au(OTf) **10** as catalyst.[19]

At this point, the regioselectivity is the most interesting aspect when the reaction occurs inside **CR$_6$**. In fact, the encapsulated catalyst **10** gives rise to different products with respect to the reaction performed in the absence of capsule and with the free catalyst. In particular, in addition to product **12** (12%), a significant yield of aldehyde **13** (4%)[19] was obtained as the hydration product, showing in this way, that the regioselectivity of the reaction in a confined environment can be differently driven with respect to the normal conditions in the absence of capsule. Furthermore, the authors [19] obtained also the formation of 1,2- dihydronaphthalene **13** (12%), a product that is formed after intramolecular rearrangement usually favored when the reaction occurs within the cavity of **CR$_6$** due to the folding of the substrate. 1D and 2D NMR studies were performed [19] in order to prove the presence of the organometallic complex inside **CR$_6$**. When the hexameric capsule **CR$_6$** was mixed with an excess of (*i*-Pr-NHC)AuOTf complex **10** (7 equiv.) in water saturated $CDCl_3$, then its encapsulation was confirmed by the appearance of a new set of shielded ^{1}H NMR signals for the *i*-Pr groups of **10** at negative value of chemical shifts. In addition, DOSY and NOESY studies confirmed the presence of the complex inside **CR$_6$**. In details, a NOESY experiment evidenced dipolar couplings between *i*-Pr groups of **10** and both the OH residues and the aromatic H-atoms of **CR$_6$**. In addition, a DOSY experiments calculated very similar diffusion coefficients for the resonances of **CR$_6$** and those of encapsulated **10**. The authors estimated that the (*i*-Pr-NHC)AuOTf complex occupy a 30 % of the volume of the cavity, leaving sufficient space to accommodate the 4-phenyl-1-butyne **11** as a substrate.

One the most intriguing aspect of natural enzymes is their ability to select a substrate in a mixture of potential candidates. [20] An example of this substrate selectivity was reported in the hydration reaction of alkyne[20] in the presence of gold-complex (*i-Pr*-NHC)Au(OTf) **10** as catalyst and **CR$_6$** as nano-reactor (Scheme 4). In this study, [20] a competition experiment was performed between ethynylcyclohexane **15**, 1-octyne **16**, and 1-dodecyne **17** (Scheme 4) which were treated at 40 °C with 5 mol % of catalyst **10** with respect to each substrate. In the absence of **CR$_6$**, the reaction showed a short induction period for all substrates, while a quantitative conversion of **15**, **16**, and **17** was obtained after 250 minutes.

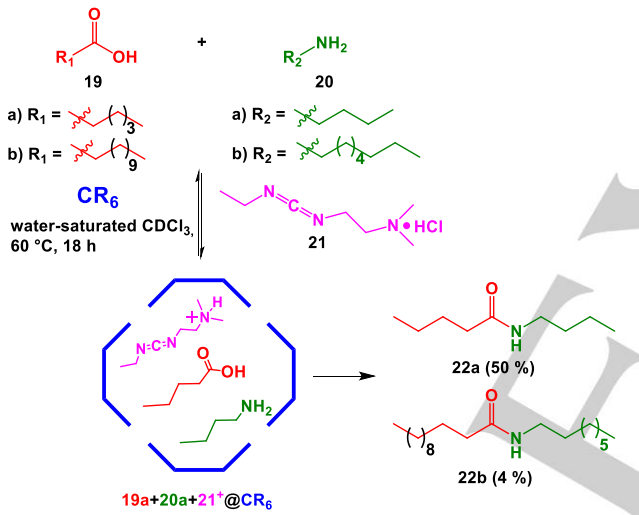


Scheme 4. Substrate selectivity displayed by **CR$_6$** in an alkyne hydration catalyzed by (*i*-Pr-NHC)Au(OTf) **10**.[20]

A close inspection of the reaction profile[20] in the absence of **CR$_6$** revealed that 95 minutes were required to reach 50 % of conversion of **15**, while longer times are required in the case of **16** and **17**. When the hexameric capsule **CR$_6$** (33 mM with respect to **1**) was added to the reaction mixture of **15**, **16**, **17** (65 mM each one), and **10** (3.3 mM), then the hydration of the

substrates became slower. In fact, a 50 % of conversion of **15** was obtained only after 4 h. Interestingly the reaction profile in the presence of **CR$_6$** showed a 48 % of conversion of **15** after 155 minutes, while **16** and **17** were converted only in 25% and 21% yield, respectively. A close inspection of the kinetic profile of the reaction in the presence of **CR$_6$** showed an initial reaction rate for **15,** three times higher than that obtained for the other two substrates **16** and **17** (3.4/1.3/1.0, ratios), while in the absence of **CR$_6$**, the reaction showed the same initial reaction rate for all the alkynes (1.5 : 1.0 : 1.0). In conclusion, these data suggested a marked preference of **CR$_6$** for the smaller alkyne **15**. Probably, this is due to the cyclic structure of **15** which matches perfectly the residual space available inside **CR$_6$** and left by the encapsulated catalyst **10.**

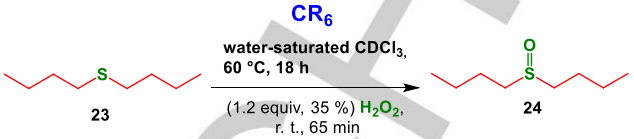
The substrate-selection ability of **CR$_6$** was also shown in the amide synthesis combining carboxylic acids and primary amines,[21] both of different lengths (Scheme 5) in the presence of carbodiimide condensing agent **21$^+$**.



Scheme 5. Substrate selectivity displayed by **CR$_6$** in amide synthesis.[21]

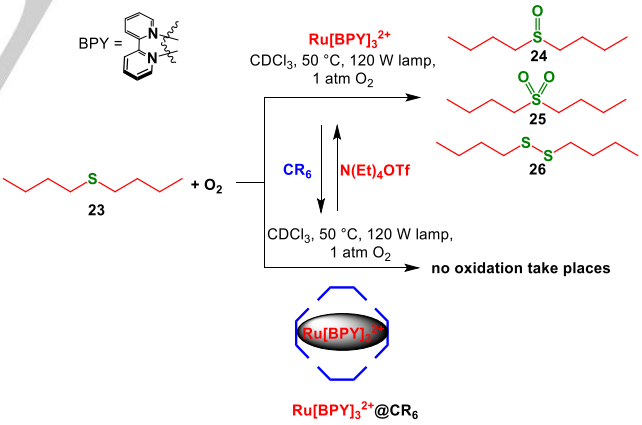
In this example **CR$_6$** doesn't work as catalyst, but through the encapsulation of reagents acts as "reagents-selector".[21] In fact, after the encapsulation of the cationic condensing agent **21$^+$** inside **CR$_6$**, stabilized by cation···π interactions, the residual space available permits the co- encapsulation of amines and carboxylic acids of appropriate length. When the hexanoic **19a** and dodecanoic **19b** acids were mixed with butylamine **20a** and octylamine **20b**, in water saturated $CDCl_3$, at 60 °C, for 18 h,[21] in the absence of **CR$_6$** the reaction, led to the formation of all four possible amides in similar amounts. Differently in the presence of the capsule (81.4 mM with respect to **1**), the shorter amide **22a** was obtained in 50 % of yield, while **22b** in 4 %.

The hexameric capsule **CR$_6$** is able to catalyze the sulfoxidation of thioethers in the presence of H_2O_2 as oxidant.[22] When dibutyl sulfide **23** was treated in the presence of 1.2 equivalents of H_2O_2 in water-saturated $CDCl_3$, at 25 °C, in the absence of **CR$_6$** only 10 % of product **24** was detected after 90 min. Differently, in the presence of 10 mol % of **CR$_6$** the oxidation of **23** to **24** was complete in 65 min (Scheme 6).



Scheme 6. Sulfoxidation of thioeters in the presence of **CR$_6$** as nano-reactor and H_2O_2 as oxidant.[22]

The authors, evidenced that the reaction is catalyzed within the nano-reactor through a dual synergic activation: (i) the capsule is able to activate the H_2O_2 through H-bond interactions with the OH resorcinol groups of **CR$_6$** (H_2O_2 displaces the bridging water molecules in the H-bond seam of **CR$_6$**) and (ii) the inner cavity of **CR$_6$** plays a crucial role in the stabilization of the polar transition state derived by the reaction between the oxidant and the thioethers. NMR experiments clearly showed the encapsulation of sulfone **24** inside **CR$_6$**, thanks to the appearance of up-field shifted resonances in the range −0.75 to −1.5 ppm attributable to sulfone **24@CR$_6$**. The sulfo-oxidation is chemoselective, in fact no oxidation of **24** to the corresponding sulfoxide was observed after 24 hours at room temperature under the conditions reported in Scheme 6.

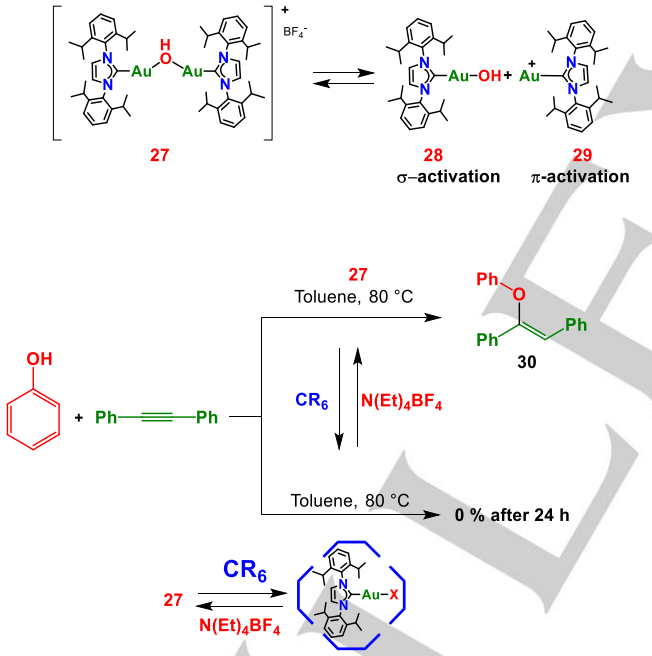


Scheme 7. Switching the activity of the photoredox catalyst $[Ru(BPY)_3]^2$ by encapsulation and release within **CR$_6$**.[24]

Zen and coworkers [23] have shown that the photoredox oxidation of thioethers to sulfoxide is mediated by the catalytic complex $[Ru(BPY)_3]^{2+}$ in the presence of O_2 (converted into H_2O_2). Prompted by these results, Scarso and Strukul[24] showed that, through reversible encapsulation and release of $[Ru(BPY)_3]^{2+}$

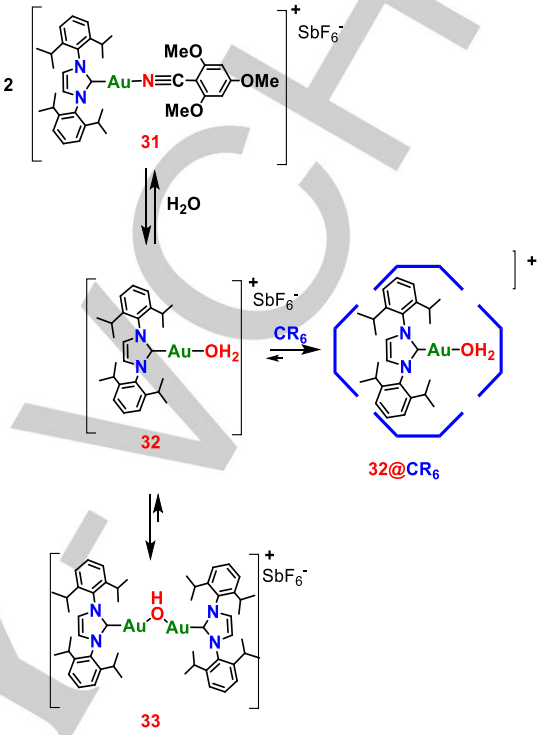
from **CR$_6$** cavity (Scheme 7), it has been possible to switch the catalytic activity of the Ru-complex.[24] When dibutyl sulfide was added to a $CDCl_3$ solution of $[Ru(BPY)_3]^{2+}$ at 50 °C, under the visible light provided by a 120 W lamp and under 1 atm of O_2, then dibutyl sulfoxide **24** was obtained in 32 % yield after 3 h (Scheme 7), while sulfone **25** and dibutyl disulfide **26** were obtained in 2 and 5 %.[24] When the reaction was repeated in the presence of 6 equivalents of **CR$_6$**, (Scheme 7) which is able to encapsulate $[Ru(BPY)_3]^{2+}$, then complete inactivity of the catalyst was observed. [24] Details of the encapsulation of $[Ru(BPY)_3]^{2+}$ within **CR$_6$** were provided by NMR spectroscopy. [24] A ^{1}H NMR spectrum of a $CDCl_3$ solution of $[Ru(BPY)_3]^{2+}$ evidenced four resonances in the aromatic region, which after addition of **CR$_6$** were upfield shifted at 6.6 ppm as a result of encapsulation. The photocatalytic activity of $[Ru(BPY)_3]^{2+}$ was switched-on after addition of a competitive guest such as $(NEt_4)(OTf)$ which was able to displace the photocatalyst from the cavity of **CR$_6$** (Scheme 7), leading to the complete restarting of its catalytic activity.[24]

Another interesting example of switching of reactivity modulated by **CR$_6$** was reported by Nolan and Reek.[25] As it is known,[26] dinuclear gold complex **27** (Scheme 8) is able to activate appropriate substrates by a dual-activation mode.[26]



Scheme 8. Switching the activity of the gold catalyst **27** by encapsulation and release within **CR$_6$**.[25]

In fact, **27** forms mononuclear complexes **28** and **29** in solution, which are able to activate substrates by σ and π–activation,[27] respectively (Scheme 8). Regarding the reaction in Scheme 8, the σ-activation and π -activation play a crucial role in the activation of the phenol and alkyne, respectively. Thus, when phenol and diphenylacetylene were mixed in the presence of **27** in toluene as solvent at 80 °C, the formation of **30** was complete in 60 minutes.



Scheme 9. Equilibria proposed by Ballester and Echavarren[28] in the process of encapsulation of the Au complex **33** inside **CR$_6$**.

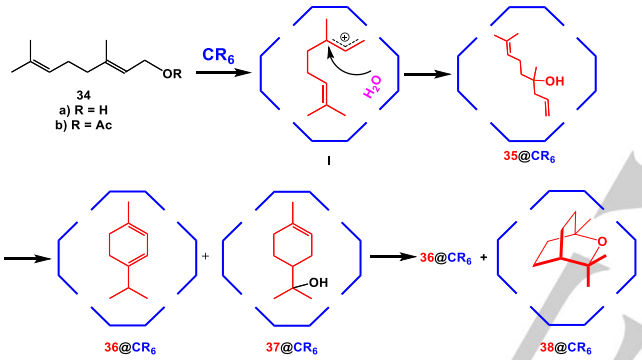
Differently, when **CR$_6$** was present in the reaction mixture no reaction takes place after 24 h, because the catalytically active mononuclear species were encapsulated inside **CR$_6$**. In summary, in the presence of **CR$_6$**, the typical dual-activation mode of **27** (Scheme 8) is inhibited by the encapsulation of the monuclear complexes which was verified by ^{1}H NMR and 2D DOSY experiments. Interestingly, the catalytic activity of **27** is switchable, by adding a competing guest that would bind more strongly to the cage than the gold catalyst. In fact, after addition of $Et_4N^+BF_4$ the catalytic activity was restored and product **30** was obtained in 89% yield after one hour.

The complexation abilities of the hexameric capsule **CR$_6$** toward mononuclear Au-complexes had previously been highlighted by Ballester and Echavarren.[28] As it is known[29] in wet $CDCl_3$ solution, the gold complexes exchange between different polynuclear species. Thus, when a $CDCl_3$ solution of resorcinarene **1** (Figure 1) and complex **31** was washed with water, then the existence of an equilibrium between *μ*-OH aqua complex **32** and dimer **33** was postulated. In the presence of **CR$_6$**, aqua complex **32**, was selectively encapsulated thanks to a better steric matching with the cavity of **CR$_6$**. Evidences for the selective encapsulation of aqua-complex **32** inside **CR$_6$** were obtained by DOSY experiments, which calculated a diffusion

coefficient value for the methyl signals assigned to the *i*Pr groups of **32@CR$_6$**, very similar to the diffusion coefficient calculated for **CR$_6$**. This confirms that the gold complex and the hexamer correspond to the same supramolecular aggregate.

1.2. The Hexameric Resorcinarene Capsule as Catalyst

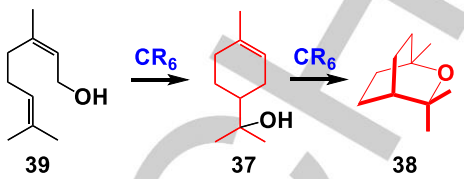
A literature survey revealed that the hexameric resorcinarene capsule is a catalyst by itself for different organic reactions. In fact, **CR$_6$** shows the following catalytically relevant features: a) ***Cation···π catalysis*** - due to the stabilization of cationic intermediates and transition states through cation···π interactions with the π-electron rich aromatic cavity of **CR$_6$**; b) ***Brønsted acid catalysis*** - **CR$_6$** shows remarkable Brønsted acidity (pK_a = 5.5-6.0 measured in water-saturated $CDCl_3$ relative to the reported amines pK_a values in water);[13] c) ***H-bond catalysis*** - the bridging water molecules of **CR$_6$** may act as H-bond donating groups.[14]



Scheme 10. The conversion of geranyl alcohol **34** to eucalyptol **38** inside the hexameric capsule **CR$_6$** (10 mol %).[30]

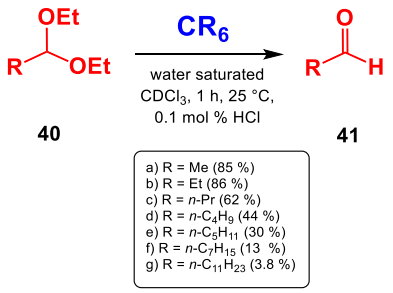
Brønsted acid and Cation···π catalysis. The cyclization of terpenes inside the hexameric resorcinarene capsule represents a milestone[5l, 30-32] in the topic of the supramolecular catalysis in confined spaces. In *Nature*, terpenes are biosynthesized through a tail-to-head cyclization catalyzed by cyclase enzymes, which are able to stabilize cationic intermediates and transition states in their hydrophobic active site. The hexameric **CR$_6$** capsule was able to mimic the enzyme pocket of cyclase enzymes. In fact, when geranyl alcohol **34** was encapsulated inside **CR$_6$** (10 mol %), then its conversion to eucalyptol **38** was observed after 72 h (Scheme 10).[30] Inside **CR$_6$**, the substrate **34a** was initially protonated and converted to allylic cation **I**, which was hydrated to linalool **35**. Within the first ten hours, other two products were formed: cyclic *α*-terpinene **36** and *α*-terpineol **37**.

This latter and linalool **35** were converted to eucalyptol **38** after 72 h (Scheme 10).[30] In a successive study,[31] the authors showed that the cyclization of geranyl acetate **34b** (Scheme 10) to *α*-terpinene **36** occurs only if the capsule **CR$_6$** and DCl acid (or HCl, in traces) are simulatenously presents. Interestingly, this study showed that **CR$_6$** and the acid work in a synergistic fashion.[31]



Scheme 11. The conversion of nerol **39** to eucalyptol **38** in the presence of **CR$_6$**.

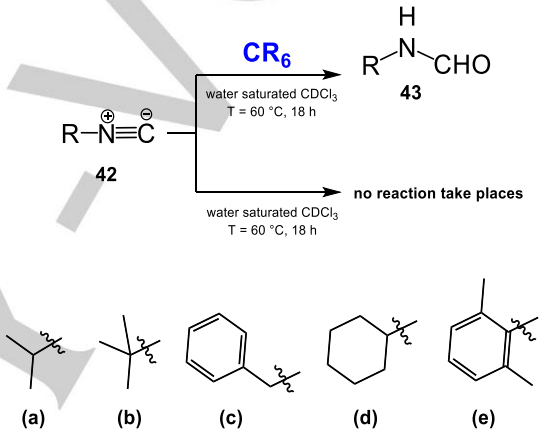
On the basis of this consideration, Tiefenbacher suggested that the capsule acts as an apoenzyme while the corresponding holoenzyme, catalytically active, is formed upon protonation by acid traces. Thus the proton transfer from the protonated **CR$_6$H$^+$** to geranyl acetate **34b** activates the substrate and favours the formation of the allylic carbocation **I** (Scheme 10) via a S_N1-type pathway. The S_N1 mechanism of the initial step in the cyclization cascade was confirmed by a control experiment in which 2-fluorogeranyl acetate was reacted with **CR$_6$H$^+$**: under standard conditions, no traces of cyclic terpene products were detected.[31] When nerol **24** was investigated as the substrate (Scheme 11), in the presence of **CR$_6$** *α*-terpineol **37** was obtained as the principal product after the first 20 h. Successively, **37** was converted into eucalyptol **38**.[30] In summary, in these works a tail-to-head cyclization of terpenes takes place inside the hexameric capsule thanks to a combination of Brønsted acid and cation···π catalysis. This example may be considered as a successfully mimicking of cyclase enzymes principally due to the strong similarities between the hydrophobic natural active site and the aromatic cavity of **CR$_6$**: both are able to stabilize cationic transition states and intermediates by cation···π interactions. Very recently, the same group reported[32] an example of terpene cyclase mimicking, in which the linear sesquiterpene (2*E*,6*Z*)-farnesyl acetate was cyclized to *δ*–selinene and 10-*epi*-zonarene in 18 and 10 % yield, respectively, in the presence of **CR$_6$H$^+$** (10 % of **CR$_6$** and 3 % of HCl). The formation of *δ*–selinene occurs inside the **CR$_6$** cavity through a 1,10-cyclization followed by a reaction cascade in which the stabilization of cationic transition states and intermediates plays a crucial role. When (2*E*,6*E*)-farnesyl acetate was used the selectivity for *δ*–selinene was significantly lower, while no-traces of *δ*–selinene was observed in the cyclization reactions of (2*Z*,6*E*)- and (2*Z*,6*Z*)-farnesyl acetate. Thus, the capsule **CR$_6$** shows a strict selectivity for the stereochemistry of the double-bonds of the farnesyl-acetate substrate. In addition, the cyclization of monocyclic sesquiterpenes was reported.[32] Thus, the cyclofarnesyl acetate was cyclized to the tricyclic sesquiterpene isolongifolene in the presence of **CR$_6$H$^+$**.



Scheme 12. Substrate selectivity in the hydrolysis of acetals **40a-g** exploiting the system **CR$_6$**/HCl.[13a,b]

The system **CR$_6$**/HCl was exploited in the hydrolysis of acetals (Scheme 12).[13a,b] When 1,1-diethoxyethane **40a** was added to a water-saturated $CDCl_3$ solution of **CR$_6$** (3.3 mM), in the presence of 0.1 mol % of HCl as cocatalyst,[13b] the corresponding aldehyde **41a** was obtained in 86 % after 1 h at 25 °C.[13a] Interestingly, the addition of a competitive guest such as Bu_4NBr to the reaction mixture in Scheme 12 (before addition of substrate) resulted in the inhibition of the catalytic activity of **CR$_6$** and the product **41a** was obtained in 1% after 1 h. In a significant way, no hydrolysis of acetals was observed when the reaction in Scheme 12 was performed in absence of **CR$_6$**.[13a] In conclusion, these results showed that the reaction take places inside the cavity of **CR$_6$** and in the presence of HCl as cocatalyst. In fact, as shown in a recent report, [13b] the inherent acidity of **CR$_6$** was not sufficient, *per se*, for the catalysis of the hydrolysis of acetals inside the capsule (Scheme 12). In fact, no hydrolysis was observed, when the reaction in Scheme 12 was performed in the absence of the cocatalyst HCl. In details, the authors show clearly[13b] that the presence of HCl (0.1 mol %) as cocatalyst in the reaction mixture in Scheme 12, accelerates the reaction, increasing both, the acidity of **CR$_6$** and the catalytic turnover inside the capsule. Encapsulation of the acetals inside **CR$_6$** was shown by ^{1}H NMR studies. In fact, the alkyl signals of encapsulated acetals were upfield shifted to the region of 0.6 to −2 ppm. The reaction rate slowed down in the presence of acetals bearing longer alkyl groups: in this case the authors suggested that the smaller acetals are cleaved much more rapidly due to a more efficient encapsulation (faster encapsulation). Interestingly, using acetic acid (*p*Ka = 4.8) instead of **CR$_6$**, under identical conditions, no hydrolysis of acetals was observed. This results evidenced the crucial role played by the **CR$_6$** cavity in the hydrolysis of acetals. Also in this case the π–electron rich cavity of **CR$_6$** is able to stabilize cationic intermediates and transition states in the hydrolysis reaction.

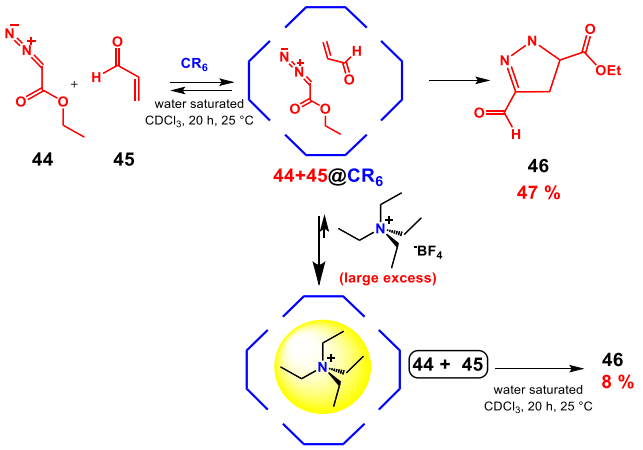
Scarso and Strukul[33] reported an example of catalysis of the hydration reaction of isonitriles to *N*-formylamides (Scheme 13), exploiting the Brønsted acidity of the hexameric capsule **CR$_6$**. First of all, the encapsulation of isonitrile derivatives was confirmed by ^{1}H NMR studies. In fact, after the addition of cyclohexyl isonitrile **42d** to a solution of **CR$_6$** in a water saturated $CDCl_3$ solution, new upfield shifted resonances appeared in the ^{1}H NMR spectrum in the range 0.1 to – 0.7 ppm. The authors postulated that the encapsulation of isonitriles within **CR$_6$** is due to the stabilization of the carbenic structure of the isonitrile in the π-electron rich aromatic cavity of **CR$_6$**. While no reaction was observed when the isonitrile derivatives were dissolved in water saturated $CDCl_3$ solution at 60 °C, a complete conversion of **42d** into the corresponding *N*-formylamide **43d** was achieved in the presence of **CR$_6$,** under the same conditions. The proposed mechanism for the general isonitrile hydration occurs via protonation of the C atom thanks to its carbenic like structure followed by water addition. Probably, after the protonation, the capsule **CR$_6$** is able to stabilize the cationic intermediate by means of interaction with the π-electron rich internal cavity of **CR$_6$**.



Scheme 13. Hydration reaction of isonitriles inside the hexameric capsule **CR$_6$**.[33]

Also in this case, a substrate selectivity was observed. In fact, in the presence of **CR$_6$** the neutral isonitriles were encapsulated inside its hydrophobic cavity where they were hydrolyzed with a substrate depending efficiency. In details, for **42a,c,d**, (Scheme 13) a quantitative hydrolysis was observed within 18 h in the presence of **CR$_6$**, while lower conversions were detected for substrates **42b,e.**[33] The ability of the hexameric capsule **CR$_6$** to encapsulate isonitrile derivatives has been exploited for the synthesis of substituted 1*H*-tetrazoles from trimethylsilyl azide.[34] Thus, when the cyclohexyl isonitrile **42d** (133 mM) and $TMSN_3$ (133 mM) were mixed in the absence of **CR$_6$**, then the reaction did not take place even after 5 h at 60 °C.[34] Differently, in the presence of **CR$_6$** (13.3 mM) the formation of the corresponding 1*H*-tetrazole was observed in quantitative yield after 6.5 h at 60 °C.[34] Generally, 1*H*-tetrazoles with substituents at position 1 are prepared by reaction of a large excess of the harmful hydrazoic acid (HN_3) with isonitriles. Thus, thanks to the catalytic efficiency of **CR$_6$** the hydrazoic acid can be replaced by $TMSN_3$. Finally, the authors showed that, from a mechanicistic point of view, an hydrogen-bonding activation of the reaction takes place inside the hexameric cage **CR$_6$**.

The hexameric capsule showed catalytic abilities toward the 1,3-dipolar cycloaddition reactions between neutral diazoacetate esters and electron-poor alkenes to give 4,5-dihydro-1Hpyrazole derivatives (Scheme 14).[35]

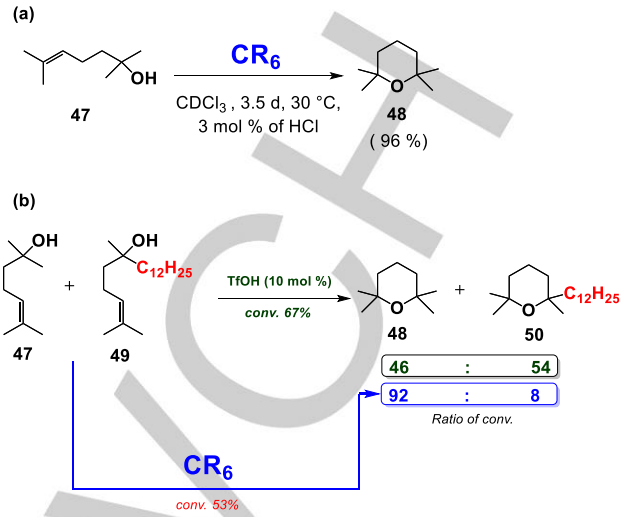


Scheme 14. Example of inhibition of the catalytic activity of the hexameric capsule **CR$_6$** with competitive tetraethylammonium guest.

When ethyl diazoacetate **44** and acrolein **45** were reacted inside the cavity of **CR$_6$** the product **46** was formed in 47% yield, while in the bulk solvent, in the absence of **CR$_6$**, only a 12% yield was obtained.[35] The presence of the neutral guest ethyl diazoacetate **44** inside the hexameric capsule **CR$_6$**, was confirmed by NMR spectroscopy. In fact, when **44** was added to a water-saturated $CDCl_3$ solution of **CR$_6$**, then new resonances at negative values appeared in the up-field region of the ^{1}H NMR spectrum. Analogous results were observed with *tert*-butyl diazoacetate and benzyl diazoacetate. Also in this case the encapsulation of diazoacetate inside **CR$_6$** was rationalized on the basis of the stabilization imparted by the electron-rich internal surface of the capsule on the carbene-like guest.

Interestingly, when a large excess of tetraethylammonium BF_4^- was added to the reaction mixture (Scheme 14) then a marked decrease of the catalytic activity of **CR$_6$** was observed and the product **46** was formed in 8% yield. [35] 1D NMR experiments clearly showed that the tetraethylammonium cation was encapsulated inside **CR$_6$** where establishes favorable cation···π interactions.

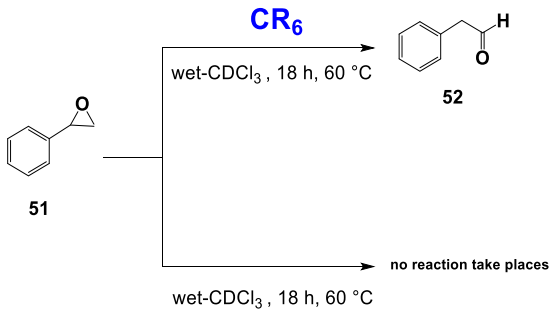
The intramolecular hydroalkoxylation of unactivated hydroxyolefins to the corresponding cyclic ethers has been catalyzed inside the hexameric capsule **CR$_6$** (3.3 mM, and 33 mM of substrate **47**)(Scheme 15a) in the presence of 3 mol % of HCl as cocatalyst.[36,13b] The reaction in Scheme 15a can occur in the bulk solution in the presence of strong Brønsted acids (like triflic acid), while surprisingly, mild conditions have been reported for the catalysis in the confined environment of **CR$_6$**.



Scheme 15. Intramolecular hydroalkoxylation of hydroxyolefins promoted inside **CR$_6$** (3.3 mM) and in the prersence of HCl as cocatalyst compared to acid catalysis in the bulk solvent.[36, 13b]

In fact, thanks to the catalytic features of the capsule **CR$_6$** in the presence of HCl as cocatalyst,[13b] the conversion of γ,δ-unsaturated alcohols gave, after few days at 30 °C, the corresponding tetrahydropyran derivatives in good yields (45-96%). Initially, the encapsulation of hydroxy olefin **47** was evidenced by the appearence of new signals in the up-field region (0.5 to –0.6 ppm) of the ^{1}H NMR spectrum of **47** in the presence of **CR$_6$**.[36] The amount of water in the reaction mixture (Scheme 15a) plays a crucial role:[36] in fact, using regular $CDCl_3$ instead of water-saturated $CDCl_3$, the reaction rate (Scheme 15a) increases. Under these conditions the hydroxy olefin **47** was converted in **48** in 96 % yield after 3.5 d at 30 °C**.** The hydroalkoxylation of **47** was slowed down by addition of Bu_4NBr to the reaction mixture (Scheme 15a). The competitive tetrabutylammonium guest, occupying the cavity of **CR$_6$** inhibits its catalytic activity. Analogously, no conversion of **47** in **48** was observed in the absence of **CR$_6$.** The reaction acceleration observed for the reaction in Scheme 15a is due to an initial protonation of the substrate inside the cavity of **CR$_6$**, favored by the presence of HCl as cocatalyst,[13b] and to the stabilization of the cationic intermediates and transition states by cation···π interactions with the aromatic walls of **CR$_6$**. Also in this case, a substrate selectivity was observed when a mixture of differently sized olefins was used (Scheme 15b). In detail, when an equimolar mixture of alcohols **47** and **49** was treated with **CR$_6$** as catalyst (3.3 mM), the reaction proceeded with high selectivity, and the smaller substrate **47** was completely converted (98%) while the larger alcohol **49** showed a lower conversion (8%). As a control experiment, when triflic acid was used as catalyst in the bulk solution, the intramolecular cyclization reaction in

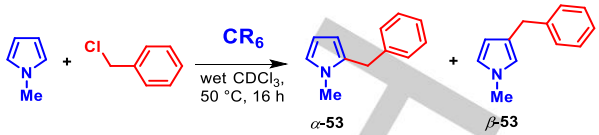
Scheme 15b afforded a 1:1.1 mixture of tetrahydropyran derivatives **48** and **50.**



Scheme 16. Epoxide isomerization promoted by **CR$_6$** (6 mM).[37]

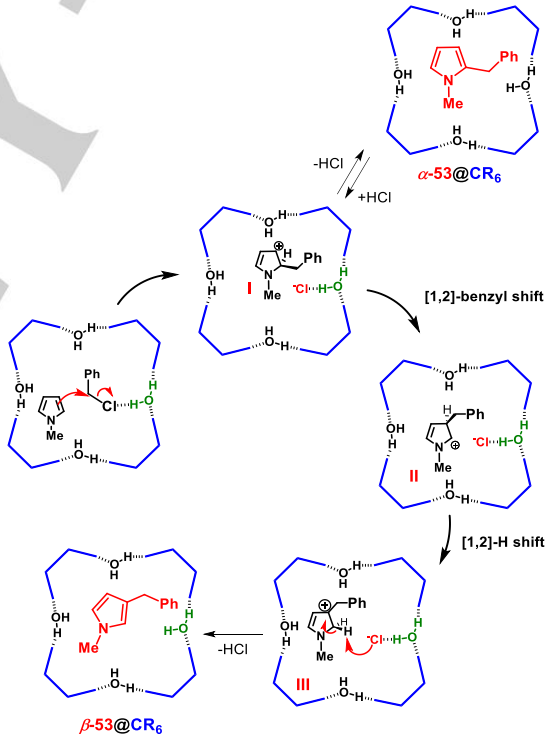
The Brønsted acidity of the hexameric capsule **CR$_6$**, has been exploited for the catalysis of isomerization of epoxides to the corresponding carbonyl compounds.[37] In details, when the styrene oxide **51** was stirred in a water-saturated solution of $CDCl_3$ at 60 °C for up to 18 h (Scheme 16), no hint of isomerization or decomposition of **52** was observed. Differently, when a catalytic amount of **CR$_6$** (6 mM) was added to the $CDCl_3$ solution of **51** (44 mM), under the same conditions, then the isomerization to phenylacetaldehyde **52** was obtained in 69% yield after 3 h, while quantitative formation of the product was achieved after 18 h. Interestingly, when the reaction was conducted in the presence of monomeric 4-*n*-hexylresorcinol no formation of **52** was observed, excluding the direct involvement of the resorcinol moieties in the catalytic isomerization reaction. It is known that the isomerization of epoxides to carbonyl compounds is an acid-catalyzed reaction, thus the reaction was repeated using acetic acid as catalyst observing no formation of **52**. This clearly indicates that both, the Brønsted acidity and the cavity effect of **CR$_6$** work in synergistic fashion. In fact, the elctron-rich aromatic cavity of **CR$_6$**, play a crucial role in the stabilization of cationic intermediates and transition states during isomerization reaction in scheme 16. In fact, when the tetrabutylammonium BF_4^- was added to the reaction mixture in Scheme 16, then the cationic guest was rapidly encapsulated with concomitant inactivation of the catalytic activity of **CR$_6$**.

Recently, our group has shown [14] that the presence of water molecules with *H-bond donating free valence* (see Figures 1 and 2) can be useful in the catalysis of Friedel-Crafts (FC) benzylation of arenes and heteroarenes with the hexameric resorcinarene capsule **CR$_6$** (Scheme 17). In details, the benzylation of *N*-methylpyrrole proceeds with high efficiency (80 % after 16 h) and regioselectivity inside the capsule **CR$_6$** (52 % mol) , in water-saturated $CDCl_3$ at 50 °C (Scheme 17).[14]



Scheme 17. Friedel-Crafts reaction between *N*-methylpyrrole and benzyl chloride catalyzed by **CR$_6$**.[14]

When the reaction was performed in the bulk solution in the absence of **CR$_6$**, no hint of products **53** was detected. These results revealed an *capsule effect* on the reaction rate acceleration, when the reagents were confined inside the cavity of **CR$_6$**. In fact, when benzyl chloride and *N*-methylpyrrole were encapsulated inside **CR$_6$** a H-bonding interaction between the bridging water molecule, as H-bond donating group, and the chlorine atom of benzyl chloride, as H-bond acceptor group, led to the activation of the C–Cl bond (Scheme 18).

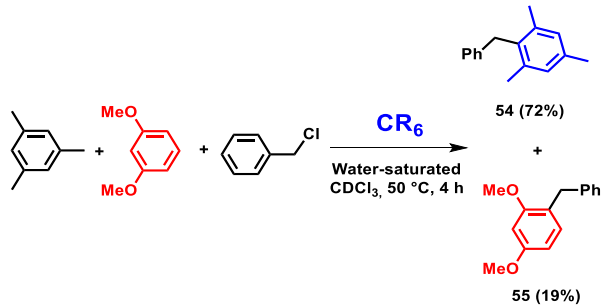


Scheme 18. Calculated[14] mechanism for the FC reaction between *N*-methylpyrrole and benzyl chloride inside the hexameric capsule **CR$_6$** .

QM calculations and experimental evidences[14] have shown that the H-bonding interaction between benzyl chloride and one bridged water molecule of **CR$_6$** plays a crucial catalytic role in the activation of the C–Cl bond (Scheme 18).

An *capsule effect* was also observed on the regioselectivity of the FC reaction in Scheme 17, which preferentially occurs at the β-position, with a β/α ratio of 90/10. This is an intriguing result. In fact, literature data showed that the α-position of *N*-methylpyrrole is the favored one in the FC benzylation. The *capsule effect* on the regioselectivity of this FC reaction was rationalized on the basis of QM calculations.

In detail, benzyl chloride was stabilized inside the **CR$_6$** capsule through the formation of a H-bonding interaction with a bridged water molecule (Scheme 18).



Scheme 19. Substrate selectivity in the benzylation of π-nucleophiles inside the hexameric capsule **CR$_6$**.[14]

At this point, an α-attack of *N*-methylpyrrole to the activated benzyl chloride occurs inside the capsule, leading to cationic intermediate **I** (Scheme 18) stabilized through cation$\cdots\pi$ interactions. This intermediate can directly evolve to the less favored α-**53** regioisomer, while the more abundant β-**53** one is formed through a [1,2]-benzyl shift to form the intermediate **II** (Scheme 18). This latter, not being able to directly lose the β-proton because posteriorly localized with respect to the chlorine atom (Scheme 18), undergoes a [1,2]-H shift, to give the intermediate **III**, which is re-aromatizated to β-**53**.The preferential formation of the β-**53** regioisomer inside the capsule **CR$_6$** is rationalized on the basis of the QM calculations, which indicate that the encapsulated product β-**53**@**CR$_6$** is thermodynamically more stable than α-**53**@**CR$_6$**. In fact, the calculations indicate that the retro-FC from α-**53**@**CR$_6$** to the cationic intermediate **I** (Scheme 18) proceeds with a low energy barrier (6.1 kcal/mol) and consequently, in the long run, the reaction exclusively provides the thermodynamic product β-**53**@**CR$_6$**.

The capsule **CR$_6$** is also able to discriminate between π-nucleophiles which occupy different positions along the Mayr's scale. [38] In fact, mesitylene was benzylated faster than 1,3-dimethoxybenzene inside **CR$_6$** capsule (Scheme 19), [14] despite the greater π-nucleophilicity of this latter.[38]

Summary

In conclusion, in this mini-review we have examined the literature data regarding the catalysis in the nanoconfined cavity of the hexameric resorcinarene capsule. The results here reassumed clearly show that the hexameric resorcinarene capsule **CR$_6$** is a valid supramolecular catalyst. Its large inner cavity can accommodate a discrete number of reactants, and in this confined space, a reaction acceleration is usually observed by virtue of the nano-confinement effect. Experimental evidences show that the regio and stereochemistry of the reactions that occur inside the **CR$_6$** capsule can diverge with respect to the results in the bulk solvent. These phenomena can be ascribed to the formation of more compact transition states and to the different spatial relationships between the molecules when these latter are blocked inside the restricted space of the capsule. Finally, the self-assembled **CR$_6$** cage show the typical catalytic features of the natural enzymes, such as the following.

- *Substrate selectivity:* numerous reports show that the hexameric cage is able to select the substrate on the basis of the steric matching with its inner cavity.
- *Regioselectivity and stereoselectivity*: The reactions catalyzed inside **CR$_6$** usually show regio- and stereoselectivity, which normally diverge with respect to the reactions in bulk solvents.
- *Stabilization of the transition state*: the hexameric capsule **CR$_6$** is able to accelerate the chemical reaction rate through the stabilization of the intermediates and transition states by secondary interactions, such as cation$\cdots\pi$ or H-bonding interactions.
- *Mechanism of catalysis:* the reactions between molecules confined inside in the hexameric capsule **CR$_6$** are accelerated by mechanisms reminiscent of the enzyme catalysis. In details, the **CR$_6$** capsule displays catalytic features such as, Brønsted acid catalysis, stabilization of cationic transition states and intermediate by cation$\cdots\pi$ interactions. Finally, the bridging water molecules in **CR$_6$** can work as H-bond donating groups playing a crucial role in the activation of the substrates by H-bonding interactions.
- *Inhibition with competitive guests:* the catalytic activity of the hexameric capsule **CR$_6$** is depressed by the presence of competitive guests, such as ammonium cations, which show high affinity for the π-electron rich cavity of **CR$_6$**.

It is now clear that the catalysis of organic reactions in nanoconfined spaces provides novel perspectives as concerns efficiency, stereo- and regiochemical outcomes, and certainly will continue to further stimulate the imagination of the scientists for a long time. It can be envisioned that future challenges will focus on the fine engineering of the space geometry and on the exploitation of further possible catalytic functions.

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Keywords: supramolecular catalysis • artificial enzyme • hexameric capsule • resorcinarene • nanoconfined environment

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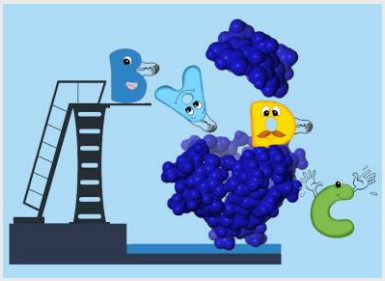
MINIREVIEW

The catalytic abilities of the hexameric capsule are reminiscent of the *modus operandi* of the natural enzymes. Inside the cavity of the capsule, the reagents are confined in a restricted space where in close proximity they react faster with regio and stereoselectivities. Like in the natural systems, the hexameric cage shows: substrate selectivity, stabilization of transition states and intermediates by secondary interactions and inhibition by competitive guests



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The Hexameric Resorcinarene Capsule at Work: Supramolecular catalysis in Confined Spaces