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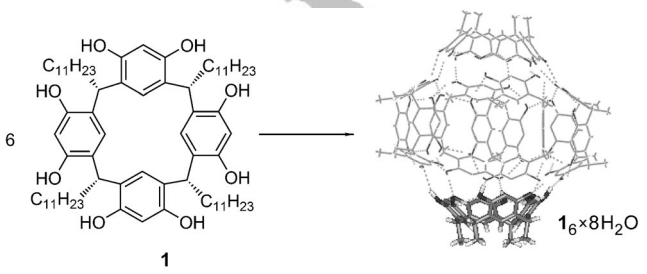
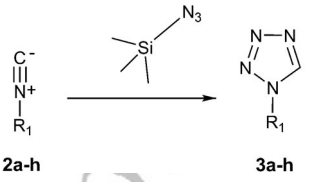
Supramolecular Catalysis

Supramolecular Catalysis in the Synthesis of Substituted 1*H*-Tetrazoles from Isonitriles by a Self-Assembled Hexameric Capsule

Sonia Giust, Giorgio La Sorella, Laura Sperni, Fabrizio Fabris, Giorgio Strukul, and Alessandro Scarso*[a]

Abstract: The synthesis of substituted 1*H*-tetrazoles from aliphatic or aromatic isonitriles and trimethylsilyl azide can be efficiently promoted by the hexameric capsule of resorcin[4]arene as a supramolecular self-assembled catalyst. The reaction is sensitive to the size and nature of the substrate and is driven by encapsulation of the reagents within the cavity of the supramolecular catalyst.





Scheme 1. Structures of Resorcin[4]arene **1** and the hexameric capsule $\mathbf{1}_6{\cdot}8H_2O$. Addition of $TMSN_3$ to isonitriles **2a**–**h** mediated by $\mathbf{1}_6{\cdot}8H_2O$, leading to the corresponding substituted 1*H*-tetrazoles **3a**–**h**.

An important requirement for bridging the gap between traditional homogeneous catalysis and enzymatic catalysis is to increase the surface interactions between catalyst and substrate, to implement recognition properties and stabilize the transition state of the reaction. Supramolecular catalysis is a growing and cross-disciplinary field that includes the implementation of weak intermolecular forces in artificial catalysts[1] to achieve high activity and both product and substrate selectivity.[2] Structures of typically active supramolecular catalysts include tubular covalent molecules such as cyclodextrins and pillararenes,[3] vase-shaped calixarenes and completely closed structures such as covalent and self-assembled capsules operating in either water or in organic media.[4] Resorcin[4]arene **1** (Scheme 1) is easy to prepare, and spontaneously self-assembles[5] in the solid state and in water-saturated chloroform or benzene, leading to the formation of the hexameric capsule $\mathbf{1}_6{\cdot}8H_2O$ (Scheme 1), which is characterized by a large cavity of approximately 1375 $Å^3$.[6] This cavity is suitable for binding quaternary ammonium compounds[7] through cation–π interactions.[8]

Examples of neutral guest molecules for the hexameric capsule exist, such as carboxylic acids, amino acids,[9] and alcohols,[10] all of which are capable of hydrogen bonding, especially if they are present in a large excess with respect to the host molecule. The hexamer provides a well-defined nano-environment that has been exploited in catalysis with three approaches: 1) as a reversible shield to control the activity of a traditional catalyst,[11] 2) as an environment to impart unique substrate[12] and product[13] selectivities, and 3) as a catalyst itself to bind substrates, stabilize transition states and accelerate reactions. Examples of the latter comprise the acceleration of Diels–Alder reactions through the fluorophobic effect,[14] and two reactions exploiting the binding of water by the hexamer. The first of these is the selective hydrolysis of acetals,[15] and the second is the hydration of isonitriles to formamides driven by encapsulation of the substrates, which was recently disclosed by our group.[16]

Herein we present an example of an efficient, supramolecular, catalytic synthesis of aliphatic and aromatic 1-substituted 1*H*-tetrazoles by addition of trimethylsilyl azide ($TMSN_3$) to isonitriles, mediated by the hexameric capsule $\mathbf{1}_6{\cdot}8H_2O$ (Scheme 1). The reaction is rapid and efficient, showing inhibition of the catalytic activity in the presence of competitive guests, which is a typical feature reminiscent of enzymatic catalysis.

Initially, we investigated the reaction between cyclohexyl isonitrile (**2a**) and $TMSN_3$ in the presence and absence of the hexameric capsule. It was observed that the spontaneous reaction between the reagents did not take place even after 5 h at

[a] *S. Giust, G. La Sorella, L. Sperni, F. Fabris, Prof. G. Strukul, Dr. A. Scarso*
Dipartimento di Scienze Molecolari e Nanosistemi
Università Ca' Foscari di Venezia
Calle Larga S. Marta 2137, 30123, Venice (Italy)
E-mail: alesca@unive.it

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Table 1. Catalysis tests for 1*H*-tetrazole **3a** synthesis by reaction of cyclohexyl isonitrile **2a** and $TMSN_3$. *t* = Reaction time.

Entry	$\mathbf{1}_6$·8 H_2O	Additive	*t* [h]	**3a** [%][a]
1	–	–	5	0
2	+	–	6.5	>98
3[b]	–	+	6	2
4[c]	–	+	6	10
5[d]	+	+	6.5	33

[**1**] = 80 mM, [**2a**] = 133 mM, [$TMSN_3$] = 133 mM, water-saturated $CDCl_3$ (0.5 mL), 60 °C; +: presence; –: absence. [a] Yield determined by ^{1}H NMR. [b] [Acetic acid] = 13.3 mM (1 equiv with respect to $\mathbf{1}_6$·8 H_2O). [c] [Resorcinol] = 318 mM (24 equiv with respect to $\mathbf{1}_6$·8 H_2O). [d] [$N(CH_2CH_3)_4BF_4$] = 133 mM (10 equiv with respect to $\mathbf{1}_6$·8 H_2O).

60 °C (Table 1, entry 1), whereas in the presence of 10 mol% capsule the reaction quantitatively yielded the corresponding 1*H*-tetrazole in 6.5 h (Table 1, entry 2).[17] 1*H*-Tetrazoles with substituents at position 5 are typically prepared from nitriles,[18] whereas 1*H*-tetrazoles substituted at position 1 are usually prepared by reaction of a large excess of the harmful ■■hydrazoic acid (HN_3) OK?■■ with isonitriles.[19] Similarly to the present work, hydrazoic acid can be replaced by $TMSN_3$ but only under much harsher experimental conditions, such as the use of strong Brønsted acids such as HCl.[20] In the presence of a Pd^{II} catalyst at 100 °C, the same combination of isonitriles and $TMSN_3$ is known to afford cyanamides rather than 1*H*-tetrazoles.[21] Recently, Zhang and Tiefenbacher demonstrated that the hexamer behaves as a weak acid with a pK_a value of approximately 5.5,[15] whereas individual resorcinol (1,3-dihydroxybenzene) units have a pK_a of 9.15. These values allow the exclusion of both a simple Brønsted acid effect and activation by hydrogen bonding with the capsule in the synthesis of 1*H*-tetrazoles. In fact, this was confirmed with two control experiments, in which **1** is replaced with either one equivalent of acetic acid (pK_a = 4.76) or with 24 equivalents of resorcinol with respect to the typical concentration of hexamer. The yields of 1*H*-tetrazole **3a** after 6 h in these controls were 2 and 10%, respectively (Table 1, entries 3 and 4). Acetic acid failed to activate the reaction, therefore the capsule, which is even less acidic, cannot act simply as a Brønsted acid. ■■It is likely that with resorcinol, hydrogen-bonding activation of the reaction takes place, however this■■"this"? the resorcinol itself? the amount used? the hydrogen bonding effect?■■ is much smaller compared to the self-assembled capsule based on the resorcin[4]arene **1**. OK?■■ As it is known from previous studies that isonitriles are good guests for the hexamer,[16] we performed another experiment, repeating the reaction between $TMSN_3$ and **2a** in the presence of capsule and 10 equivalents of tetraethylammonium tetrafluoroborate as a competitive guest[7] for the capsule (Table 1, entry 5). Under these experimental conditions the catalytic activity decreased markedly, indicating the importance for the catalytic activation of the reaction of having a capsule with an accessible cavity.

^{1}H NMR spectra of the free capsule (Figure 1 A) and in the presence of ten equivalents of **2a** and $TMSN_3$ (Figure 1 B) were measured. The latter spectrum clearly shows upfield-shifted

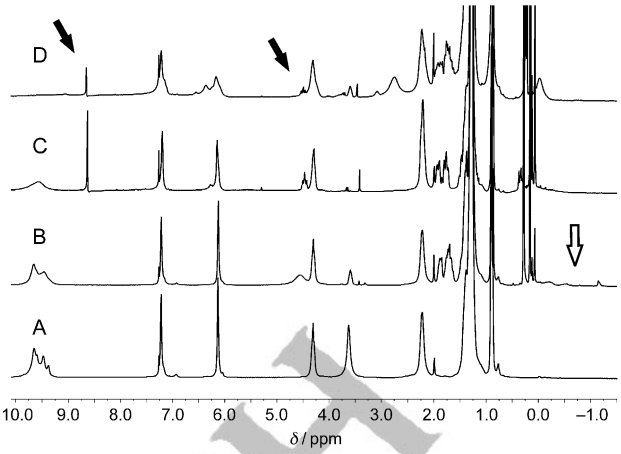


Figure 1. ^{1}H NMR spectra in water-saturated $CDCl_3$: A) $\mathbf{1}_6$·8 H_2O (13.3 mM); B) **2a** (133 mM), $TMSN_3$ (133 mM), and $\mathbf{1}_6$·8 H_2O (13.3 mM) after mixing; C) **2a** (133 mM), $TMSN_3$ (133 mM), and $\mathbf{1}_6$·8 H_2O (13.3 mM) after 6.5 h at 60 °C; D) $N(CH_2CH_3)_4BF_4$ (133 mM), **2a** (133 mM), $TMSN_3$ (133 mM), and $\mathbf{1}_6$·8 H_2O (13.3 mM) after 6.5 h at 60 °C; ↓ (open arrow) encapsulated isonitrile, ↓ (closed arrow) 1*H*-tetrazole product (**3a**)■■ok?■■.

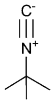
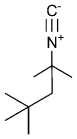
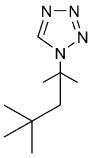
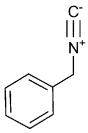
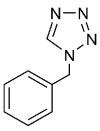
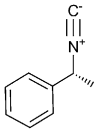
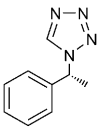
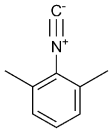
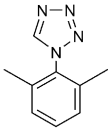
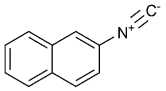
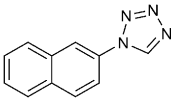
resonances for the isonitrile hosted within the cavity of the capsule. Integration of the resonances indicates encapsulation of one molecule of **2a**, whereas no evidence of the preferential binding of $TMSN_3$ was observed. Spectra of the reagents and capsule after 6 h at 60 °C, either in the absence (Figure 1 C) or in the presence (Figure 1 D) of the competitive ammonium guest, were also measured. Under these experimental conditions, ^{1}H NMR spectroscopy indicated that the cavity was occupied by the ammonium species thereby inhibiting the binding of the isonitrile within the cavity and leading to substantial inactivation of the cycloaddition reaction.

All of these control experiments clearly indicates the activation of the reaction occurs by encapsulation of the reagents,[16] and the possible stabilization by the electron-rich surface of the cavity rather than activation by hydrogen bonding between the reagents and the hydroxyl groups of **1**. It is also notable that in all experiments, only trace amounts of the corresponding formamides—the products of isonitrile hydration[16]—were observed, which are instead formed when $TMSN_3$ is present in the reaction mixture. This demonstrates that the 1*H*-tetrazole synthesis is chemoselective in the presence of the capsule.

It is known that 1-substituted aromatic 1*H*-tetrazoles could be formed from the corresponding formamides,[22] therefore we performed the hydration of **2a** catalyzed by the capsule, using the previously identified[16] conditions and adding $TMSN_3$ to the system at 60 °C for 18 h. The formation of the corresponding 1*H*-tetrazole was not observed. This allowed us to rule out the formation of the formamide derivative as an intermediate and confirmed that the synthesis of the 1*H*-tetrazole occurred directly by reaction of the isonitrile with $TMSN_3$.

The scope of the reaction was subsequently investigated testing different aliphatic as well as aromatic isonitriles (Table 2). The reaction of all aliphatic isonitriles, except *tert*-butyl isonitrile (**2c**), in the presence of the free capsule led to

Table 2. 1*H*-Tetrazole **3b–h** synthesis mediated by $\mathbf{1}_6{\cdot}8H_2O$.

Entry	Substrate	Product		*t* [h]	Yield [%][a]
1		**2b**		**3b**	6.5	87 24[b]
2		**2c**		**3c**	6	36 41[b]
3		**2d**		**3d**	20	94 66[b]
4		**2e**		**3e**	5.5	93 6[b]
5		**2f**		**3f**	20	>98 19[b]
6		**2g**		**3g**	6	40 2[b]
7		**2h**		**3h**	6	81 4[b]

[**2b–h**] = 133 mM, [**1**] = 80 mM, water-saturated $CDCl_3$ (0.5 mL), 60 °C. [a] Determined by ^{1}H NMR. [b] In the presence of $N(CH_2CH_3)_4BF_4$ (133 mM, 10 equiv with respect to $\mathbf{1}_6{\cdot}8H_2O$).

higher yields of the corresponding 1-substituted 1*H*-tetrazoles (**3b–h**) compared to the same reaction in which the cavity was occupied by the competitive tetraethylammonium guest. Under these conditions a smaller space is available for encapsulation of the isonitrile substrate, which leads to larger differences in 1*H*-tetrazole yields between the free and occupied capsules with increasing size of the isonitrile.[23]

Aromatic isonitriles such as 2,6-dimethylphenyl isonitrile (**2g**) and 2-naphthyl isonitrile (**2h**) reacted with $TMSN_3$ in the presence of the capsule, providing the expected corresponding 1*H*-tetrazole derivatives **3g** and **3h**, respectively, in moderate to good yields (Table 2, entries 6 and 7). Notably, the GC–MS analysis of aromatic 1*H*-tetrazoles **3g** and **3h**, dissimilar to the aliphatic-substituted derivatives, showed their thermal lability to form the corresponding cyanamides (see the Supporting Information). For aromatic isonitriles **2g** and **2h**, the inhibition of the catalytic activity in the presence of tetraethylammonium bromide was more evident.

As $\mathbf{1}_6{\cdot}8H_2O$ promotes the reaction by encapsulating the isonitrile substrates, we investigated the ability of the supramolecular catalyst to discriminate among pairs of substrates by means of competitive tests using two isonitriles in equimolar amounts as reactants. We compared the results observed with the same reaction using 20 mol% methanesulfonic acid with respect to each isonitrile as a traditionally strong Brønsted acid catalyst that is unable to impart recognition of the substrates, simply to underline the intrinsic relative activity of pairs of isonitriles towards $TMSN_3$. The competition tests performed using 1,1,3,3,-tetramethylbutyl isonitrile (**2d**) and (*S*)-(−)-α-methylbenzyl isonitrile (**2f**) with methanesulfonic acid showed a ratio between the amounts of the two corresponding 1*H*-tetrazoles (**3d**/**3f**) of around 0.3 at the beginning of the reaction (isonitrile conversion < 25%). The same pair of substrates, without methanesulfonic acid but in the presence of the capsule, gave a ratio **3d**/**3f** of approximately 1.1. For the competitive substrates cyclohexyl isonitrile (**2a**) and benzyl isonitrile (**2e**) the ratio **3a**/**3e** was approximately 0.4 with methanesulfonic acid and 2.2 with the hexameric capsule. Although the selectivity imparted by the capsule is not large, probably because of the large space available within the cavity, it is interesting to note that the capsule tends to invert the higher intrinsic reactivity of benzylic isonitriles such as **2f** and **2e** and favor the encapsulation and reaction of the intrinsically less-reactive di- and trisubstituted isonitriles **2a** and **2d**.

In conclusion, we have described an example of supramolecular catalysis in which the hexameric self-assembled capsule $\mathbf{1}_6{\cdot}8H_2O$ promotes the synthesis of 1-substituted 1*H*-tetrazoles by addition of $TMSN_3$ to a wide range of aliphatic and aromatic isonitriles. The capsule binds the isonitrile substrate and favors its chemoselective reaction with $TMSN_3$, avoiding or limiting the competitive addition of water that would lead to formamide products. The reaction is inhibited by guests competitive for the capsule, confirming the supramolecular catalytic effect imparted by the nanoreactor. The capsule was demonstrated to impart a degree of substrate selectivity due to the preferred encapsulation of aliphatic rather than benzylic isonitriles.

Experimental Section

Catalytic Reactions of Isonitriles 2 with Trimethylsilyl Azide

Water-saturated solvent was prepared by shaking $CDCl_3$ with bidistilled water at room temperature in a separation funnel. ■ ■phases separated, bottom layer (organic) taken? if not, please add ratios■ ■ Resorcin[4]arene **1** (6 equiv, 79.6 mM) was placed in a screw-capped vial equipped with a silicone septum and dissolved in water-saturated $CDCl_3$ (0.5 mL) and stirred for a few minutes. The chosen isonitrile (**2**, 10 equiv, 132.6 mM) and trimethylsilyl azide (10 equiv, 132.6 mM) were added to this solution. The reaction was then thermostated at 60 °C and its progress was monitored by ^{1}H NMR and GC analysis after periodic sampling directly from the reaction mixture. Conversion, product assignment and product distribution were determined using direct GC, GC–MS and ^{1}H NMR analysis of the reaction mixture as the average of three experiments.

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Keywords: 1*H*-tetrazoles · encapsulation · isonitriles · resorcinarenes · supramolecular catalysis

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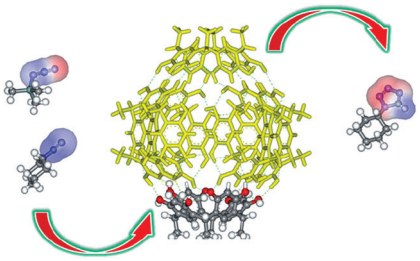
COMMUNICATION

Step inside: A self-assembled capsule of hexameric resorcin[4]arene promotes the synthesis of 1-substituted 1*H*-tetrazoles from a wide range of aliphatic and aromatic isonitriles. The capsule binds the isonitrile substrate and favors its chemoselective reaction with trimethylsilyl azide over hydration to a formamide. The capsule exhibits a degree of substrate selectivity due to its preference for binding aliphatic rather than aromatic isonitriles. ■■OK?■■



Supramolecular Catalysis

*Sonia Giust, Giorgio La Sorella, Laura Sperni, Fabrizio Fabris, Giorgio Strukul, Alessandro Scarso**

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Supramolecular Catalysis in the Synthesis of Substituted 1*H*-Tetrazoles from Isonitriles by a Self-Assembled Hexameric Capsule

#Tetrazoles from #isonitriles using #supramolecular #catalysis by Scarso et al @CaFoscari SPACE RESERVED FOR IMAGE AND LINK

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