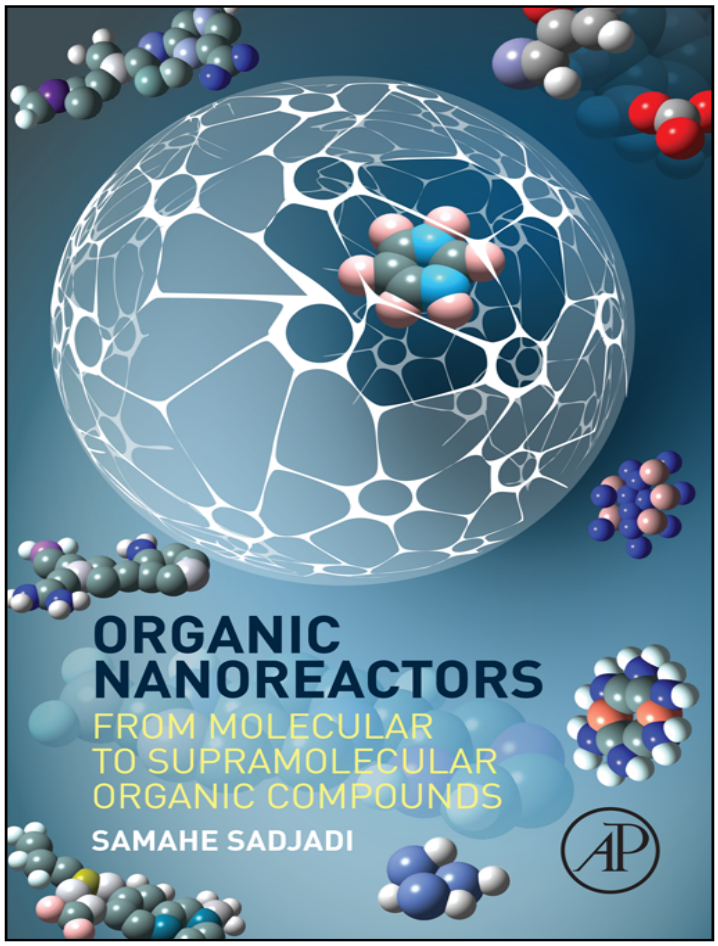




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Chapter 7

# Catalysis Within the Self-Assembled Resorcin[4]arene Hexamer

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## 1 CATALYSIS WITHIN CAVITIES

Since most chemical processes require the presence of a catalyst in order to be synthetically effective, the study of catalysis at all levels is one of the fundamental topics in chemistry. The development of new systems able to mimic some of the astonishing features typical of enzymes is a strategic issue for the scientific community and one of the main endeavors of research in the field of catalysis. Enzymes are polypeptidic molecules that, thanks to their folding in water and sometimes aided by the presence of specific molecular species as coenzymes, are able to impart accelerations of several order of magnitude to organic transformations, showing also high chemo-, regio-, and/or enantioselectivity and specificity [1]. These properties are basically due to recognition events between enzyme and substrate, that is, selected from the medium, but even more importantly by recognition and stabilization of the reaction transition state hosted by the active site. In this specific cavity, substrate molecules can be bound and selectively transformed into products through a perfectly juxtaposed combination of supramolecular weak interactions as well as reversible covalent interactions. The affinity between the active site and the substrate has been extensively investigated to explain the remarkable catalytic activity of enzymes. At first sight the high size and shape complementarities between the two are quite evident, especially considering the adaptation undergone by the enzyme during the process. In fact, a sort of continuous variation in the cavity shape ensures efficient substrate recognition, desolvation, preorganization, and the stabilization of the transition state of the reaction [2], eventually leading to substrate selective conversion [3].

The fascinating properties characterizing enzymes are still unrivaled by artificial catalysts. For this reason, an increasing number of research groups

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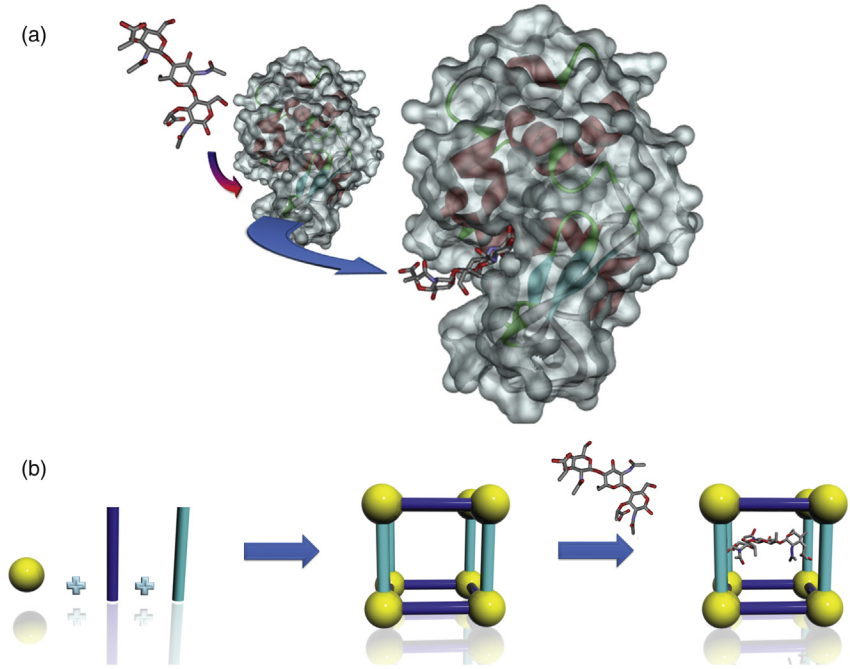


**FIGURE 7.1** Comparison between (a) the binding of the substrate by the enzyme and (b) the construction of supramolecular assemblies exploiting weak intermolecular interactions to obtain supramolecular self-assembled catalysts.

are focusing their activities toward the development of artificial homogeneous catalysts capable of mimicking some of the properties of natural enzymes. Even though molecular recognition in artificial host–guest systems has reached extremely high levels of sophistication, the application of these principles to the stabilization of transition states is still an uphill struggle. As one of the most obvious and peculiar properties of enzymes is the presence of a very large surface area compared to the substrate size, the creation of de novo–designed catalysts has to face the difficulty of synthesizing elaborated tridimensional structures large enough to completely surround the substrates in order to provide a large surface for contact. Examples of templated polymeric catalysts and dendrimers have appeared in recent years, but supramolecular chemistry and self-assembly processes provide in some cases much simpler solutions.

The idea consists in spontaneously creating the catalyst in solution through the self-assembly of simple units, thus creating higher molecular weight structures by highly directive and predesigned interactions [4] with proper cavities or environments where substrates can be bound and transformed (Fig. 7.1) [5], with the ultimate goal of enzyme mimic [6].

Depending on the chemical nature of the solvent, examples of self-assembling supramolecular catalysts [7,8] have been found in water using

surfactants forming micelles characterized by catalytic properties [9] or with metal–ligand-based capsules [10,11] and hydrophobic capsules [12], all showing excellent examples of artificial enzymes (Fig. 7.2a–d) driven by a combination of hydrophobic effect, ion pairing, and other weak interactions.

As far as artificial catalysts in organic solvents are concerned, the formation of large assembled structures able to provide cavities to bind substrates is a rather difficult task and, compared to supramolecular catalysis in water, hydrogen-bonded capsules are the most rewarding structures for the development of self-assembled supramolecular catalysts, thanks to the reversible formation of the assemblies that ensures easy substrate ingress and product egress (Fig. 7.2e). Nevertheless, because of the necessity of excluding substrates and experimental conditions that compete with H-bond formation, the use of hydrogen bond-based assemblies in catalysis is less developed compared to supramolecular catalysis in water, as previously mentioned.

It is worth noting that the first landmark example of supramolecular catalysis within a self-assembled capsule was the so-called "soft ball," a larger version of the original "tennis ball" [13] reported by Rebek and coworkers operating in aromatic solvents. The softball capsule is a reversible supramolecular dimer obtained through hydrogen bonding between two subunits in which two glycoluril moieties are linked through rigid spacers. The cavity within this capsule has a volume of about 240–320 $Å^3$, that is capable of accommodating up to two guests slightly larger than benzene. This enabled the use of the "softball" as supramolecular catalyst for the bimolecular Diels–Alder reaction between benzoquinone and cyclohexadiene (Fig. 7.3a). The fast encapsulation of the two substrates within the "softball" promoted the formation of the Diels–Alder adduct with an acceleration of about two orders of magnitude with respect to the same reaction carried out in *p*-xylene in the absence of the supramolecular vessel. Unfortunately, the product proved to be an excellent guest for the capsule, and because of that the system was unable to perform more than one catalytic cycle [14]. To enable this supramolecular catalytic system to perform catalytic cycles, Rebek and coworkers simply optimized the size and shape of the two reagents with the aim of forming cycloaddition products characterized by low affinity for the capsule cavity. To this end, cyclohexadiene was replaced by 2,5-dimethylthiophene dioxide, and the Diels–Alder reaction was carried out in the presence of a catalytic amount of "softball" (10% with respect to each substrate) (Fig. 7.3b). Interestingly, the reaction rate was enhanced by the "softball" observing a 75% yield after 4 days at 40°C, while under the same condition only 17% yield was achieved in the absence of the supramolecular vessel [15]. Similarly to enzymes, the supramolecular catalyst showed a marked decrease of catalytic activity in the presence of *p*-cyclophane as competitive inhibitor that occupied the cavity, thus disabling access for the substrates that did not get converted into products.

Since this pioneering contribution, the development of artificial supramolecular catalysis within self-assembled capsules in organic solvents passed through the development of several new capsules characterized by different sizes, shapes,

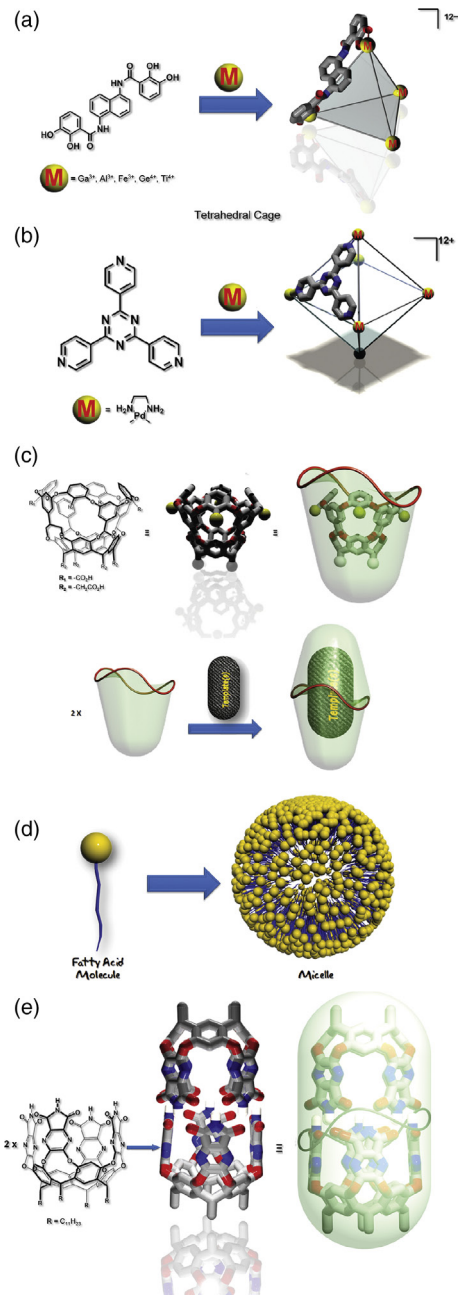


**FIGURE 7.2** Examples of supramolecular capsular catalyst in water: (a) tetrahedral capsule, (b) octahedral capsule, (c) hydrophobic dimeric capsule, (d) micelles from surfactants. Example of supramolecular capsular catalyst in organic solvent (e) H-bonded cylindrical capsule. *(Adapted from Zecchina A, Bordiga S, Groppo E, editors. Selective nanocatalysts and nanoscience. Weinheim: Wiley-VCH Verlag GmbH; 2011.)*

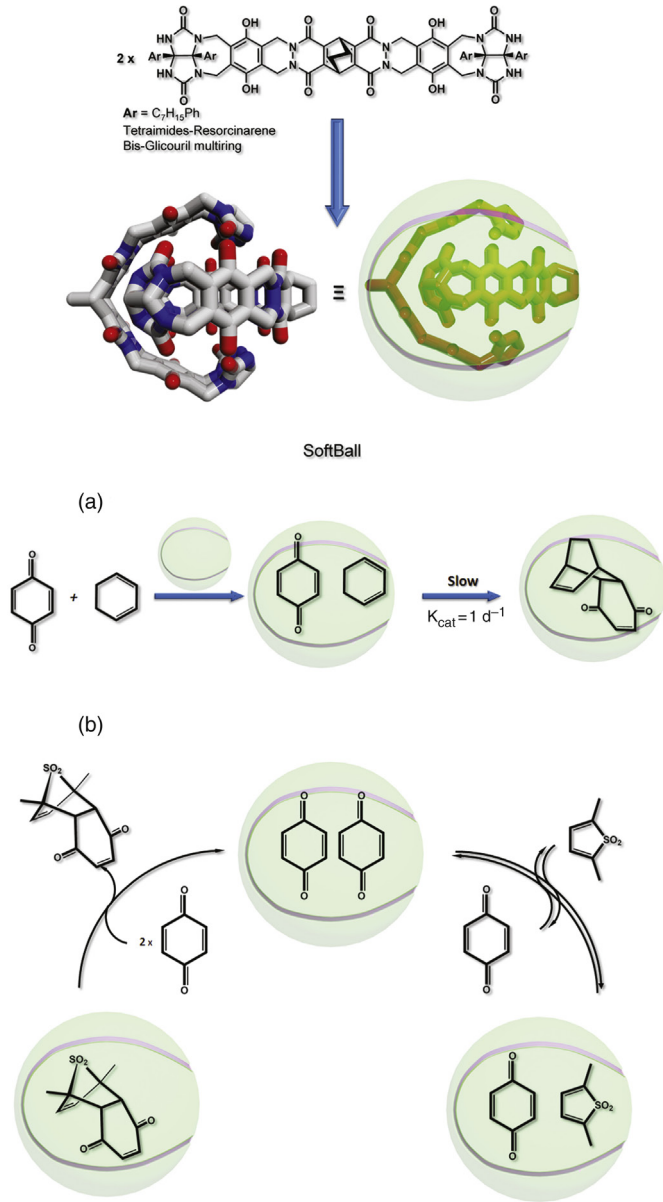


**FIGURE 7.3** Molecular structure of the "softball" (a) Diels–Alder reaction between benzoquinone and cyclohexadiene mediated by the "softball" in stoichiometric amount and (b) the catalytic cycle of the "softball" in the Diels–Alder reaction between benzoquinone and 2,5-dimethylthiophene dioxide. *(Adapted from Zecchina A, Bordiga S, Groppo E, editors. Selective nanocatalysts and nanoscience. Weinheim: Wiley-VCH Verlag GmbH; 2011.)*

and properties. Recently, the attention has been focused on the employment of one of the largest known self-assembling capsules in organic solvents based on the interaction between monomeric resorcin[4]arene structures, greatly favored by its simple and straightforward synthesis in multigram scale and its large cavity that allows multiple encapsulation of substrates and catalysts.

## 1.1 Hexamer of Resorcin[4]arene: Synthesis and Properties

Resorcin[4]arene is an easy to prepare molecule directly available by condensation between one to one stoichiometric amount of resorcinol and aliphatic aldehydes under acid catalysis in ethanol [16]. The calyx-like monomeric unit is obtained with all the OH moieties on one rim of the calyx structure; when long aldehydes are employed, nonflipping of the aromatic units is possible and the molecule is conformationally stable.

In 1997 MacGillivray and Atwood demonstrated the peculiar behavior in the crystal state of six resorcin[4]arene units and eight water molecules to self-assemble forming a spherical hexamer [17] through the simultaneous formation of 60 O—H…O hydrogen bonds in appropriate apolar organic solvents such as deuterated chloroform or benzene. Each water molecule develops three hydrogen bonds with the OH groups of three neighboring resorcin[4]arene molecules, while each monomer interacts through four intramolecular hydrogen bonds with other neighboring resorcin[4]arene causing a pseudospherical chiral racemic structure with a cavity of about 1375 $Å^3$. The retention in solution of the same hexameric structure observed in the crystal state was further demonstrated a few years later through NMR diffusion experiments by Cohen and coworkers that disclosed that C-undecyl-resorcin[4]arene self-assembles in water-saturated chloroform-d without any guest showing that eight solvent molecules fill the cavity (Fig. 7.4) [18]. Concomitantly, Rebek and coworkers showed that a positively charged guest with appropriate shape and size, such as quaternary ammonium compounds, could be encapsulated [19] thanks to extended cation-π interactions [20,21] with the internal surface of the capsule due to the high number of electron-rich aromatic rings present.

Moreover Tiefenbacher and coworkers reported the encapsulation of tertiary amines that are neutral guests incapable of developing hydrogen bonds. These authors studied the encapsulation of amines with different basicity demonstrating that the protonation of the amines was the cause of the encapsulation. The results showed that the delocalization of the negative charge along the entire structure of the self-assembled hexamer causes an acidity of the hexameric capsule considered as a sole entity much higher than the single molecules of resorcin[4]arene, estimating a $pK_a$ of about 5.5–6 that could be further increased through encapsulation of ammonium salts [22]. Apart from cationic guests, the capsule was shown to efficiently bind neutral species through H-bonding like carboxylic acids, aminoacids [23], and alcohols [24], present in large excess, even though in these cases it was not

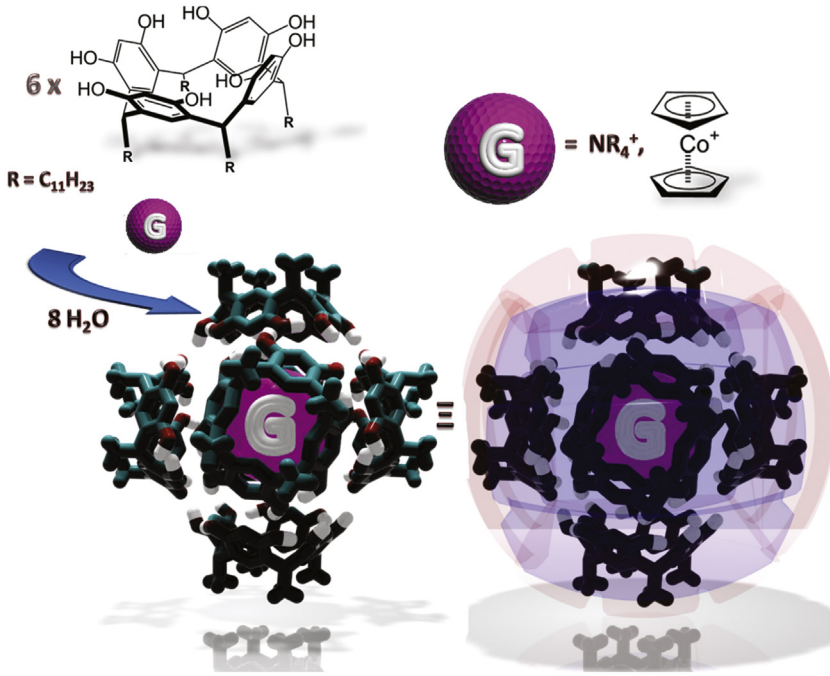


**FIGURE 7.4 Resorcin[4]arene in a wet organic solvent self-assembles forming the hexameric capsule that can host cationic guests.** *(Adapted from Scarso A, Borsato G. Self-assembly of organic supramolecular capsules. In: Gale PA, Steed JW, editors. Supramolecular chemistry: from molecules to nanomaterials, vol. 5. Chichester, UK: Wiley; 2012, p. 2085–2114.)*

clear whether the binding was between one resorcin[4]arene and one guest or between the self-assembled hexamer and six guests.

Soon after the discovery of the traditional host–guest properties of the resorcin[4]arene capsule, it became evident that this capsule represents an ideal supramolecular structure for several applications in homogeneous catalysis. Its use in catalysis is spurred by the simple and accessible synthesis of the monomer combined with the formation of a very large cavity that is a feature extremely difficult to find in other structures.

## 2 HEXAMERIC CAPSULE AS AN INHIBITOR

The first example published in the literature concerning the use of the hexameric capsule in catalysis was actually an example of catalytic modulation through encapsulation. Scarso and coworkers selected the very well known photocatalyst $[Ru(bpy)_3]^{2+}$ (bpy, 2,2′-*bis*-pyridine) that, thanks to its pseudospherical shape and its cationic character, perfectly fits the cavity of the capsule with the aim of investigating the effect of reversible binding on the photocatalytic activity of the metal catalyst [25].

It is in fact known that $[Ru(bpy)_3]^{2+}$ under visible light irradiation and in the presence of oxygen provides reactive species like singlet oxygen [26] or hydrogen peroxide [27]. The latter terminal oxidants can efficiently transform electron-rich substrates like sulfides into the corresponding sulfoxides. In their work, Scarso et al. investigated the possibility of modulating the catalytic activity of the $[Ru(bpy)_3]^{2+}$ by changing the solvation sphere of the catalyst through encapsulation and release in solution, while maintaining all the other experimental conditions such as temperature, presence of oxygen, and light irradiation unaltered.

The encapsulation of the Ru(II) complex in the presence of one equivalent of a capsule was confirmed by $^1$H-NMR analysis, demonstrating the complete disappearance of the four resonances of the original metal species in the aromatic region of the spectrum while new, extremely weak, broad resonances emerged upfield at 6.6 ppm. The complex could be released in solution with reappearance of the corresponding resonances by addition of an excess of a competitive cationic guest [28] such as $(NEt_4)(OTf)$. The reversible binding within the cavity was confirmed by UV-vis analyses demonstrating that, upon encapsulation, the maximum of absorbance for the complex at 455 nm slightly shifted about 8 nm to shorter wavelengths, and that in the presence of an excess of competitive cationic guest, the maximum of absorption in the UV-vis spectrum was restored to 453 nm. This showed that no alteration of the absorption properties of the complex was caused by encapsulation.

In the presence of visible light irradiation provided by a 120 W lamp and with 1 atm of $O_2$, the Ru(II) complex in solution promoted the oxidation of dibutyl sulfide to the corresponding dibutyl sulfoxide obtained in 32% yield. Under identical experimental conditions but in the presence of the capsule, the reaction did not occur as a consequence of the encapsulation of the Ru(II) photocatalyst. The catalytic activity was restored when repeating the same experiment with $[Ru(bpy)_3]^{2+}$ in the presence of both capsule and tetraethylammonium competitive guest, due to the displacement of the metal catalyst from the cavity of the capsule. Similar results were observed with other thioethers showing conversions to the corresponding sulfoxides that were dependent on the electron density on the sulfur atom; in all cases, no conversion was observed with the encapsulated Ru(II) catalyst. Since it was demonstrated that the absorption properties of the Ru(II) metal center were substantially not influenced by the capsule, it is likely that the inactivation provided by the capsule could be due to interrupted energy transfer from the Ru(II) center to $O_2$.

Operating a series of alternating additions of capsule to stop the oxidation reaction by encapsulation of $[Ru(bpy)_3]^{2+}$ (OFF state) followed by additions of excess of tetraethylammonium competitive guest with concomitant release in solution of $[Ru(bpy)_3]^{2+}$ (ON state), it was possible to operate a reversible switching of the photocatalytic activity of the complex, simply changing its solvation sphere without changing either the coordination on the metal or the experimental conditions (Fig. 7.5). Overall a stepwise kinetic profile for the

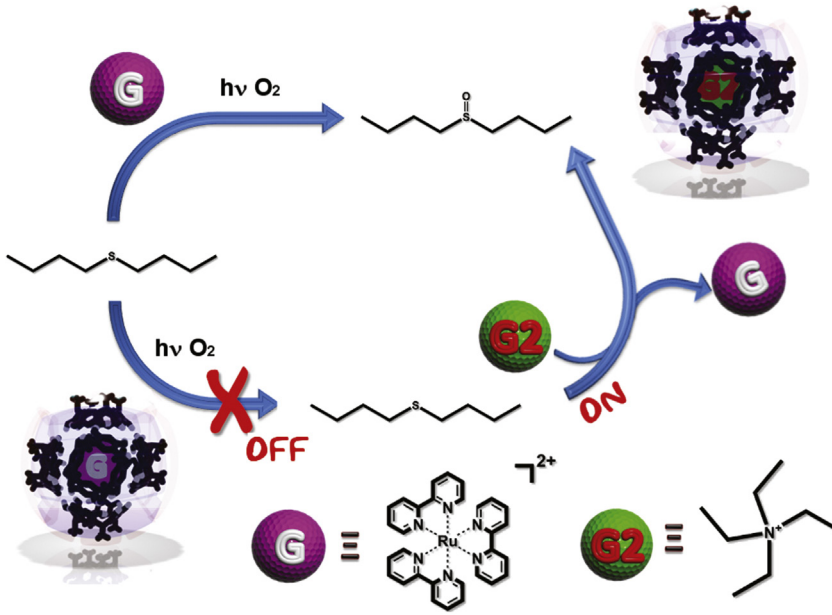


**FIGURE 7.5 Reversible sulfoxidation reaction in the presence of visible light and 1 atm. of $O_2$ mediated by encapsulation (OFF state) of $[Ru(bpy)_3]^{2+}$ and release in the presence of tetraethylammonium competitive guest (ON state).** *(Adapted from Ref. [25].)*

formation of the sulfoxide was obtained, representing the first example of this ON/OFF modulation. Instead of operating in a covalent manner on the catalyst, it worked at a supramolecular level on its solvation sphere.

## 3 HEXAMERIC CAPSULE AS A SUPRAMOLECULAR NANOREACTOR

The size of the cavity of the hexamer is sufficiently large to accommodate several solvent molecules, and the encapsulation of metal catalysts can be exploited to steer the reaction pathway of a catalytic reaction toward unexpected products due to the steric hindrance experienced by the substrate within the cavity on the way to the catalyst. It is known that, for several encapsulation phenomena, the space occupied by the guest molecules is slightly larger than the total volume available; in other words, the packing coefficient given as the ratio between the total volume of guests and the volume of the cavity is usually in the range 0.45–0.55, which is the same observed for most liquids [29].

Therefore, choosing transition metal catalysts characterized by the positive charge (a crucial need for encapsulation) and with reduced volume to allow the coencapsulation of substrates, it is possible to design reactions where the capsule dramatically changes the fate of the chemical transformation. This is a

typical property of enzymes where substrate binding, preorganization, and folding are pivotal for high levels of chemo, regio, and stereoselectivities.

In the following sections, examples are presented where the synergic effect between transition metal catalysts and the hexamer of resorcin[4]arene imparts unique product and substrate selectivities. In all cases, coencapsulation of the substrate and the catalyst is crucial.

## 3.1 Effects on Product Selectivity

While the study and the application of transition metal catalysis within water-soluble supramolecular hosts have been reported in recent years, the extension of the same approach to H-bonded capsules in organic solvent is still a rather uninvestigated field. The first example was reported by Scarso and coworkers using a cationic elongated Au(I) organometallic complex bearing a NHC ligand (NHC═the N-heterocyclic carbene 1,3-*bis*(2,6-diisopropylphenyl)imidazol-2-ylidene) that was suitable for encapsulation within the cavity of the resorcin[4]arene capsule. These complexes are well known for their catalytic activity in the alkyne hydration reaction; since the hexameric capsule requires the presence of water for self-assembling, the complex was investigated to compare the effects on its activity and selectivity of being free in solution or within the cavity of the capsule [30]. 4-Phenyl-1-butyne was selected as substrate since it could provide two hydration products, 4-phenyl-2-butanone or 4-phenyl-butanal, respectively obtained by attack of the water molecule either on the C2 of the alkyne moiety or on C1, together with a cyclic 1,2-dihydronaphthalene product derived by an intramolecular ring-closing reaction when activated by the Au(I) catalyst in the absence of water (Fig. 7.6).

Initially, the quantitative encapsulation of the cationic Au(I) complex was investigated, showing that in the presence of the equivalent of one capsule, all the resonances of the free complex disappeared and the $^{1}$H-NMR spectrum clearly revealed the presence of new upfield shifted resonances at −0.26 and 0.37 ppm attributed to the *i*-Pr residues of the ligand, while the vinyl resonances of the encapsulated complex appeared between 5 and 7 ppm. It is worth noting that the cationic nature of the complex is an extremely important prerequisite, as observed when comparing the affinity of the neutral (NHC)AuCl complex with one equivalent of capsule that showed only partial encapsulation and much larger amounts of free complex in solution. Confirmation of the quantitative encapsulation when using the cationic NHC–Au complex was obtained by 2D NOESY experiments that showed close contacts between the *i*-Pr residues of the Au complex and both the OH residues and the aryl proton in between the OH groups of the capsule, while DOSY experiments showed similar diffusion coefficients for the resonances of the capsule and those attributed to the encapsulated complex. Similarly to what was previously observed with the Ru(II) photocatalyst, the encapsulated NHC–Au(I) catalyst could be released in solution by addition of an excess of cationic tetraethyl ammonium tetrafluoroborate as competitive guest.

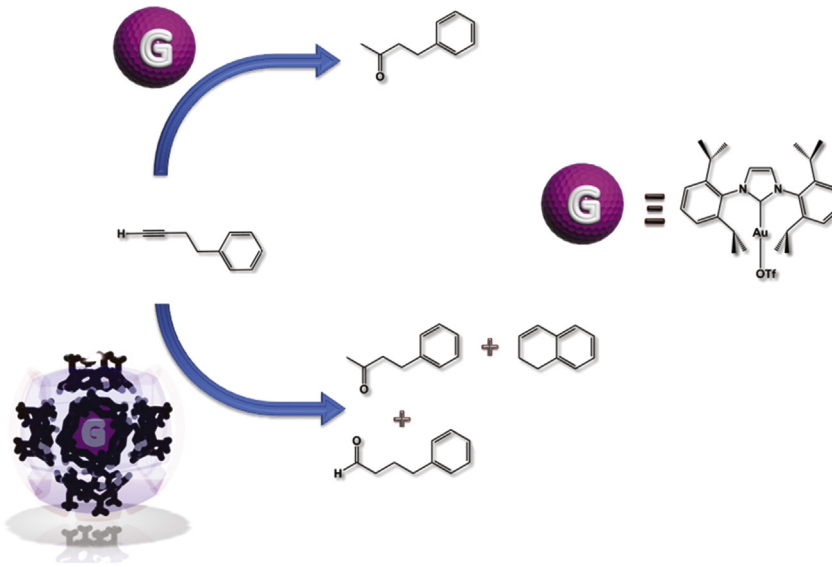


**FIGURE 7.6 The encapsulation of the NHC–Au(I) catalyst within the hexamer of resorcin[4]arene drastically changes the product distribution in the terminal alkyne hydration of 4-phenyl-1-butyne.** *(Adapted from Ref. [30].)*

When the Au(I) catalyst was tested at 70°C in the hydration reaction of 4-phenyl-1-butyne, two different scenarios were observed for the free complex in solution and for the encapsulated complex. In the first scenario, the reaction led exclusively and quantitatively within 30 min to the formation of the methyl ketone hydration product. In the second, the reaction was slower, showing after 400 min only 28% of conversion of the substrate; more interestingly, apart from the expected methyl ketone with 12% yield, significant amounts (4%) of the aldehyde were obtained, a novelty for Au catalysts. This demonstrates that the sterically constrained environment within the cavity was responsible for the steering of the regioselectivity of the reaction. Even more unexpected were both the presence of 1,2-dihydronaphthalene (12%), whose formation is likely to be favored by unusual folding of the substrate, and the difficult encapsulation of water, making the intermolecular hydration reaction comparable in rate with the intramolecular one.

As a further confirmation for the effect of the simple change of the solvation sphere of the catalyst, the hydration reaction with the encapsulated NHC–Au(I) complex was repeated, and after 400 min a large excess of tetraethylammonium competitive guest was added with concomitant release in the solution of the catalyst, changing the catalyst's selectivity and forming exclusively the methyl ketone as hydration product.

Overall, these experiments demonstrated that simply by changing the solvation sphere of the NHC–Au(I) catalyst, it is possible to drastically alter

the product distribution of the reaction, showing that yields and in particular chemo- and regioselectivities can be strongly affected by the capsule, leading to the formation of unusual products. In fact, the Au(I) catalyst has a volume of about 400 $Å^3$ and its packing coefficient is roughly 30%, leaving sufficient space for coencapsulating from two to four solvent molecules that can be replaced by the substrate that however, experiences more stringent steric requirements with respect to the reaction in the bulk solvent. The unusual regioselectivity observed in the hydration products could be due to the forced folding of the substrate, while the partial formation of the cyclic product could be due to difficult access for water into the cavity.

## 3.2 Effects on Substrate Selectivity

Selectivity is an extremely important property of chemical transformations, but usually we consider only the right side of a chemical equation. For catalytic reactions, the presence of several competitive substrates introduces another kind of selectivity, this one related to the ability of the catalyst to pick preferentially one substrate from the mixture and to convert the substrate into the corresponding products while leaving the other substrates behind. Artificial catalysts developed to display substrate selectivity are rare; in particular, heterogeneous catalysts such as zeolites due to their porosity can display this kind of selectivity due to their porosity, and selected examples are also known with catalytic polymers [31,32] and imprinted polymers [33]. As far as homogeneous catalysts are concerned, examples are limited to the kinetic resolution of racemates in which one of the enantiomers reacts more rapidly than the other [34] through covalent interaction of the substrate with the catalyst, while other examples deal with mixtures of substrates that differ quite remarkably in their structure away from the reacting functional group. Far less frequent are examples related to "homologous" series of substrates tested together toward a certain catalyst [35].

Conversely, enzymes, as hypothesized for the first time by Arrhenius in 1888 [36], are known for also being extraordinarily substrate–selective catalysts [37–40], and at first sight their ability to select substrates is related to their mechanism of action, which involves a recognition event forming a substrate–enzyme adduct before the true catalytic event (Fig. 7.7). To observe this property, a three-dimensional structure and a large interacting surface are required. To implement such concepts into traditional homogenous catalysts, it is necessary to increase the contact surface between catalyst and substrate, and this is possible through the use of encapsulated catalysts where the capsule impart the steric and electronic rules for the selection of the substrate. The substrate that is preferentially bound has access to the catalyst and is therefore converted. This approach has been observed more frequently for encapsulated metal catalysis within water-soluble capsules [41,42], while examples in organic solvents are very limited [43–45].

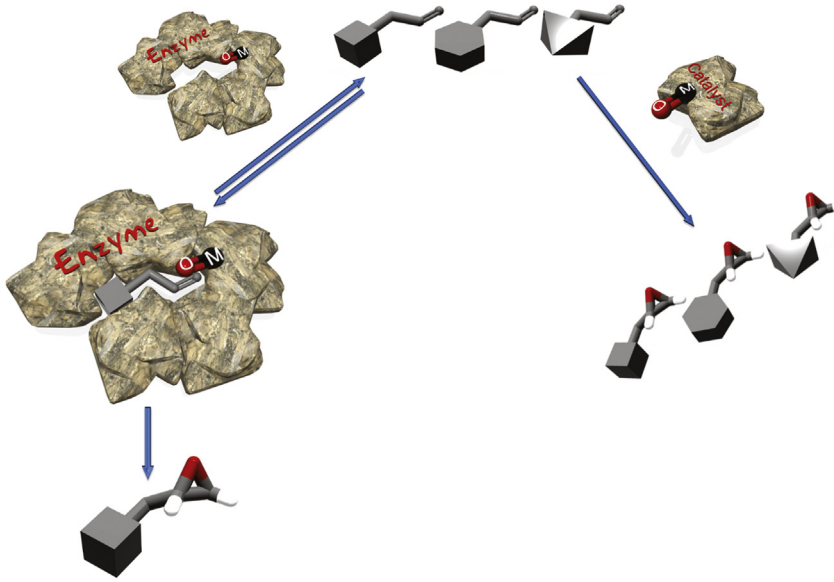


**FIGURE 7.7 Comparison between typical poor substrate selectivity displayed by a traditional homogeneous catalyst and the extremely high substrate selectivity typical of enzymes.** *(Adapted from Ref. [46].)*

On the basis of the effects observed on product selectivity in the alkyne hydration reaction mediated by the encapsulated NHC–Au(I) catalyst within the hexamer of resorcin[4]arene, Scarso and coworkers investigated the ability of the same supramolecular catalytic system in the selection of homologous series of substrates [46].

The competitive experiments were carried out with a series of terminal alkynes characterized by similar electronic properties but differing in portions of the molecule remote from the reaction site. For aliphatic alkyne, the three substrates ethynyl cyclohexane, 1-octyne (which represents an acyclic isomer of the former substrate), and 1-dodecyne were tested, with the free catalyst compared to the encapsulated catalyst. In the former case, after a short induction time, the initial reaction rate for the three substrates showed similar behavior for 1-dodecyne and 1-octyne, while the cyclic isomer, being slightly more electron rich, reacted 1.5 times faster (Fig. 7.8a). Encapsulation of the catalyst led to a magnification of the favorable hydration of the cyclic substrate that reacted more than twice as rapidly as the longer substrate. It is likely that extended linear substrates, that in their extended conformation are approximately 1.4 and 2.1 times longer than ethynyl cyclohexane, have to fold to better complement the residual space left available within the cavity occupied by the catalyst.

In order to exclude folding effects, three rigid aromatic terminal alkynes like phenylacetylene, 4-methyl-phenylacetylene, and 4-*t*-butyl-phenylacetylene, characterized by the same general shape but different lengths and electronic properties, were tested with the free and the encapsulated catalyst. In the bulk

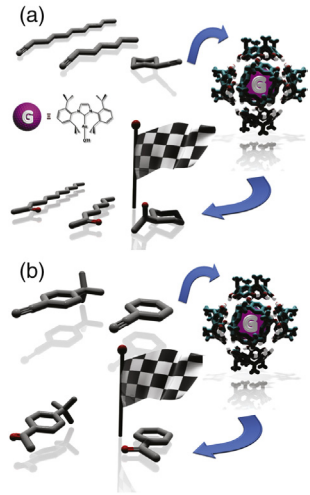


**FIGURE 7.8** Comparison of substrate selectivity displayed by the NHC–Au(I) catalyst in the hydration reaction of alkynes free in solution and encapsulated in the hexamer: (a) preferential hydration of cyclic ethynyl cyclohexane rather than acyclic aliphatic terminal alkynes and of (b) shorter rather than longer aromatic rigid alkynes.

solvent, the reaction was faster with the more electron-rich substituted alkynes, with relative initial rates of reaction equal to 1 to 1.4 to 1.5 for phenylacetylene, 4-methyl-phenylacetylene and 4-*t*-butyl-phenylacetylene, respectively. It is worth noting that, upon encapsulation, a complete inversion of the substrate selectivity was observed, with the smaller substrate that is more easily hosted in the residual space within the cavity, reacting faster than the 4-substituted phenylacetylenes (phenylacetylene:4-methyl-phenylacetylene:4-*t*-butyl-phenylacetylene 1.6:1.3:1.0) (Fig. 7.8b).

The previously described results represent another example of how the hexameric capsule can be efficiently employed as a nanometric reactor that provides unexpected selectivities by simply changing the second coordination sphere around a given homogeneous catalyst; especially because of the restricted space, selection of the substrates is possible, based on steric ground. The differences observed are quite significant if one considers that, apart from catalyst and substrates, space is also available for solvent molecules in order to reach the optimal packing coefficient range [29].

Aiming at demonstrating the potentialities of the hexameric capsule as a substrate selective nanoreactor, Scarso and coworkers extended the concept to a stoichiometric reaction. In particular, the steric hindrance due to the confined space within the cavity of the capsule was exploited in the substrate selective amide synthesis mediated by the cationic condensing agent 1-ethyl-3-(-3-dimethylaminopropyl) carbodiimide hydrochloride [47]. Similarly to the encapsulation of other cationic species, the cationic condensing agent that in

**TABLE 7.1** Catalytic Tests for the Competitive Coupling of Pairs of Amines with one Acid and Pairs of Acids with one Amine Mediated by the Carbodiimide Cationic Condensing Agent in the Presence or Absence of the Hexameric Capsule as Supramolecular Nanoreactor at 60°C, Time 18 h. +: Presence; −: Absence

| # | Acid | Amine | Capsule | Short/long amide ratio |
|---|---|---|---|---|
| 1 | $C_4$ | $C_4$<br>$C_8$ | − | 1.7 |
| 2 | $C_4$ | $C_4$<br>$C_8$ | + | 2.2 |
| 3 | $C_{12}$ | $C_4$<br>$C_8$ | − | 1.2 |
| 4 | $C_{12}$ | $C_4$<br>$C_8$ | + | 2.0 |
| 5 | $C_6$<br>$C_{12}$ | $C_4$ | − | 0.5 |
| 6 | $C_6$<br>$C_{12}$ | $C_4$ | + | 8.1 |
| 7 | $C_6$<br>$C_{12}$ | $C_{16}$ | − | 1.2 |
| 8 | $C_6$<br>$C_{12}$ | $C_{16}$ | + | 28 |

Adapted from Ref. [47], Royal Society of Chemistry.

chloroform exists as a mixture of two isomers (an an acyclic and a cyclic one) showed complete disappearance of all the resonances at the $^1$H-NMR upon addition of the equivalent of one capsule. The condensing agent did not suffer the presence of water when encapsulated, since the carbodiimide structure remained stable for several days without formation of the corresponding urea derivative. Conversely, addition of 10 equivalents of a competitive tetraethylammonium guest was sufficient to induce the release of the carbodiimide cation from the capsule.

Initially, solutions of the free and encapsulated condensing agent were tested for amide synthesis using combinations of two aliphatic amines characterized by different length of the aliphatic chain and one aliphatic carboxylic acid monitoring the formation of the two amides (Table 7.1). Under these conditions the substrate selectivity imparted by the capsule was not so high and the presence of the supramolecular system caused only a slight improvement in the short versus long amide products. The reason for the low substrate selectivity was ascribed

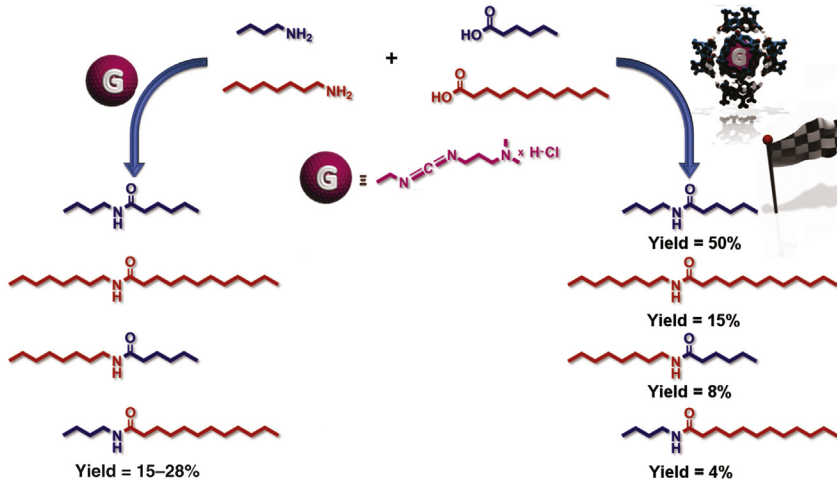


**FIGURE 7.9 Competitive coupling of a pair of carboxylic acids with a pair of amines mediated by the carbodiimide cationic coupling agent either in the presence or in the absence of the resorcinarene capsule.**

to the mechanism of the carbodiimide coupling, where the rate-determining step of the reaction is the attack of the carboxylic acid on the condensing agent forming an activated O-acylisourea followed by fast amine attack [48]. Better results were observed testing pairs of acids with one amine.

Much better substrate selectivity was observed in this second case, as the carbodiimide species reacted much faster with the shorter acids that are more easily accommodated within the cavity than the longer ones. Values for the shorter/longer amide ratios were observed between 8 up to 28 in the case of hexadecylamine (Table 7.1). No selectivity was observed with the condensing agent free in solution.

A further series of competitive experiments comprising two amines (butylamine and octylamine) and two (hexanoic and dodecanoic acid) acids were carried out, with the carbodiimide in pure solvent showing no selectivity and the four possible amide products being obtained in similar amounts (yields 28–12%). Conversely, when using the encapsulated condensing agent, the capsule showed a marked preference for selecting the combination of the shorter acid and the shorter amine; this led to the corresponding amide in 50% yield, while the longer amide was formed with only 4% yield (Fig. 7.9).

Overall, the hexameric resorcin[4]arene capsule showed very interesting selective properties for the condensation reaction between carboxylic acids and amines mediated by a cationic carbodiimide-based condensing agent; similarly to what was observed in the previous case for the alkyne hydration reaction, the capsule prefers the encapsulation of smaller and more compact substrates that react faster than longer ones.

## 4 HEXAMERIC CAPSULE AS A CATALYST

Examples of the application of the resorcin[4]arene capsule as the true organocatalyst are the majority. This is a consequence of the great opportunities offered by the capsule for the stabilization of reactions involving cationic intermediate species.

### 4.1 Hydrolysis and Hydration Reactions

Recent examples of promotion by the resorcin[4]arene hexameric capsule are the hydrolysis of acetals[22], exploiting the presence of water molecules as hydrogen-bonding units present in the supramolecular assembly. As an example, 1,1-diethoxyethane was efficiently converted into the corresponding carbonyl compound acetaldehyde in 85% yield after 1 h at room temperature in the presence of only 10 mol% of capsule, while negligible conversion was observed with the concomitant presence of tetrabutylammonium as a competitive guest for the cavity. The reaction proved to be sensitive to the substrate size, showing a gradual decrease of activity with the increase in the length of the acetal, with butanal formed in 62% yield, pentanal in 44%, octanal 13% and dodecanal in less than 4% yield. This observation was probably due to more efficient binding of smaller substrates within the cavity in combination with some solvent molecules to fit the proper packing coefficient [29].

As a simple example of competitive substrate selection, the reactivity of two very different substrates was considered in a competitive experiment. In a control experiment, the reaction of 1,1-diethoxyethane and the much longer 1,1-diethoxydodecane in the presence of trifluoroacetic acid led to the formation of both aldehydes in 24 and 41% yield, respectively. When the capsule was used as a supramolecular catalyst, the reaction was much more selective, with 83 and 2% yield for the shorter and longer aldehyde, respectively (Fig. 7.10).

The high electron density present in the cavity of the hexamer spurred the investigation of other classes of molecules that, apart from cationic species and H-bonding molecules, could be encapsulated and eventually act as substrates.

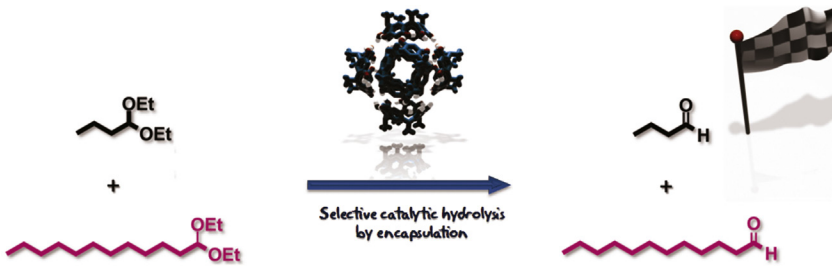


**FIGURE 7.10 Supramolecular catalysis in the hydrolysis of acetals imparted by the hexameric capsule that showed to be sensitive to the size of the substrate.** *(Adapted from Ref. [22] with permission of American Chemical Society.)*

Isonitriles are a special class of molecules [49], characterized by an extremely repellent odor, where the R—N≡C functional group can be described with either the zwitterionic form with positive N and negative C, or the predominantly carbenic electron-poor structure [50] that overall confer a linear geometry to the NC bond. Because of its electronic structure, isonitriles are largely investigated in multicomponent reactions, since the C atom of the isonitrile moiety reacts either as an electrophile [51] or as a nucleophile [52].

Scarso and coworkers disclosed the unique affinity of this class of neutral molecules for the cavity of the hexamer, observing that several isonitrile species, either with aliphatic or aromatic residues, were encapsulated in the presence of the resorcin[4]arene capsule [53], with the usual disappearance of the $^1$H NMR resonances for the free isonitrile and appearance of new broad upfield shifted resonances. For instance, addition of cyclohexyl isonitrile led to the formation of new resonances in the NMR spectrum in the range 0.1 to −0.7 ppm. In the cases of isopropyl-isonitrile, several new resonances were observed in the range −0.3 to −0.7 ppm and with *t*-butyl isonitrile a major single sharp resonance at −0.62 ppm (Δδ −2.07 ppm) was present. Similar results were observed for benzyl isonitrile and for an aromatic derivative. It was proposed that encapsulation of isonitriles was driven by the stabilization imparted by the electron-rich cavity to the electron-poor carbenic partial character of this class of molecules. Even more interestingly, it was observed that, upon gentle heating the system at 60°C, the complete conversion of the cyclohexyl isonitrile took place, with concomitant formation of the corresponding *N*-formylamide due to water addition to the R-NC moiety [54], while in the absence of capsule hydration of the substrate was negligible (Fig. 7.11).

After a series of control experiments carried out excluding the effect of the Brønsted acidity of the capsule and the involvement of the OH functional groups of the resorcin[4]arene, the effect of the cavity on the catalytic supramolecular hydration reaction was confirmed. In order to further substantiate this hypothesis, experiments were carried out repeating the hydration reactions of several isonitriles in the presence of the capsule and with an excess of tetraethylammonium as competitive guest, observing in all cases a marked decrease of the formation of the corresponding formamides.

Considering all the isonitriles tested, the catalytic activity of the supramolecular capsule was highly dependent on the size, shape, and electronic properties of the substrates, once again underlining the importance of proper packing coefficient of the coencapsulated species in the cavity. The catalytic activity of the capsule was due both to its mild acidity [22] that favors the protonation of the C atom of the isonitrile unit, and the stabilizing effects of the electron-rich cavity through cation-π interactions, which facilitated the hydration reaction.

## 4.2 C—C Bond-Forming Reactions

Diazoacetates represent a class of organic compounds bearing a nitrogen molecule as a terminal functional group (general formula $R_2C{=}N_2$) characterized

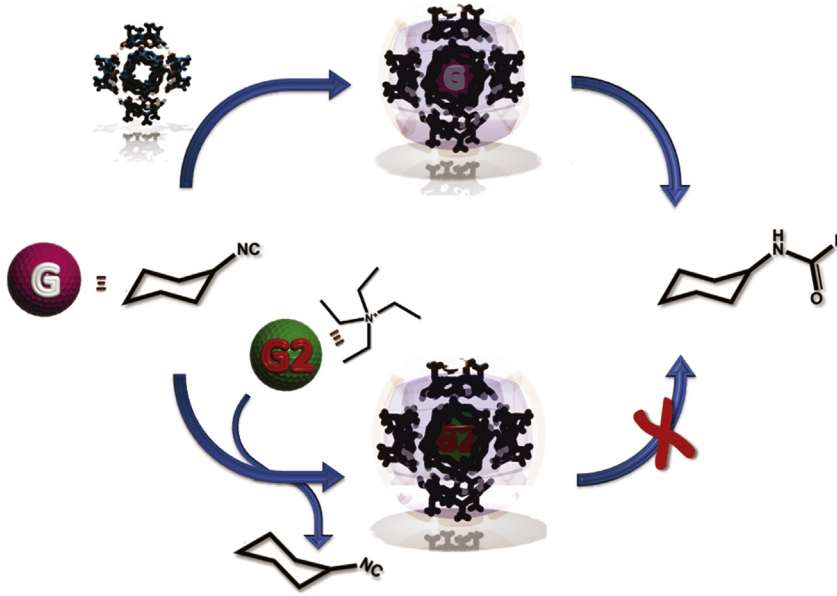


**FIGURE 7.11 Hydration reaction of cyclohexyl isonitrile catalyzed by the hexameric capsule and inhibited by the presence of tetraethylammonium cation as a competitive guest for the cavity.** *(Adapted from Ref. [53].)*

by an electronic structure with a positively charged central nitrogen atom and a negative charge delocalized between the terminal nitrogen and the carbon [55]. Beside this, these compounds are well-known carbene-precursors simply through the loss of a neutral di-nitrogen molecule [56]. Their carbene-like character prompted their employment as potential substrates for the hexamer capsule. Scarso and coworkers investigated their encapsulation in the resorcin[4]arene assembly and found that the efficient capsule catalyzed 1,3-dipolar cycloaddition between diazoacetate esters and electron-poor alkenes, leading to 4,5-dihydro-1*H*-pyrazole derivatives [57]. It is worth noting that Diels–Alder reactions are among the most investigated chemical transformations, displaying the effects of supramolecular unimolecular, or self-assembled capsules in water [58,59], while examples in organic solvents are rare apart from the seminal work of Rebek [15].

By means of $^{1}$H-NMR investigation, it was possible to observe the affinity of diazoacetate esters for the resorcin[4]arene capsule. In fact, in the presence of 10 equivalents of ethyl, *t*-butyl, or benzyl diazoacetate with respect to the capsule, in all cases new upfield shifted resonances appeared related to the encapsulated substrate in slow exchange on the NMR timescale (at $\delta = -0.86$ to $-1.06$ ppm for ethyl diazoacetate, $\delta = -0.50$ and $-0.52$ ppm for *t*-butyl diazoacetate, at $\delta \approx 6.4$ ppm and 3.8 ppm for benzyl diazoacetate, respectively). Simple integration of the resonances attributed to the encapsulated substrates

revealed a slightly higher affinity for *t*-butyl diazoacetate with respect to ethyl diazoacetate, while for benzyl diazoacetate the determination was not possible due to partial signal overlap. Especially with *t*-butyl diazoacetate, further 2D NMR experiments supported the encapsulation of the substrate with the NOESY spectrum that showed cross-peaks between the *tert*-butyl moiety of the diazoacetate compound and the aromatic CH group between the hydroxyl groups of resorcin[4]arene and the DOSY spectrum, showing same diffusion coefficients for the resonances of the capsule and those at $\delta \approx -0.50$ ppm for the encapsulated *t*-butyl moiety.

The interaction of the capsule with the diazoacetate esters did not lead to their decomposition. In fact, all substrates remained unaltered both in the presence and in the absence of the capsule, even at 50°C for 20 h in water saturated chloroform-d. More interestingly, since this class of molecules are good partners for the 1,3-dipolar cycloaddition reactions with a large series of dipolarophiles [60], their interaction with electron-poor alkenes was investigated in the presence and in the absence of the capsule in order to ascertain its supramolecular catalytic effects.

The cycloaddition reaction usually occurs under high concentration conditions, or it can be promoted by the presence of Lewis acids, leading initially to the formation of 4,5-dihydro-3*H*-pyrazoles that are unstable intermediates and that later convert into the corresponding 4,5-dihydro-1*H*-pyrazole isomers [61]. To explore the reactivity of diazoacetate esters in the cycloaddition reaction, initial experiments were carried out with acrolein. These showed that, in the absence of the capsule, the spontaneous formation of the corresponding 4,5-dihydro-1*H*-pyrazole was low (12% yield), while in the presence of the capsule it increased up to 47% in yield. Usual experiments with tetraethylammonium as competitive guest for the cavity added in large excess led to the formation of only 8% yield of the cycloaddition product, indicating a drop in the reaction rate when the cavity was occupied. In the presence of reduced amounts of competitive ammonium cation, an increase of product formation was observed as a consequence of the more accessible cavity of the capsule. In order to exclude a possible catalytic effect due to interactions between the hydroxyl group of the capsule and the substrate molecules, the reaction with 24 equivalents of resorcinol as a capsule mimic was carried out without observing substantial catalytic effects imparted by the hydroxyl groups of resorcinol.

The same catalytic effect imparted by the empty capsule was observed changing the diazoacetate ester in the reaction with acrolein. In fact, with the *t*-butyl derivative the reaction with the capsule led to 97% yield, and with benzyl diazoacetate 54% yield of the corresponding cycloaddition product was observed. In both cases, the presence of the capsule occupied by the ammonium inhibitor led to a marked decrease of product formation. The higher conversions obtained in the presence of *t*-butyl diazoacetate as substrate were probably due to the good affinity with the cavity by means of CH-$\pi$ interactions.

The catalytic effect of the capsule was extended also to the use of *t*-butyl diazoacetate, with other less reactive electron-poor alkenes following the reactions

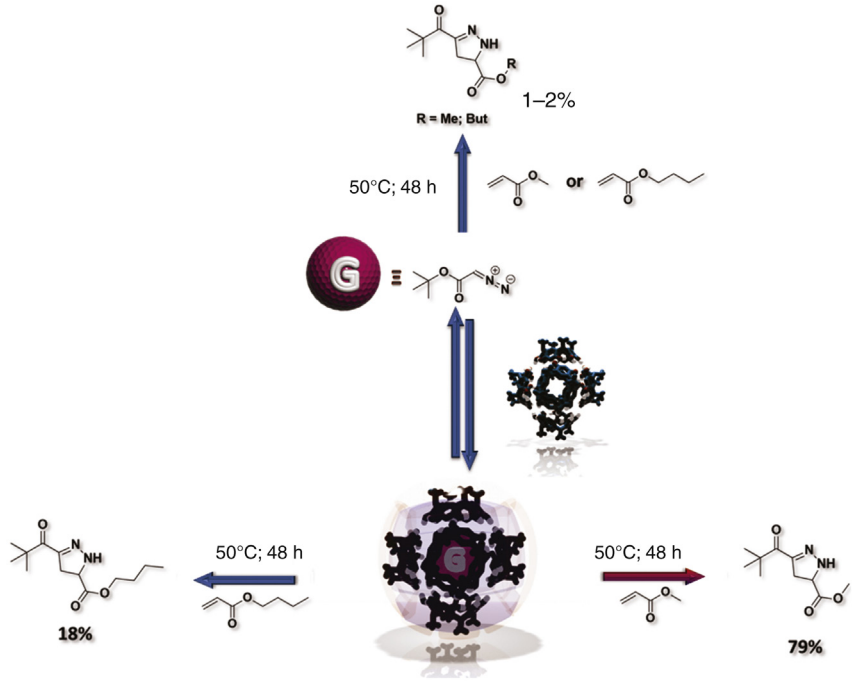


**FIGURE 7.12 1,3-Dipolar cycloaddition reaction between diazoacetate esters and electron-poor alkenes like acrylate esters mediated by the hexameric capsule.** *(Adapted from Ref. [57].)*

at 50°C because of the intrinsic lower reactivity of these alkenes. In particular, the reaction with $\alpha,\beta$-unsaturated aldehydes crotonaldehyde and *trans*-2-hexenal did not lead to the formation of the corresponding 4,5-dihydro-1*H*-pyrazoles when the reaction was carried out in the absence of the capsule or with the capsule occupied by the ammonium competitive guest, while with the free capsule yield of 95 and 79% for the corresponding cycloaddition products were observed after 48 h at 50°C.

The reaction, as further extended to acrylate esters such as methyl-acrylate and butyl-acrylate, displayed 79 and 18% yield in the reaction with *t*-butyl diazoacetate catalyzed by the resorcin[4]arene capsule, while with the occupied cavity yields were both lower than 5% and in the absence of the capsule decomposition products were detected (Fig. 7.12).

The results demonstrated the versatility of the resorcin[4]arene capsule in closely favoring the encapsulation of neutral diazoacetate esters and promoting through encapsulation the reaction with electron-poor alkenes with, once again, a supramolecular catalytic effect imparted by the electron rich cavity of the capsule.

Another example of the use of a modified hexameric resorcin[4]arene capsule for the activation of a cycloaddition reaction was reported by Shimizu and

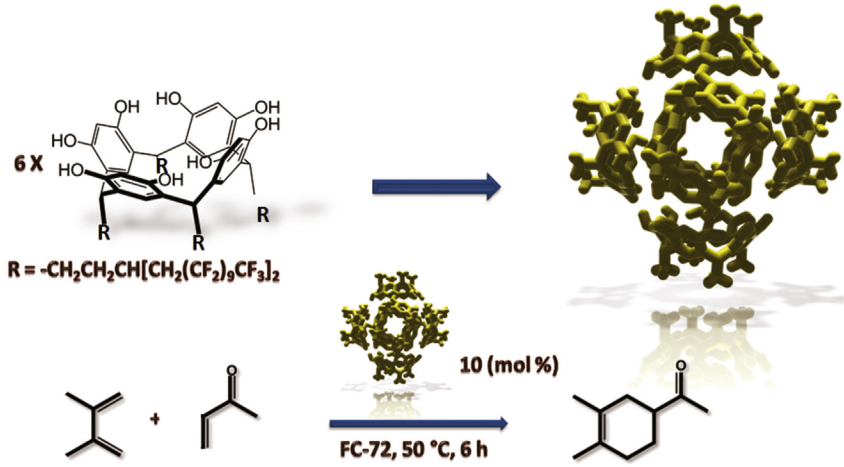


**FIGURE 7.13 Diels–Alder cycloaddition mediated by a hexameric capsule bearing fluorous feet operating in a fluorinated solvent and recycle of the supramolecular catalytic system.** *(Adapted from Ref. [62].)*

coworkers based on the fluorophobic effect exploiting the use of a hexameric capsule bearing fluorinated ponytails and operating in a biphasic fluorous/organic phase [62], with the latter composed of the mixture of diene and dienophile. It was demonstrated that the modified partially fluorinated resorcin[4]arene self-assembles in fluorinated solvents with small amounts of water, forming the hexameric capsule exactly as in traditional organic solvents. Considering the rather low solubility of traditional organic dienes and dienophiles for the fluorinated liquids, the idea was to force the reagents through the fluorophobic effect to enter the cavity of the capsule, thus favoring their cycloaddition reaction as a consequence of their high local concentration and proximity. The authors investigated initially the reaction between methyl vinyl ketone with 2,3-dimethyl-1,3-butadiene in perfluorohexane FC-72 at 50°C for 6 h observing only 10% yield in the absence of capsule, while with the capsule the yield of the adduct increased to 74% (Fig. 7.13). In order to prove that the reaction takes place within the cavity, a control experiment with a tetra-acetylated version of the resorcin[4]arene that cannot form the capsule was used, showing less than 18% yield, an indication that in this case too the reaction occurs predominantly within the cavity and that easy egress of the products and ingress of fresh substrates are possible, leading to interesting turnover numbers.

The effect of the composition of the fluorous solvent (from pure perfluorobenzene to pure perfluorohexane) was investigated observing higher yields in the cycloaddition products with higher fluorous content of the solvent, with a plateau region at approximately 50:50 perfluorobenzene:perfluorohexane; this is because of increased association constant of the capsule. The study was further extended to other combinations of dienes and dienophiles, showing in all cases increases from 2.3- to 21-fold in the experiments carried out in the presence of

the capsule, with interesting changes in the regioselectivity of the reaction showing higher *endo*/*exo* ratios than those obtained in the control reactions without a capsule, as in the case of the reaction between cyclopentadiene and methyl acrylate, with an increase of the *endo*/*exo* ratio from 2.9:1 to 5.5:1. The biphasic nature of the reaction spurred the investigation of the recyclability of the catalytic system. In fact, in the reaction between 2,3-dimethyl-1,3-butadiene and 3-buten-2-one in perfluorohexane with the capsule it was possible to recycle the supramolecular catalyst for overall five consecutive runs observing yields in the range 50-61% were observed for overall five consecutive runs. This represented the first example of the application of the resorcin[4]arene capsule in a catalytic reaction displaying efficient recycling of the supramolecular catalyst.

## 4.3 C-heteroatom Bond-Forming Reactions

The good affinity of isonitrile substrates for the cavity and the wide range of possible reactions offered by this class of molecules spurred the research of other chemical transformations where the capsule could act as a supramolecular catalyst. It is important to note that the combination with another substrate should be much faster than the reaction with water that is always present in the reaction medium because it is important for the self-assembling of the capsule. After seeking for various nucleophiles, Scarso and coworkers disclosed that the reaction between isonitriles and trimethylsilyl azide could be promoted by the capsule, leading to the rapid formation of the corresponding 1*H*-tetrazoles [63] without observing the formation of formylamide products typical of the hydration reaction.

In particular, the reaction between cyclohexyl isonitrile and the $TMSN_3$ was investigated both in the presence and in the absence of the hexameric capsule in water-saturated chloroform-d. While the reaction did not occur spontaneously, in the presence of a catalytic amount of capsule (10 mol%), the reaction was complete in slightly more than 6 h (Fig. 7.14). Also in this case, rigid control experiments like the use of a weak Brønsted acid of comparable acidity of the capsule and the use of resorcinol as a H-bond activating species similar to resorcin[4]arene did not justify the catalytic activity observed. Experiments in the presence of the capsule occupied by a competitive tetraethylammonium guest showed a marked decrease of product formation after the same reaction time (33% yield), confirming the crucial role of the encapsulation in the catalytic activity of the supramolecular capsule.

It also ruled out the formation of the tetrazole from the prior reaction of the corresponding formylamide with trimethylsilyl azide, which is a viable alternative reaction pathway [64]. In fact, the reaction of only the isonitrile with the capsule led to the formation of the corresponding formylamide and subsequent addition of trimethylsilyl azide to the this solution did not lead to the formation of the corresponding tetrazole.

The inhibiting effect imparted to the reaction by the presence of the ammonium species was even more evident with isonitrile substrates bearing

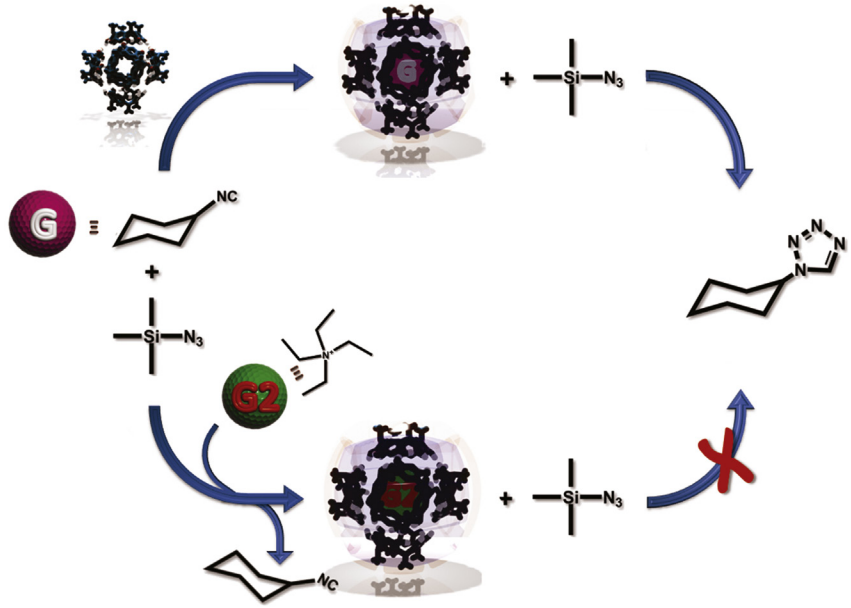


**FIGURE 7.14 Cycloaddition reaction between cyclohexyl isonitrile and trimethylsilyl azide catalyzed by the hexameric capsule and hampered by the rpesence of tetraethylammonium as a competitive guest for the cavity of the capsule.** *(Adapted from Ref. [63].)*

aromatic moieties in their molecular structure, as with benzyl isonitrile (free capsule 93% yield, occupied capsule 6% yield) and naphthyl isonitrile (free capsule 81% yield, occupied capsule 4% yield). The catalytic activity observed in this cycloaddition reaction was a further confirmation of the ability of the hexameric capsule to favor the stabilization of isonitrile addition intermediates.

## 4.4 Cyclization Reactions

As mentioned in the introduction, exploiting the known weak Brønsted acidity of the capsule (pKa 5.5–6) in combination with its affinity to uptake alcohols as neutral guests through H-bonding, Tiefenbacher and coworkers investigated the effect of the capsule in the uptake and intramolecular hydroalkoxylation of unactivated hydroxy olefins catalyzed inside a self-assembled cavity of the hexamer behaving as an enzyme-like host structure [65]. This reaction can be promoted by a series of strong Brønsted acids like triflic acid, leading initially to the protonation of the C═C double bond forming cationic intermediate species, with subsequent intramolecular attack of the hydroxyl alcoholic moiety. Usually this reaction is carried out in rather harsh conditions that often lead to the possible formation of acid-promoted side reactions also due to poor functional group compatibility that overall limits the applicability of this chemical transformation.

The addition of 2,6-dimethylhept-5-en-2-ol to a solution of the resorcin[4]arene led firstly to the encapsulation of the substrate as evidenced by the formation of new upfield shifted resonances in the region of 0.5 to −0.6 pm in the $^{1}$H-NMR spectrum, while within a few days at 30°C the formation of the corresponding cyclic 2,2,6,6-tetramethyltetrahydro-2*H*-pyran product was observed in 96% yield; the control experiment without capsule showed only 7% yield of the product. The reaction turned out to be sensitive to the content of water present in solution under better conditions, with regular chloroform-d rather than with water-saturated chloroform-d. As observed in several formed examples, the reaction with the capsule occupied by the tetrabutyl ammonium as a competitive guest under identical experimental conditions showed only weak background conversion of 7%, confirming that the reaction occurs within the cavity through stabilization imparted by the aromatic electron-rich internal surfaces on cationic intermediates and transition states, with the eventual release of the product ether product in favor of new incoming alcoholic substrate.

The catalytic method was extended to a series of different unsaturated alcohols in order to investigate the scope of the reaction. More specifically, only substrates leading upon protonation to the formation of tertiary carbocations turned out to be suitable substrates for the reaction. In all cases, the synthesis of a wide range of differently substituted tetrahydropyran and oxepane derivatives was achieved under mild experimental conditions within up to 6 days, with only 10 mol% of the supramolecular capsule as catalyst, while in the presence of the ammonium competitive guest the reactions were sluggish. For all substrates, the hydroalkoxylation always showed the formation of the cyclic product corresponding to the Markovnikov addition to the unsaturated double bond.

The substrate selectivity of the capsule on this reaction was investigated for the substrates reported in Fig. 7.15. The two alcohols reacted in the presence of the capsule, leading to formation of the cyclic product derived from the smaller substrate with respect to the longer substrate in a 98:2 ratio, while the same pair of substrates with just acid catalysis provided by triflic acid reacted almost with comparable rates, leading to the corresponding cyclic products in a 46:54 ratio. This selectivity arises by the preferential binding of the capsule for smaller, more globular substrates with respect to longer and more elongated ones as observed also in other catalytic reactions [65].

Another striking example of the combination of the weak acidity of the capsule and its ability to stabilize cationic intermediates and related transition states is the reaction of acyclic terpene derivatives, which was found by Tiefenbacher and coworkers [66]. In particular, it was observed that the capsule could efficiently activate substrates like geraniol, nerol, linalool, and related acetate esters because of the presence in all of them of allylic moieties with leaving groups sensitive to the presence of acids like hydroxyl moiety or acetate. All these substrates could be converted into complicated mixtures of cyclic products deriving from the formation of intermediate allylic cationic species that eventually undergo intramolecular cyclization reactions or that

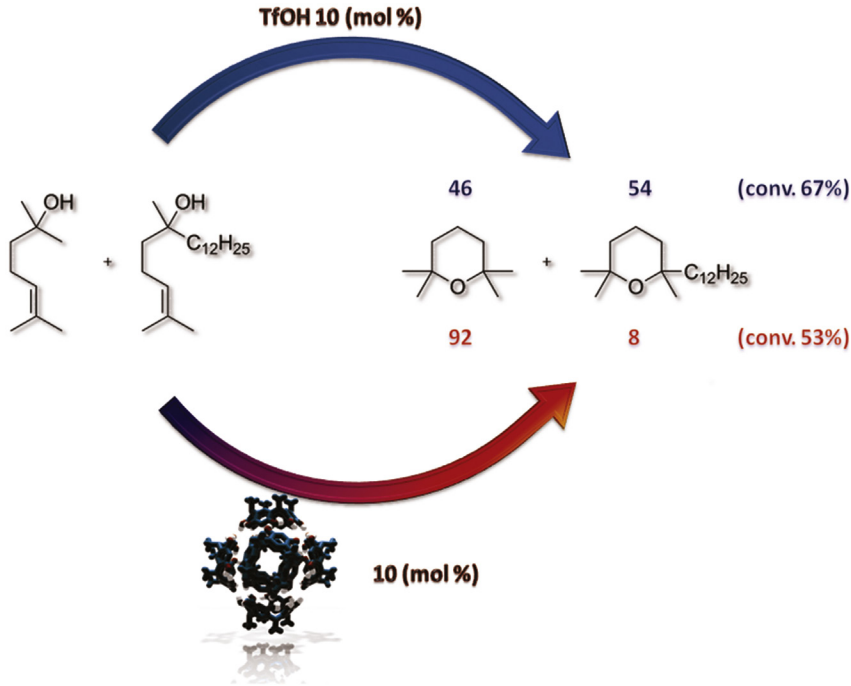


**FIGURE 7.15 Intramolecular hydroalkoxylation of unactivated hydroxy olefins promoted by the hexameric capsule of resorcin[4]arene through encapsulation compared to triflic acid catalysis.** *(Adapted from Ref. [65].)*

isomerize and subsequently react with nucleophiles. Looking at this extremely complicated scenario composed of several intermediate species and even more possible products, it is really impressive that enzymes like *cyclases* and *terpene synthases* operate on the similar substrates bearing phosphate-leaving groups, but in this case the reactions are much more selective. The key to the success for the enzymes consists in the sequestration of the substrate-limiting side reactions due to the attachment of different nucleophiles, the stabilization of the cationic allylic intermediates, and their preorganization and folding, thus promoting the formation of only certain cyclic products.

The resorcin[4]arene capsule was shown to efficiently mimic enzymes when it came to these aspects, thanks to its ability to stabilize the cationic allylic intermediate, limiting the attack from undesired nucleophiles and favoring the selective cyclization to certain products. In fact, it was observed that geranyl alcohol could be a suitable guest for the capsule that, in the presence of 10 mol% of capsule at 30°C, could be completely converted in 28 h with the initial formation of terpinene, linalool, and α-terpineol, all species derived from the selective formation of the intermediate carbocation. The two intermediate alcohols formed were further converted over time, giving rise to eucalyptol (Fig. 7.16a). Confirmation of the peculiar role played by the cavity of the

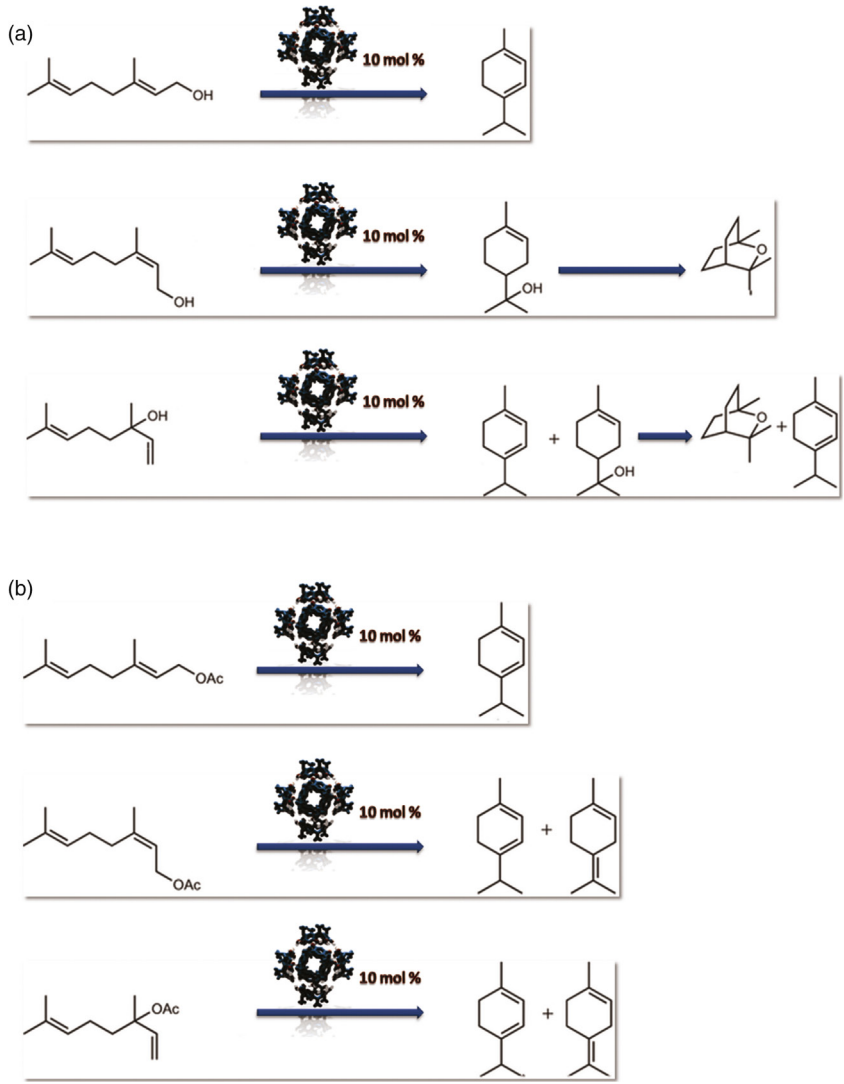


**FIGURE 7.16** Intramolecular acyclic terpene derivatives isomerization through the formation of allylic cationic species and the effect of the resorcin[4]arene capsule on the product distribution of the reaction for (a) allyl alcohols and corresponding (b) acetate esters as substrates. *(Adapted from Ref. [66] with permission of Nature Publishing.)*

capsule in the reaction was demonstrated using tetrabutylammonium as competitive guest, showing no conversion of the substrate, thus excluding simple Brønsted acid catalysis effects of the capsule.

When nerol as a similar substrate was investigated as substrate in the presence of the capsule in catalytic amounts, α-terpineol was observed as a dominant product that further converted into eucalyptol together with other products but

with an overall higher selectivity. The formation of eucalyptol from nerol and geraniol as acyclic terpenes was an unprecedented result that underlined the product selectivity features possible when using the resorcin[4]arene capsule.

Using acetate esters of geraniol and nerol, it was possible to greatly favor the formation of a different product distribution (Fig. 7.16b), limiting the amounts of linalool and $\alpha$-terpineol and favoring the 1,2-hydride shift to form the intermediate cationic species, eventually leading to $\alpha$-terpinene, which is an impressive result difficult to achieve in the absence of well-defined nanoenvironments. The capsule demonstrated great acceleration ofthe cyclization reaction with $k_{cat}$ only two orders of magnitude lower than *cyclase* enzymes. A deep investigation of the possible mechanism of action of the capsule to explain the formation of the different possible products led to the conclusion that a possible transoid–cisoid isomerization of the intermediate cation should be possible and the same could be possible also in natural *cyclase* enzymes.

Overall, the earlier described reactions of terpene derivatives mediated by the capsule really represents important examples of how, with simple self-assembled nanometric containers endowed with a few functionalities, it is possible to mimic some of the fundamental properties of enzymes. This demonstrates that the way opened by the development of supramolecular catalysis will soon reward the scientists with better and better catalytic systems.

## 5 CONCLUSIONS AND FUTURE PERSPECTIVES

Supramolecular catalysis is now enriched by a new principal actor: the resorcin[4]arene hexamer as an example of a very large, substrate-selective nanohost able to greatly stabilize reactions involving electron-poor and cationic intermediates. This simple and pseudospherical aggregate that spontaneously forms in organic solvents from a vase-shape molecule obtained in a single synthetic step, has been exploited as a well-defined nanoreactor for a wide range of chemical transformations. All the features observed are consequences of the encapsulation of the substrates or of specific cationic catalysts. These species experience unique solvation effects imparted by the electron-rich aromatic surfaces of the assembly. Thanks to its very large cavity, this assembly has attracted the interest of several research groups looking to use it as a simple but efficient example of artificial nanoenzyme.

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