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Resorcin[4]arene Hexamer: From Nanocontainer to Nanocatalyst

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24.1 Introduction

Homogeneous catalysis is witnessing a radical change in perspective, with an increasing awareness that a clear understanding of the nanometric tridimensional space where the reactions take place plays a key role in controlling both the activity and even more importantly the different selectivities of chemical transformations. The understanding of what happens at this level during a catalytic process can spur further achievements in deciphering biological phenomena such as enzyme activity. Supramolecular interactions are currently considered in homogeneous catalytic reactions, and a better definition of the nano-space around the active site is the target for developing more active and selective systems.

Nanoconfinement effects in chemical transformations [1] and supramolecular strategies in catalysis are gaining momentum [2]. Encapsulation phenomena in catalysis have been broadly described in the recent years, in particular for self-assembling capsules held together by metal–ligand coordination operating in water where the hydrophobic effect represents a powerful driving force to promote encapsulation. Much less investigated are encapsulation phenomena in catalysis in organic media where the recognition of the reactive species involves weaker supramolecular interactions.

The resorcin[4]arene unit reported in Figure 24.1 bearing long alkyl chains to impart solubility in apolar solvents is a typical easy-to-synthesize product that can be obtained in multigram scale with no particular instrumental requirements, starting from simple reagents using hydrochloric acid as catalyst. Moreover, its supramolecular self-aggregation in apolar media, leading to the formation of hexameric capsules where the resorcin[4]arene are held together with eight water molecules through a seam of overall 60 hydrogen bonds, makes this capsule a real benchmark host for supramolecular applications.

Its large pseudo-spherical cavity of about ~1375 $Å^3$ with an internal diameter of ~13 Å provides sufficient space for the co-encapsulation of different species such as

Supramolecular Catalysis: New Directions and Developments, First Edition.
Edited by Piet W.N.M. van Leeuwen and Matthieu Raynal.
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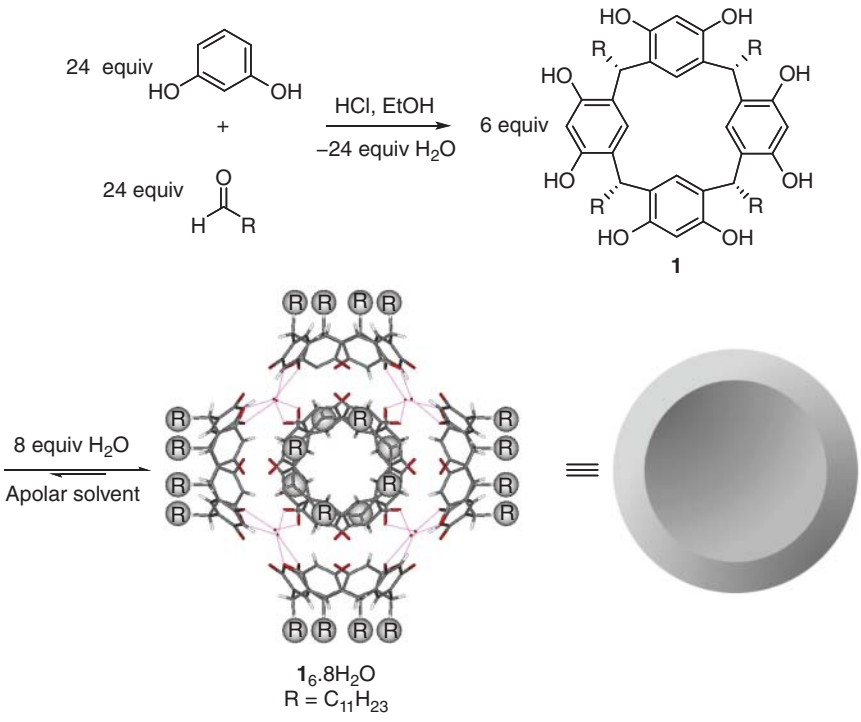


Figure 24.1 Synthesis of resorcin[4]arene **1** and its self-assembly in organic media forming $\mathbf{1}_6 \cdot 8H_2O$ driven by the formation of 60 hydrogen bonds involving 8 water molecules leading to the hexameric capsule.

substrates, reagents, or catalysts. The aromatic electron-rich panels that adorn the cavity not only promote the quantitative binding of cationic guests of suitable size and shape but can also be exploited to stabilize transient cationic or electron-poor intermediate species typical of several organic transformations. Many of these opportunities have been investigated by us and other research groups [3]. In Sections 24.2 and 24.3, our contribution to the field is described classifying the role of the capsule initially as a nanoreactor, where stoichiometric or catalytic reactions take place with confinement effects on substrate and product selectivity, and later reporting examples in which the capsule itself catalyzes organic transformations due to stabilization of intermediate species within the electron-rich cavity.

24.2 Resorcinarene Capsule as Nanoreactor

The rigid cavity of the capsule, in combination with its slow in–out of guests on the NMR timescale, makes the hexamer a perfect nanocontainer to investigate confinement effects. The high affinity of the capsule for cationic guests spurred our interest in considering this nanoreactor for the amide condensation between aliphatic carboxylic acids and primary aliphatic amines mediated by a common cationic coupling agent 1-ethyl-3-(-3-dimethylaminopropyl)carbodiimide hydrochloride **2**. The latter

species showed quantitative encapsulation in the hexameric capsule leaving a residual space in the cavity that was exploited to impart substrate preferences in the amide coupling reaction [4].

Specifically, when combining hexanoic acid with equimolar amounts of octyl and butyl amines in the absence of the capsule, the reaction led to the formation of the shorter amide in 2.5 times larger amounts with respect to the longer one. The selectivity was further steered toward the shorter products when running the reaction with the condensing agent hosted within the hexameric capsule. Similarly, the reaction of hexadecylamine with equimolar amounts of hexanoic and dodecanoic acid showed a 1,2 preference for the shorter amide product when the reaction was run in solution, while in the presence of the capsule, the selectivity increased up to 28 : 1 for the shorter amide product. For all tested competitive experiments, the capsule showed to favor the combination of shorter substrates. A competitive experiment involving butylamine and octylamine with hexanoic and dodecanoic acid is reported in Figure 24.2. While in the absence of the capsule the four possible amide products

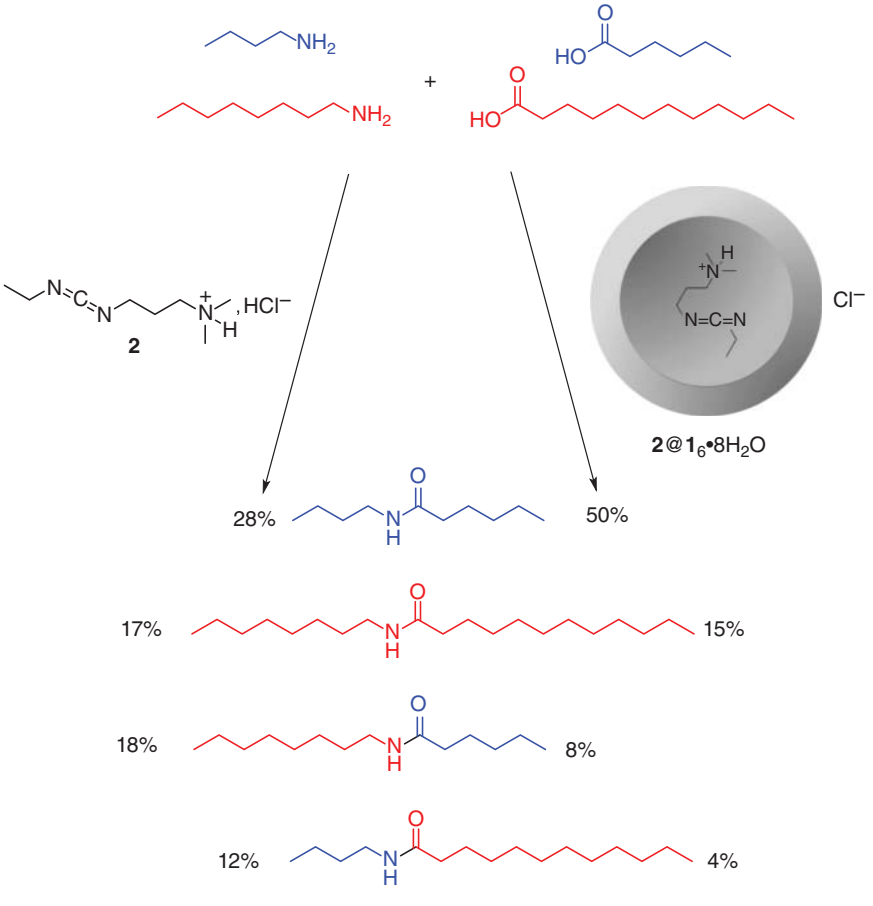


Figure 24.2 The encapsulation of the cationic carbodiimide steers the substrate selectivity in amide coupling toward the shorter combination of amines and carboxylic acids.

were obtained with comparable yields in the range 28% to 12%, in the presence of the capsule as nanocontainer in which the reaction takes place, the shorter amide product was obtained in 50% yield, while the longer one in only 4% yield.

The nanoreactor properties of the hexameric capsule were further investigated in combination with cationic transition metal catalysts. In consideration of its nice matching of size and shape, the encapsulation of $[Ru(bpy)_3]^{2+}\cdot(OTf)_2$ **3** was investigated.

By ^{1}H NMR (nuclear magnetic resonance) and DOSY (diffusion ordered spectroscopy) experiments, it was observed that the metal species could be quantitatively encapsulated in one equivalent of capsule, and it could be released back in solution using an excess of a competitive cationic guest such as tetraethylammonium. The reversible binding of the complex was exploited to modulate the catalytic properties of the metal catalyst, which is well known as a sensitizer under visible light irradiation to activate triplet oxygen to the corresponding singlet species to oxidize thioethers to the corresponding sulfoxides (Figure 24.3) [5]. Thanks to the above-mentioned reversibility, it was possible to modulate off/on the activity of the metal catalyst using the hexameric capsule initially as a trap with immediate interruption of the sulfoxide formation, further releasing the catalyst in solution with reactivation of the sulfoxidation reaction using an excess of tetraethylammonium. In this case, the role of the capsule corresponds to caging on-demand the catalyst that assumes an off-state, while it returns in the on-state when displaced back into solution by a competitive guest.

The OH moieties present on the rim of the resorcin[4]arene could act as coordinating ligands for hard metal catalysts, while soft metal catalysts and complexes do not interfere with the hydrogen-bonding seam. Based on this, we selected the carbene-based Au(I) metal complex **4** reported in Figure 24.4 as a suitable catalyst that showed quantitative encapsulation in the presence of one equivalent of capsule. The catalyst is well known for its ability to activate terminal alkynes promoting their rapid hydration to the corresponding ketone products. Using 4-phenyl-butyne as substrate, when the catalyst is free in solution only the formation of the corresponding methyl ketone is observed, while the encapsulated catalyst showed unexpectedly the additional formation of the aldehyde and 1,2-dihydronaphthalene (Figure 24.4) [6].

The aldehyde is a completely unprecedented product for Au(I)-catalyzed terminal alkyne hydrations, while the formation of the cyclic product is known for reaction under dry conditions. Overall, the encapsulation of **4** can change the product distribution of the reaction, probably affecting the transition state of the reaction, demonstrating the fundamental role of confinement effects, even if with loss of regioselectivity in the present case.

The effect of the encapsulation of **4** was also investigated in terms of substrate selectivity for a series of homologous aliphatic or aromatic terminal alkynes (Figure 24.5) [7]. The reaction of a mixture of equimolar amounts of 1-dodecyne, 1-octyne, and the isomeric ethynyl-cyclohexane with the free catalyst in solution showed a slight preference in terms of rate of reaction in favor of the latter substrate probably because it is slightly more electron rich compared to the other two.

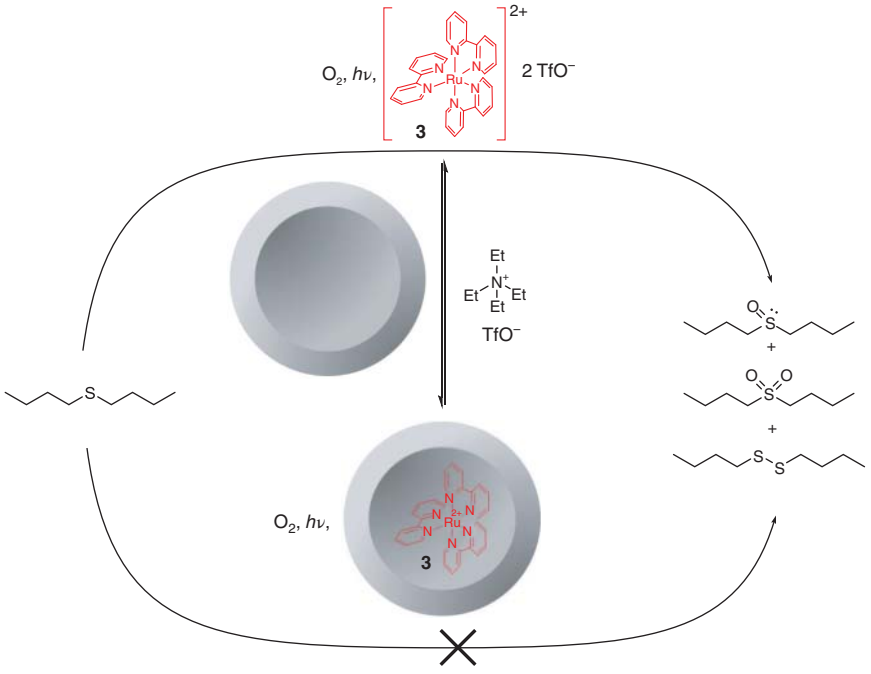


Figure 24.3 Under visible light and in the presence of O_2, $[Ru(bpy)_3](OTf)_2$ provides singlet oxygen that oxidizes dibutyl sulfide mainly to sulfoxide. The activity of the catalyst can be triggered off and on by encapsulation and release from the capsule.

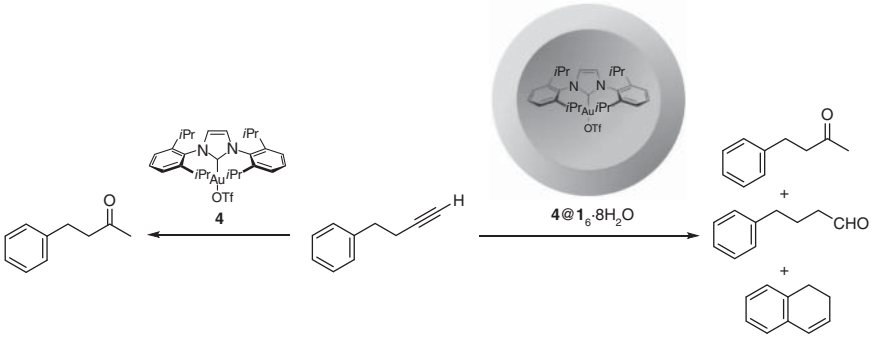


Figure 24.4 The cationic Au(I) catalyst **4**, that in solution promotes the Markovnikov hydration of 4-phenyl butyne, once encapsulated leads to the formation also of the corresponding aldehyde and 1,2-dihydronaphthalene.

The reaction under identical experimental conditions with **4** hosted within the capsule showed an increased preference for the cyclic substrate whose conversion after 155 minutes was 48%, compared to 25% and 21% for 1-octyne and 1-dodecyne, respectively (Figure 24.5a). Similar competitive experiments were run using rigid phenylacetylene derivatives characterized by small size differences, observing an inversion of the substrate selectivity trend when the reaction was carried out

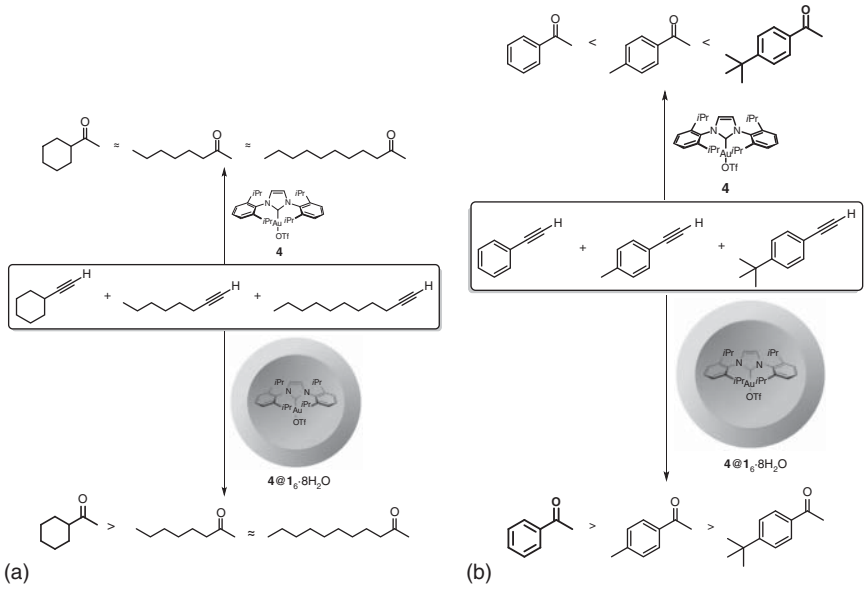


Figure 24.5 The substrate selectivity for the free and encapsulated Au(I) catalyst **4** was investigated with (a) aliphatic terminal alkynes and (b) aromatic terminal alkynes.

with the encapsulated **4**. In fact, using the three phenyl acetylene derivatives reported in Figure 24.5b, the reaction with the free catalyst in solution showed a decreasing order of activity from the more electron-rich *tert*-butyl derivative to the phenylacetylene substrate. On the contrary, with the encapsulated catalyst, the reactivity order was reversed with the smaller phenylacetylene reacting faster than the methyl and *tert*-butyl substituted analogues. Once again, the capsule imparts a steric selection on the substrates leading to the preferential conversion of the smaller derivatives with respect to the longer ones, even though the differences in size are rather small.

24.3 Resorcin[4]arene Capsule as Nanocatalyst

One unusual activation mechanism imparted by the hexameric capsule involves hydrogen peroxide. This molecule can substitute one of the eight water molecules in the hydrogen-bonding network of the capsule. This effect provides an electrophilic activation of the oxidant that enabled the oxidation of electron-rich substrates such as thioethers, leading to the formation of the corresponding sulfoxides with high chemoselectivity (Figure 24.6) [8].

More in detail, while the reaction in the absence of the capsule was sluggish with just 10% product formation after 90 minutes, in the presence of 10 mol% of the hexameric capsule, the reaction was complete in 65 minutes. Control experiments using resorcinol to mimic the hydrogen-bonding properties of the resorcin[4]arene or acetic acid to simulate the Brønsted acidity of the capsule, all showed marked

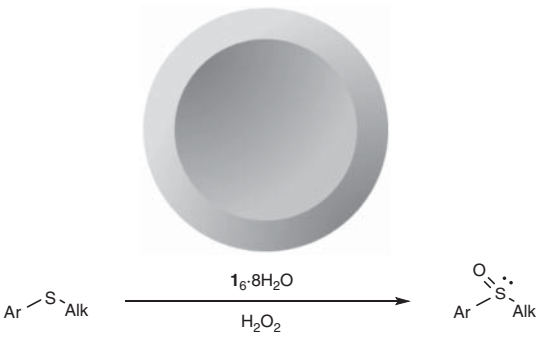


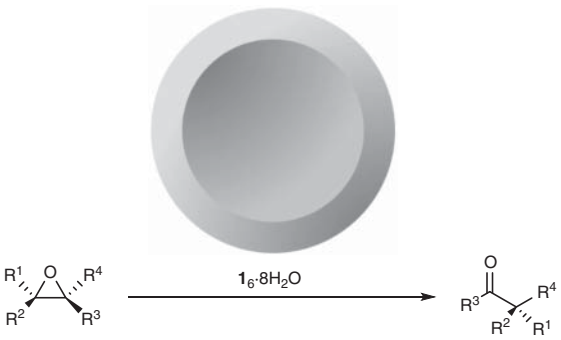
Figure 24.6 The hexameric capsule activates hydrogen peroxide for the electrophilic oxidation of thioethers forming selectively the corresponding sulfoxides.

decrease of activity. These results further confirmed that the capsule acted as a true organocatalyst activating the oxidation toward dialkyl, aryl-alkyl, and diaryl thioethers (Figure 24.6). Several substrates were tested observing in all cases large inactivation of the catalytic activity of the capsule when using a competitive guest, which suggests a stabilizing effect imparted by the electron-rich cavity on the polar transition state derived by the combination of the oxidant and the substrate. In all cases only the sulfoxide product was observed, indicating a good chemoselectivity of the reaction with short reaction time representing one of the most effective organocatalyst for sulfoxidation reaction with hydrogen peroxide.

Some of the specific properties of the hexameric capsule such as a weak Brønsted acidity and the presence of water molecules on the edges of the aggregate as H-bond donors pointing inside the cavity spurred the investigation of some classical organic transformations known to be sensitive to this kind of activation process. Epoxide isomerization leading to carbonyl compounds is a typical reaction that can be promoted under homogeneous conditions by a wide range of catalysts such as metal species, protic acids, and H-bonding units. The hexameric capsule proved to promote this reaction but only with activated substrates such as epoxides bearing aryl substituents directly connected to the C atoms of the oxirane ring or α-pinene oxide and norbornene oxide (Figure 24.7). For example, the reaction with styrene oxide was complete forming the isomerization product phenyl acetaldehyde in 18 hours using 13 mol% of capsule. Control experiments confirmed that the activation imparted by the capsule was not due to just Brønsted acidity or mere H-bonding [9].

The accepted mechanism for epoxide isomerization involves the formation of carbocationic species. It is likely that the electron-rich inner cavity of the capsule can stabilize these charged intermediate species, thus explaining the acceleration observed. It is also interesting to observe that α-pinene oxide, which by isomerization can provide a wide range of possible isomers, led to the formation of the campholenic aldehyde with 82% yield with minor isomeric by-products after only four-hour reaction.

The stabilizing properties provided by the inner surfaces of the cavity of the capsule could be exploited, in combination with protic acids, to promote the organocatalytic hydration of terminal alkynes (Figure 24.8). The reaction was investigated on aromatic terminal alkynes using catalytic amounts (10 mol%) of the capsule and of



R^1 = Ar, R^2 = R^3 = R^4 = H
R^1 = Ar, R^2 =H, R^3 = H, R^4 = Ar
R^1 = Alkyl, R^2 = Alkyl, R^3 = H, R^4 = Alkyl

Figure 24.7 The hexameric capsule promotes the isomerization of epoxides to the corresponding carbonyl compounds.

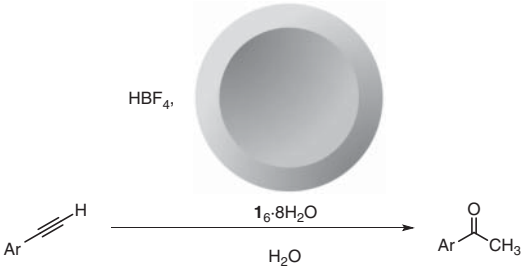


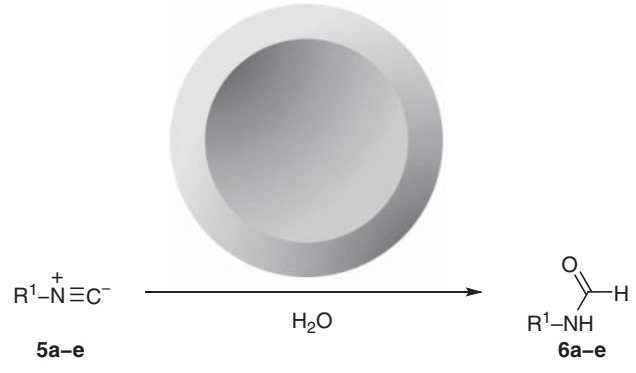
Figure 24.8 The capsule, in combination with HBF_4 as strong Brønsted acid, promotes the Markovnikov hydration of terminal aromatic alkynes to methyl aryl ketones.

HBF_4 (50 mol%) observing the formation of the corresponding methyl ketones in a few hours at 60 °C [10].

The scope of the reaction was limited to phenylacetylene derivatives bearing activating aliphatic or alkoxy substituents on the aromatic ring; larger substrates such as 9-ethynyl-phenanthrene and 1-ethynyl-4-phenoxybenzene showed much lower conversion into the corresponding methyl ketones. Since in this reaction, the protonation is likely to be the rate-determining step, the stabilizing nano-environment provided by the capsule for the protonated substrate efficiently favors the reaction.

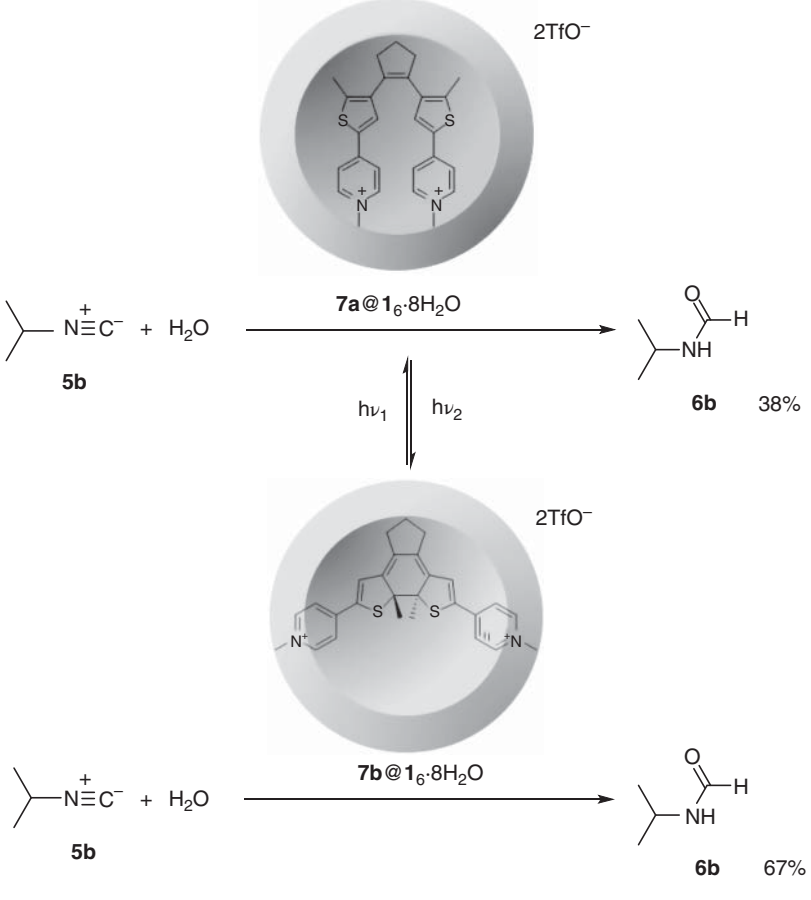
The electronic properties of the capsule turned out to efficiently promote encapsulation of neutral compounds such as isonitrile derivatives characterized by a particular electronic configuration of the R-NC moiety, with a predominant carbenic behavior and electrophilic character of the C atom (Figure 24.9a). Several alkyl and aryl isonitrile derivatives were investigated showing in all cases spontaneous encapsulation within the cavity of the hexameric capsule, as observed by the appearance of new upfield shifted resonances on the ^{1}H NMR spectra in slow exchange with the external isonitrile. It was also observed that within a few hours at 60 °C, the isonitrile compounds could be transformed into the corresponding formylamide hydration product (Figure 24.9a) [11].

The general mechanism for the reaction involves protonation of the terminal carbenic C atom forming a cationic intermediate that is stabilized by the cavity



a: R^1 = Cy; **b**: R^1 = *i*Pr; **c**: R^1 = *t*-Bu; **d**: R^1 = Bn; **e**: R^1 = 2,6-Me_2Ph

(a)



(b)

Figure 24.9 (a) Neutral isonitriles **5a–e** can be efficiently encapsulated within the hexameric capsule leading to the formation of the corresponding formyl amides **6a–e**. (b) The encapsulation of a photo-modulable cationic guest **7a** or **7b** provides different catalytic activity to the capsule.

of the capsule and that further reacts with water leading to the corresponding formylamides. The catalytic activity of the capsule was further modulated by the co-encapsulation of a photo-switchable bis-cationic diarylethene guest reported in Figure 24.9b whose geometry can be regulated by irradiation at a proper wavelength. In particular, both open **7a** and closed **7b** isomeric forms of the photo-switchable cationic guests demonstrated to be fully encapsulated with a stoichiometric amount of capsule. The inner volume of the cavity left accessible by the diarylethene guest showed to favor the co-encapsulation of the isonitrile and its hydration, even though with lower rate and conversion. In particular, it is worth to notice that the open isomer **7a** led to higher inhibition of the hydration reaction with respect to the closed isomer **7b**, probably because the latter, being more rigid, leaves more space for the isonitrile reagent. The different inhibition activity of the open and closed forms of the cationic guest was better observed running the two separate experiments at room temperature for seven days observing 38% with **7a** and 67% with **7b** for the corresponding *N*-isopropylformylamide, respectively.

Spurred by the unprecedented host properties of the resorcin[4]arene capsule for isonitriles as neutral guests, we investigated other reactions involving this class of reagents in combination with trimethylsilyl azide for the formation of the corresponding 1-substituted 1*H*-tetrazole cycloaddition products (Figure 24.10) [12].

In the absence of the capsule, the reaction was sluggish even at 60 °C for five hours, while with 10 mol% of the hexameric capsule, the reaction between cyclohexyl isonitrile and trimethylsilyl azide led quantitatively to the corresponding 1*H*-tetrazole, demonstrating the good catalytic effect of the capsule considering that this reaction is usually carried out under harsh conditions with strong acids and at high temperature. Control experiments allowed to rule out a simple Brønsted acid role of the capsule and further confirmed that encapsulation of the isonitrile was a key aspect of the activation observed, with almost no tetrazole products observed when the cavity was occupied by a competitive guest. Moreover, the capsule showed a certain degree of substrate selectivity between two competitive substrates preferring the aliphatic reagent cyclohexyl isonitrile with respect to benzyl isonitrile, forming the corresponding products in a 2.2 ratio, while the reaction catalyzed by a strong acid led to the two products in 0.4 ratio. This is a clear consequence of the preferential encapsulation dictated by the cavity of the capsule.

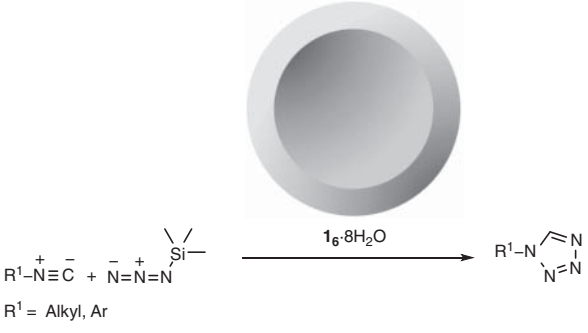
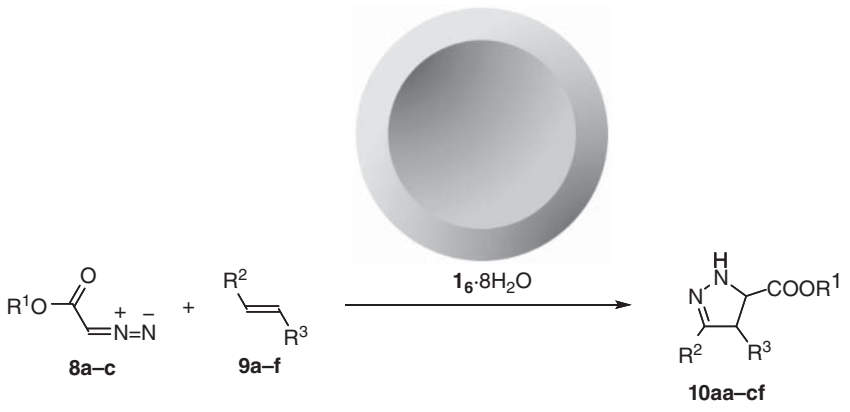


Figure 24.10 Isonitriles in the presence of trimethylsilyl azide are converted selectively into the corresponding tetrazoles by the activation provided by the hexameric capsule.



8a: R^1 = Et; **8b**: R^1 = *t*-Bu; **8c**: R^1 = Bn
9a: R^2 = CHO, R^3 = H; **9b**: R^2 = CN, R^3 = H; **9c**: R^2 = CHO, R^3 = Me;
9d: R^2 = CHO, R^3 = *n*–Pr; **9e**: R^2 = COOMe, R^3 = H; **9f**: R^2 = COO*n*-Bu, R^3 = H

Figure 24.11 Neutral diazoacetate esters **8a–c** show encapsulation within the hexameric capsule and together with electrophilic dipolarophiles **9a–f** lead to the corresponding 4,5-dihydro-1*H*-pyrazoles **10** promoted by the supramolecular capsule.

The investigation of possible alternative neutral compounds showing affinity for the cavity of the capsule led to the discovery that ethyl, *tert*-butyl, and benzyl diazoacetate esters **8a–c** are suitable guests thanks to their carbene-like properties and an electron-poor character. ^{1}H NMR confirmed the encapsulation of this class of compounds showing in all cases new upfield shifted resonances for the encapsulated diazoacetate esters. The capsule was exploited to promote the atom-efficient 1,3 dipolar cycloaddition reaction between diazoacetate esters **8** and dipolarophiles **9** such as acrolein, acrylonitrile, acrylate esters, and many others to form 4,5-dihydro-3*H*-pyrazoles as primary products that underwent further tautomerization to the corresponding more stable 4,5-dihydro-1*H*-pyrazoles **10** (Figure 24.11) [13].

Also in this case, substantial inhibition of the catalytic activity was observed by employing competitive guests such as tetraalkylammonium ions to fill the cavity of the capsule or using resorcinol as a mimic of the H-bonding properties of the capsules. The observation that encapsulation of the reagents was fundamental for the reaction was further evidenced by the preferential combination of acrylonitrile with respect to the longer *trans*-crotonaldehyde and *trans*-2-hexenal for the reaction with *tert*-butyl-diazoacetate **8b**.

24.4 Concluding Remarks

In recent years, the resorcin[4]arene hexameric capsule emerged as one of the most versatile self-assembled nano-aggregates that can be exploited either as a nanoreactor or as a nano-organocatalyst. Taking advantage of its electron-rich cavity, we

reported several applications of this capsule as a well-defined environment, roomy enough to host cationic substrates or metal catalysts. This led to several examples in which the limited space available can greatly affect the approach of the substrates changing their relative rate of reaction, or it can impart steric requirements leading to unexpected product distributions. These confinement effects are gaining momentum and will help to shed light on much more complicated systems such as the active site of enzymes. Moreover, we demonstrated that the hexameric capsule, with its particular electronic properties, can greatly accelerate a wide range of organic reactions characterized by the formation of cationic intermediates that inside the cavity experience marked stabilization. In combination with its weak intrinsic Brønsted acidity or aided by added protic acids, the capsule demonstrated to activate several reactions ranging from epoxide isomerization, isonitrile and alkyne hydration, diazoacetate cycloaddition reactions with unsaturated carbonyl compounds and tetrazole synthesis from isonitriles, as well as hydrogen peroxide activation toward sulfides leading to the corresponding sulfoxide products. More reactions driven by similar mechanistic profiles are likely to be disclosed, leading to better levels of selectivity and activity: these are intriguing challenges for future investigations. The full understanding of the potential of this host is far from being complete.

Acknowledgments

Financial support for this research from Università Ca' Foscari Venezia, Ministero Università e Ricerca and Fondazione CARIPARO SELECT project is gratefully acknowledged.

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