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Hydration of Aromatic Alkynes Catalyzed by a Self-Assembled Hexameric Organic Capsule

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The combination of a Brønsted Acid catalyst and the supramolecular organic capsule formed by the self-assembly of six resorcin[4]arene units efficiently promotes the mild hydration of aromatic alkynes to the corresponding ketones. The capsule provides a suitable nanoenvironment that favor protonation of the substrate and addition of water

Introduction

In the recent years supramolecular catalysis[1] is growing as a new cross-discipline that exploits the recognition properties of host structures to promote reaction catalysis through the implementation of weak intermolecular forces in the stabilization of reaction intermediates and transition states. The role of the catalytic host is to achieve high activity and both product and substrate selectivity[2] with the ultimate goal of enzyme mimic.[3] While in the past unimolecular host structures featuring relatively small inner cavities, like cyclodextrins[4] and cucurbiturils,[5] have been investigated as catalysts, more recently supramolecular hosts displaying significantly larger cavities have become fashionable. The increase in volume size of the container host enabled co-encapsulation of multiple substrates, as well as the nesting of metal catalysts and substrates. The inclusion of a metal complex catalyst can drastically alter its properties compared to those exhibited in bulk solution.[6]

As a function of the solvent nature, different approaches were considered in the development of synthetic supramolecular catalysts. For example, water soluble capsular containers were assembled through the hydrophobic effect and explored as supramolecular catalysts for several chemical transformations in water.[7] On the other hand, Rebek et al. introduced the assembly of hydrogen bonded capsules in organic solvents as supramolecular catalysts for cycloaddition reactions.[8]

Resorcin[4]arene **1** is an easy to prepare molecule that through hydrogen bonding interactions spontaneously self-assembles[9] into the hexameric $\mathbf{1}_6.(H_2O)_8$, stable both in the solid state and in water saturated chloroform and benzene solutions. The hexameric capsule is characterized by a large cavity of about 1375 Å^3 [10] and encapsulates quaternary ammonium compounds[11] and some transition metal complexes by establishing cation-π interactions with the electron-rich internal lining of its aromatic rings.[12] Alternatively, the capsule interacts with hydrogen bonding species like alcohols,[13] or acids.[14] These properties have been exploited to develop supramolecular catalytic systems based on the resorcin[4]arene hexameric capsule. In particular, the capsule has been used as i) a reversible shield to control the activity of a photo-catalyst[15] ii) a nano-reactor to impart unique substrate[16] and product[17] selectivities and iii) a supramolecular catalyst itself.[18]

Some of the latter examples are related to the capsule mediated activation of water as a nucleophile towards the addition to different classes of substrates. in particular, the selective hydrolysis of acetals[19] and the hydration of isonitriles to formamides driven by encapsulation of the substrates in the capsule that was recently disclosed by our group.[20]

Alkyne hydration is an atom efficient reaction that transforms alkynes into carbonyl compounds such as ketones and aldehydes.[21] The reaction is usually carried out with the aid of transition metal catalysts spanning from traditionally employed Hg species[22] to more recent examples based on Au(I),[23] Pt(II)[24] and Ru(II).[25] Alternatively, the reaction can be catalyzed by strong Brønsted acids like sulphuric acid in extremely large excess,[26] as well as other strong organic acids that require harsh experimental conditions and long reaction times.[27] For example, intrinsically electron rich internal aryl alkynes require the presence of *p*-toluensulfonic acid in ethanol solution under reflux conditions for several hours or

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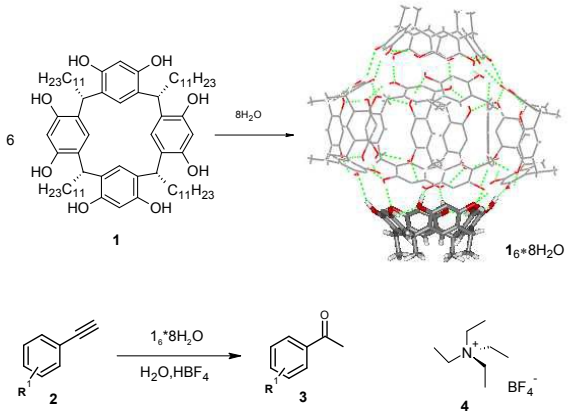
heating with MW irradiation.[28] The use of microemulsion conditions in water with the aid of surfactants and HCl 0.33 M by heating the system from 100 to 140 ° C for hours are also competent for the hydrolysis of alkynes.[29] Recently it was also disclosed that the combination of sulphuric acid with an ionic liquid favoured the hydration of alkynes under mild reaction conditions.[30,31] Likewise, the combination of a weak Brønsted acid as solvent with a strong Brønsted or Lewis acid catalyst like $Ga(OTf)_3$ enabled good yields of the carbonyl compound by heating at 100°C for few hours with reduced catalyst loading.[32]

Results and Discussion

Herein we present an example of very efficient supramolecularly promoted hydration of terminal aromatic alkynes mediated by the combination of a strong Brønsted acid with the self-assembled supramolecular organic capsule of resorcin[4]arene $\mathbf{1}_6.(H_2O)_8$ (Scheme 1). The capsule acts as an organocatalyst and in the presence of the Brønsted acid efficiently transforms aromatic alkynes into the corresponding ketones at reaction temperatures of 60 °C or lower, within a few hours. The catalytic effect was observed exclusively when the capsule cavity was accessible. The addition of competitive guests that preferentially encapsulate inhibited the catalytic activity of the hexamer. This behaviour resembles the functioning of enzymes active sites.



Scheme 1. Hydration reaction of terminal aromatic alkynes 2 leading to the corresponding ketones 3 in the presence of tetrafluoroboric acid and mediated by the capsule $\mathbf{1}_6.(H_2O)_8$ and the competitive guest tetraethyl ammonium tetrafluoroborate 4.

The hydration reaction of phenylacetylene **2a** as model substrate was monitored over time by means of ^{1}H NMR spectroscopy. The reaction was initially investigated at 60°C and for just a few hours. In the presence of the sole supramolecular capsule $\mathbf{1}_6.(H_2O)_8$ no reaction was observed (Table 1, entry 1). Similarly, in the presence of only strong Brønsted acids such as HBF_4, HCl or HNO_3 the hydrolysis reaction did not proceed (Table 1, entries 2-4). Only methanesulfonic acid, as expected[27a] and because of a better solubility in chloroform led to the partial formation of acetophenone **3a** and small amounts of products derived from acid addition that were confirmed by GC-MS (Table 1, entries 5-6). Only when catalytic amounts of the capsule $\mathbf{1}_6.(H_2O)_8$ were combined with strong Brønsted acids the quantitative hydration of **2a** to the corresponding acetophenone **3a** took place. In particular, using 10 mol% of capsule and 50 mol% of HBF_4 with respect to the substrate **2a** produced quantitative hydration in slightly more than one hour (Table 1, entry 7).

Table 1. Catalytic tests for the hydration of **2a**.

#	Brønsted Acid	Acid/2a	Time (h)	$\mathbf{1}_6$·8H$_2$O	4	3a (%)[a]
1	-	-	24	+	-	0
2	HBF_4	0.5	1	-	-	<2
3	HCl	0.5	1	-	-	<2
4	HNO_3	0.5	1	-	-	<2
5	CH_3SO_3H	0.5	1	-	-	57 (19)[e]
6[b]	CH_3SO_3H	0.2	18	-	-	13 (3)[e]
7	HBF_4	0.5	1.2	+	-	>98
8[b]	HBF_4	0.2	18	+	-	>98
9	HCl	0.5	1.5	+	-	>98
10[b]	HCl	0.2	24	+	-	10
11	HNO_3	0.5	1	+	-	18
12	CH_3SO_3H	0.5	1	+	-	>98
13[b]	CH_3SO_3H	0.2	24	+	-	59 (17)[e]
14	HBF_4	0.5	24	+	+	<2
15	HBF_4	0.5	24	-	+	<2
16[c]	HBF_4	0.5	24	-	-	<2
17[d]	HBF_4	0.1	24	+	-	>98
18[f]	HBF_4	0.5	24	-	-	39

Experimental conditions: [**1**]= 36 mM, [**2a**]= 60 mM, [Brønsted acid]= 30 mM, [**4**]= 60 mM (10 eq. with respect to the capsule), water saturated chloroform-d 1.5 mL, T= 60°C. +: presence; -: absence; a) Determined by ^{1}H-NMR; b) [**1**]= 18 mM, [**2a**]= 60 mM, [Brønsted acid]= 12 mM; c) [resorcinol] = 140 mM (24 eq. with respect to $\mathbf{1}_6$·8H$_2$O); d) [**1**] = 18 mM [**2a**]= 120 mM, [Brønsted acid]= 12 mM; e) amount of Brønsted acid addition products; f) [4-*n*-hexyl-resorcinol] = 140 mM (24 eq. with respect to $\mathbf{1}_6$·8H$_2$O).

Analogous result were obtained using longer reactions times (18 hours) and decreasing both the amount of the capsule and the acid (Table 1, entry 8). Similarly, HCl and methanesulfonic acid in combination with the capsule efficiently promoted the hydration reaction of **2a**. However, in this case a decrease in the amounts of both species had a detrimental effect on the catalytic activity of the mixture (Table 1, entries 9-10 and 12-13). Conversely, the use of nitric acid as Brønsted acid in the hydration reaction was not improved by the addition of $\mathbf{1}_6.(H_2O)_8$ (Table 1, entry 11).

It is widely accepted that the hydration reaction of alkynes occurs by water addition to the previously activated alkyne through protonation or coordination to a metal center. Both reaction mechanisms involve the enhancement of the electrophilicity of the substrate thus favoring the addition of water. Recently Tiefenbacher and coworkers demonstrated that the resorcin[4]arene hexamer behaves as a weak acid with a pKa of about 5.5,[19] while free resorcinol, not bound as in **1a**, has a pKa of 9.15. The weak acidity of the capsule is not enough to induce the protonation of the substrate to a significant extent, as shown by the lack of reactivity in the presence of the capsule alone (Table 1 entry 1). The cooperation of the capsular hexamer with strong Brønsted acids like HBF_4 and HCl turned out to be much more efficient to catalyze the hydration reaction. As described above, it is

well established that the hexamer favors the encapsulation of cationic guests and cationic reaction intermediates.[18,33] Thus, a plausible, albeit not proven, explanation of the catalytic effect exerted by the capsule in the hydration of alkynes would possibly reside in the stabilization of positively charged species that are formed by Brønsted acid protonation of the triple bond.

In order to support this hypothesis, a series of control experiments were carried out. In order to exclude the involvement of the resorcinol moieties of **1** in the reaction, we replaced the hexameric capsule with 24 equivalents of resorcinol with respect to the original amount of capsule. We observed that under these reaction conditions the formation of **3a** was negligible (Table 1, entry 16). We repeated the same control experiment using 4-*n*-hexyl-resorcinol as a more soluble resorcinol derivative observing 39% yield of **3a** only after 24h at 60°C. These experiments were indicative of the minor effect exerted by the resorcinol units to the reaction catalysis.

The hydration of **2a** was also investigated in the presence of HBF_4, capsule and tetraethylammonium tetrafluoroborate **4**, as a competitive cationic guest for the capsule's interior.[34] The tetralkyl ammonium guest **4** was rapidly encapsulated as demonstrated by the appearance of a broad resonance at –0.05 ppm in the ^{1}H NMR spectrum (Figure 1) with concomitant inactivation of the catalytic activity of the hexamer (Table 1, entry 14 and Figure 1E).

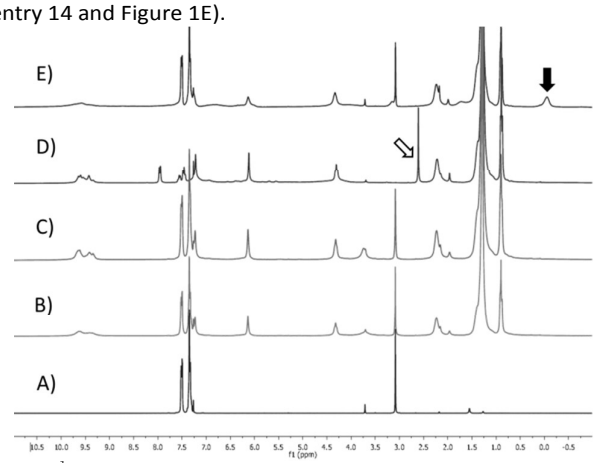
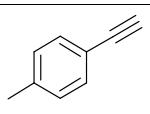
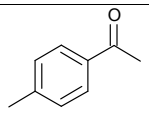
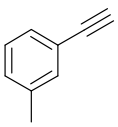
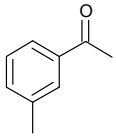
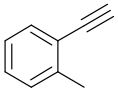
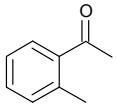
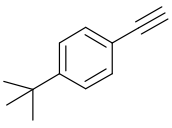
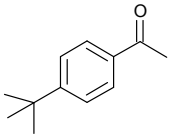
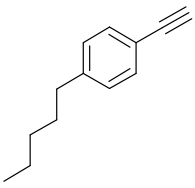
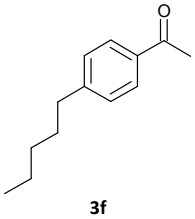
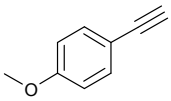
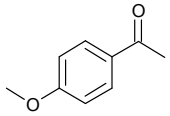
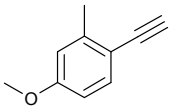
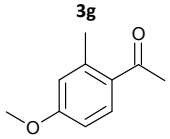


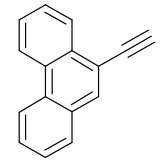
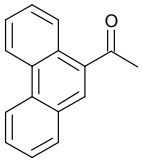
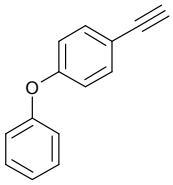
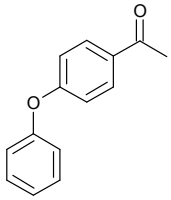
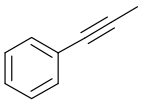
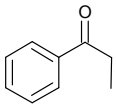
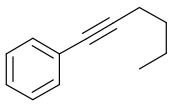
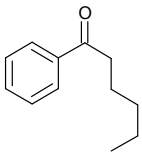
Figure 1. ^{1}H NMR spectra in water saturated chloroform-d: A) phenylacetylene **2a** (60 mM); B) phenylacetylene **2a** (60 mM) and $\mathbf{1}_6{\cdot}8H_2O$ (6 mM) after 18 at 60°C; C) phenylacetylene **2a** (60 mM) with HBF_4 (0.5 eq.) and $\mathbf{1}_6{\cdot}8H_2O$ (6 mM); D) phenylacetylene **2a** (60 mM) with HBF_4 (0.5 eq.) and $\mathbf{1}_6{\cdot}8H_2O$ (6 mM) after 70 minutes at 60°C; E) phenylacetylene **2a** (60 mM) with HBF_4 (0.5 eq.), $\mathbf{1}_6{\cdot}8H_2O$ (6 mM) and 4 (60 mM) after 18h at 24°C; ⇓ encapsulated ammonium, ⇩ acetophenone.

All reported data suggest that the cavity of the hexamer must be empty to allow the reaction to proceed. The ^{1}H-NMR analysis of a solution containing the capsule, the substrate phenylacetylene **2a** or **2a** and HBF_4 did not show evidence of encapsulated species (Figure 1C). Most likely, the reaction requires the initial, rate-determining, alkyne protonation by the strong Brønsted acid. The resulting cationic species is stabilized by encapsulation followed by a rapid attack of water that leads to the methyl ketone **3a**. Indeed, what matters is not the stabilization of the cationic species itself but the effect on the transition state yielding the charged intermediate, hence both substrate and vinyl cation are expected to be within the cavity even if the former is not macroscopically revealed by NMR.

The scope of the hydration reaction was investigated applying the catalytic system obtained by combination of HBF_4 and $\mathbf{1}_6{\cdot}8H_2O$ to a wide range of aromatic terminal alkynes as summarized in Table 2. With the aim of investigating the turnover properties of the catalytic system under investigation, catalytic tests were performed with 50 mol% of HBF_4 and 10 mol% of $\mathbf{1}_6{\cdot}8H_2O$ at 60°C for 1h and with 10 mol% of HBF_4 and 5 mol% of $\mathbf{1}_6{\cdot}8H_2O$ at the same temperature for 24h.

Table 2. Hydration reaction of **2b-2m** with HBF_4 mediated by the capsule $\mathbf{1}_6{\cdot}8H_2O$.

#	Substrate	Product	Yield (%)[a]
1	 **2b**	 **3b**	>98 2[b] >98[c] 18[b,c]
2	 **2c**	 **3c**	56 <2[b] 78[c] <2[b,c]
3	 **2d**	 **3d**	78 <2[b] 40[c] <2[b,c]
4	 **2e**	 **3e**	60 <2[b] 98[c] <2[b,c]
5	 **2f**	 **3f**	47 7[b] 83[c] 8[b,c]
6	 **2g**	 **3g**	>98[c] 72[b,c]
7	 **2h**	 **3h**	>98 >98[b]

8	 **2i**	 **3i**	40 <2[b]	85[c] 3[b,c]
9	 **2j**	 **3j**	54	17[b]
10	 **2l**	 **3l**	50[d]	<2[b,d]
11	 **2m**	 **3m**	25[d]	<2[b,d]

Experimental conditions: [**1**] = 36 mM; HBF_4/Substrate = 0.5 [**2b-m**]= 60 mM, water saturated chloroform-d 1.5 mL, T= 60°C; time = 1 h; a) Determined by ^1H NMR; b) reaction in the presence of [**4**]= 60 mM, c) [**1**] = 18 mM; HBF_4/Substrate = 0.1, T= 60°C; time = 24 h; d) [**1**] = 180 mM; HBF_4/Substrate = 0.5.

The hydration reaction turned out to be extremely sensitive to the electron density of the aromatic ring of the alkyne, providing higher yields for the more electron rich substrates. Furthermore, *N*-protonable 3- and 4-ethynyl pyridine derivatives did not produce the corresponding ketones in the presence of the capsule. On the other hand, extremely electron rich substrates bearing methoxy substituents i.e. *p*-methoxy-phenylacetylene **2g** and 4-methoxy-2-methyl-ethynylbenzene **2h** can react at 60°C both in the presence of the free hexamer and with the hexamer encapsulating the tetra-alkylammonium salt **4**. These results indicate that, for these activated substrates, the Brønsted acidity of HBF_4 was enough to catalyze the hydration reaction (Table 2, entries 6 and 7). In these cases, the presence of the capsule either filled by the cationic species **4** or free is substantially not influencing the reactivity of those activated substrates.

Substrates bearing alkyl substituents in the aromatic ring showed a clear improvement of the hydration reaction in the presence of the capsule as reported in Table 2 entries 1-5. It is noteworthy that a gradual decrease in the yield of the corresponding methyl ketone **3** was observed by increasing the size of the aromatic substrate **2**, regardless of its electronic nature (Table 2, entries 1-5). This suggests that the encapsulation of the protonated intermediate is size selective. The cavity of the hexamer can accommodate about 6-8 chloroform or benzene molecules. The encapsulation of the cationic intermediate of the reaction must occur together with a finite number of solvent molecules. In all cases, an agreement with the typical packing coefficient values observed for host-guests systems in solution is mandatory.[35] Further evidence of the selective encapsulation of the cationic intermediate was provided by the hydration reactions of large substrates such as 9-ethynyl-phenanthrene **2i** and 1-ethynyl-4-phenoxybenzene **2j** that led to much lower conversion to the corresponding ketone compared to the hydration of **2a** under similar experimental conditions (Table 2, entries 8 and 9). It is noteworthy that, even with some differences related to the intrinsic reactivity of the different aromatic alkynes, the inhibition effect imparted by the presence of the competitive ammonium guest **4** was observed in almost all substrates investigated in Table 2.

Other electron poor substrates like *p*-bromo-phenylacetylene, 1-(4-ethynylphenyl)ethanone and methyl-4-ethynylbenzoate failed to react in the presence of the capsule.

Finally, the hydration reaction was also tested using internal aromatic alkynes. We observed that 1-phenyl propine **2l** and 1-phenyl-hexyne **2m** formed the corresponding ketones with moderate yields and required the presence of higher amounts of both capsule and Brønsted acid (Table 2, entries 10 and 11). Conversely, 1,1'-ethyne-1,2-diyldibenzene and several terminal aliphatic alkynes did not show formation of the corresponding hydration products.[36]

Conclusions

In conclusion, we have described another example of supramolecular catalysis in which catalytic amounts of the hexameric self-assembled capsule $\mathbf{1}_6 \cdot 8H_2O$ in combination with sub-stoichiometric amounts of HBF_4 produced the hydration of aromatic alkynes **2** to the corresponding methyl ketones **3** in a few hours using a water saturated chloroform solution heated at 60°C. The Brønsted acid induces the protonation of the substrate while the supramolecular capsule likely provides a suitable nano-environment to stabilize the transition state leading to the positively charged vinyl cation intermediate species,[37,38] as would be expected by the protonation being the rate determining step of the reaction. Moreover, we demonstrated the inactivation of the supramolecular catalyst by addition of a competitive cationic ammonium guest **4** that is preferentially encapsulated. We also proved the sensitivity of the reaction to the size and shape of the substrates. These findings clearly speak for the occurrence of the hydration reaction within the cavity of the organocatalyst thus mimicking the active site of enzymes.

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