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Hexameric Resorcinarene Capsule is a Brønsted Acid: Investigation and Application to Synthesis and Catalysis

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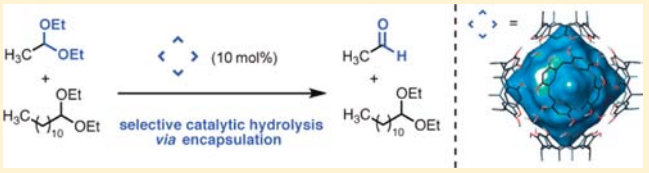
Supporting Information

ABSTRACT: Molecular capsules have attracted interest as simple enzyme mimetics and several examples of catalytic transformations in water-soluble metal−ligand based systems have been reported. This is not the case for hydrogen-bond based molecular capsules, which in contrast can be employed in organic solvents. We describe herein our investigations of such a system: The resorcin[4]arene hexamer is one of the largest hydrogen bond-based self-assembled capsules and has been studied intensively due to its ready availability. We present evidence that the capsule acts as a reasonably strong Brønsted acid (pK_a approximately 5.5−6). This finding explains the capsule's high affinity toward tertiary amines that are protonated and therefore encounter cation-π interactions inside the cavity. We were able to translate this finding into a first synthetic application: A highly substrate-selective Wittig reaction. We also report that this property renders the capsule an efficient enzyme-like catalyst for substrate selective diethyl acetal hydrolysis.



INTRODUCTION

Nature's capability to enzymatically catalyze reactions under mild conditions—ambient temperature or slightly higher "body" temperature and necessarily without any precautions against water and oxygen—has been fascinating synthetic organic chemists for decades. Enzymes selectively isolate suitable substrates inside a hydrophobic reaction pocket, adjust them into the reactive orientation and/or conformation, alter or enhance their reactivity by noncovalent or covalent interactions, stabilize the transition state of the reaction, and finally expel the product to complete the catalytic cycle.[1] Additionally, contributions to catalytic efficiency from quantum mechanical tunneling, matching of pK_a values in the transition state and protein dynamics have been identified.[1g]

Naturally, numerous attempts have been made to mimic such biological catalysts: Early examples of discrete entities included functionalized cyclodextrins, cyclic porphyrin oligomers, spherands, and cyclophanes, which were investigated among others by the groups of Breslow, Sanders, Cram, and Diederich, respectively.[1a,b,2] Beside such covalently linked host structures, noncovalently self-assembled structures also have been developed. These molecular capsules spontaneously form in solution via hydrogen bonds, metal−ligand interactions, or the hydrophobic effect and were mainly investigated by the groups of Rebek, Raymond, and Fujita, and Gibb, respectively.[3] Since such host structures self-assemble from smaller components, their preparation usually requires less synthetic effort and, additionally, they completely surround the encapsulated guests. Therefore, attention has shifted toward these systems as enzyme mimetics. The investigation of metal−ligand based molecular capsules has yielded numerous examples of catalytic transformation.[4] Interestingly, this is not the case with hydrogen-bonded capsules: There are only two examples of reactions catalyzed inside such molecular flasks.[5] In most cases, product inhibition prevents a catalytic turnover.[3k,m]

We wanted to explore the possibility of utilizing hydrogen-bonded molecular capsules as catalysts, not only because examples are scarce but mainly due to the fact that such systems are − in contrast to most metal−ligand capsules − soluble in organic media. This should allow the use of reagents which are not compatible with excess water. Since dozens of structurally different hydrogen-bonded molecular capsules have been described in the literature,[3] we screened for the following two properties: (1) ease of preparation: wider applications seem conceivable only if the capsule can be readily synthesized in large quantities; (2) large cavity size: to allow for experiments with a variety of different guest sizes and to prevent excessive binding of substrates (via strong contacts to multiple capsule walls), which usually translates into strong binding of the products (product inhibition). We identified the hexameric resorcin[4]arene capsule **I** (Figure 1), which was reported by the group of Atwood[6] in 1997, as an ideal candidate. It spontaneously forms in apolar solvents from six resorcin[4]-arene units **1**, which are readily prepared in multigram quantities in a single step. And with an internal volume of approximately 1400 Å^3, it also represents one of the largest hydrogen-bonded molecular capsules.

The structure of **I** was elucidated by single crystal X-ray analysis.[6] In addition to the six resorcin[4]arene units, eight water molecules participate in its formation and indeed also proved essential to its formation in solution.[7] The encapsulation of different guests[8] and the formation of the capsule itself have been investigated extensively in solution.[9] Also, the

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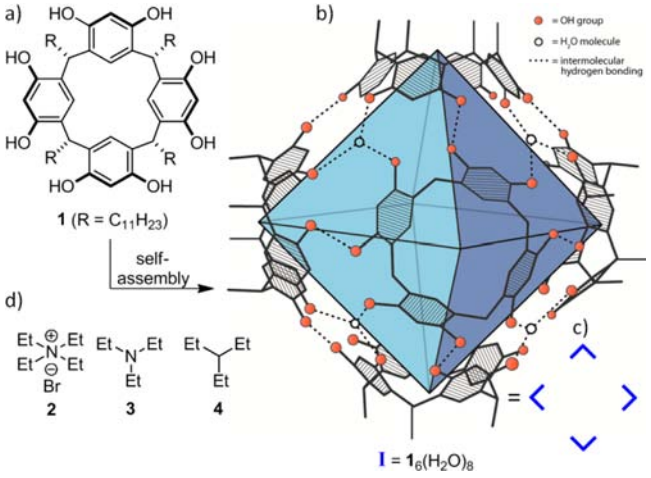

Figure 1. (a) Structure of resorcin[4]arene **1**; (b) schematic representation of the hexameric resorcin[4]arene capsule **I**, emphasizing the octahedral cavity space (blue); alkyl groups have been omitted for clarity; (c) simplified symbolic representation of the hexameric capsule; and (d) guest molecules first investigated for encapsulation in **I**.

stability toward polar additives[10] and the assembling properties in the presence of alcohols has been studied.[11] Besides NMR spectroscopy, EPR spectroscopy[12] and mass spectrometry[13] have been used to analyze molecular capsule **I**. A recent review also discusses the field of hexameric capsules.[14]

RESULTS AND DISCUSSION

Acidity of the Hexamer. Our investigations into this field started with the reproduction of an intriguing observation[8e,f,9c] described in the literature: Capsule **I** binds well both tetraalkylammonium salts and trialkylamines. While the strong interactions of alkylammonium compounds can be explained by cation-π stabilization inside the aromatic cavity, the efficient binding of amines was surprising to us. We reinvestigated this issue and quantified the encapsulation by separately adding 0.5 equiv of quaternary ammonium salt **2** (Figure 1) and triethylamine (**3**) to a solution of **I** in water-saturated $CDCl_3$ (3.3 mM in capsule **I**). Indeed, in both cases, the respective guests were completely encapsulated, as evidenced by integration of the upfield-shifted guest signals in the ^{1}H NMR spectrum. This seemed even more interesting, as the carbon analog of triethylamine (**3**), 3-ethylpentane (**4**), completely resisted encapsulation under such conditions, indicating that the amine functionality is responsible for the observed difference. We speculated that the tertiary amine is encapsulated so well only because it was protonated somehow.

Initial evidence in this direction and toward identifying the origin of the proton was found in the ^{1}H NMR spectrum of the experiment with triethylamine (**3**). Integration of the phenolic OH signals of assembly **I** at 9.75−9.31 ppm indicated that approximately 40% had shifted to higher field (broad signal 4.9−3.6 ppm). Evidence that this new signal corresponded to phenolic OH signals was obtained from NOESY-experiments: Correlation to the neighboring *ortho*-aromatic proton and the methine was observed (Supporting Information, SI, Figure 4). A similar pattern is seen with the phenolic protons of assembly **I**. If the capsule itself was acting as Brønsted acid, then the addition of 0.5 equiv of amine **3** would indeed affect up to half of the capsular assemblies and shift their OH signals to higher field due to the increased electron-density of the anionic species, while the signals of the remaining part would be unaffected. To investigate this phenomenon more closely, a capsule solution was titrated with incremental amounts (0.2 equiv) of triethylamine (**3**) (Figure 2). Several changes can be

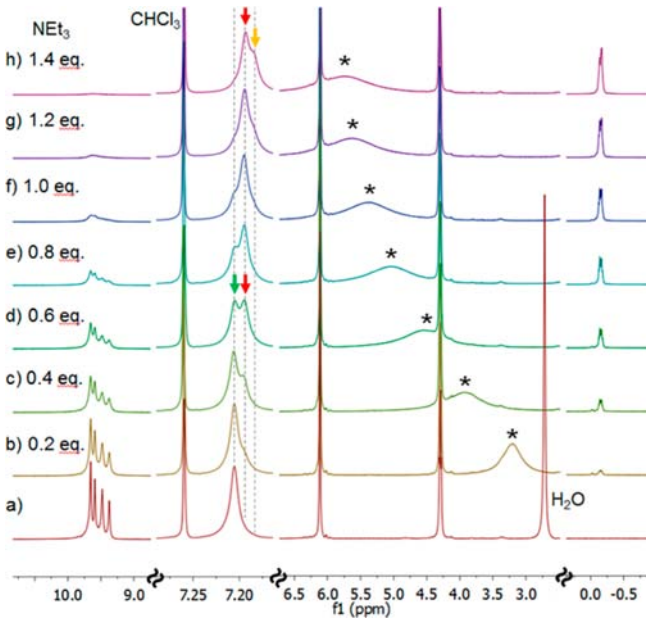

Figure 2. ^{1}H NMR titration of capsule **I** (a) in water-saturated $CDCl_3$ (3.3 mM) with various amounts of NEt_3 (b−h). Three different aromatic peaks at 7.20 ppm, indicating the encapsulation of different guests, are observable and are highlighted by colored arrows. The asterisk marks the shifted phenolic signals after deprotonation of the capsule.

observed in the ^{1}H NMR spectra: (1) The integral of the multiplet at 9.75−9.31 ppm, corresponding to the phenolic OH signals of the capsule, decreases inversely with added amounts of NEt_3. (2) The aromatic signal of the capsule at 7.20 ppm (*meta* to the phenol groups) is split; indicating in total three different species (highlighted by arrows). These changes are less pronounced in the other aromatic signal at ca. 6.11 ppm. (3) The water peak (which before amine addition appears at 2.72 ppm) is gradually shifted to lower field (indicated with an asterisk) and its integral gradually increases. Careful integration of the broad signal (see SI Table 1) indicated that in fact the phenolic signals at 9.75−9.31 ppm that had disappeared had shifted to the broad peak. Its integral closely matches the original water amount plus the shifted phenolic protons. This indicates a fast exchange of protons between phenols and water, which is not observed in the original capsule **I**. (4) Guest signal peaks appear at −0.10 to −0.15 ppm. Integration indicates that the added guest is completely encapsulated at all concentrations. Accordingly, no free guest signals can be observed in the ^{1}H NMR spectra.

These observations indicate protonation of the added amine by capsule **I**. However, it was not clear if the hexameric capsular structure was still intact as an anionic species after deprotonation, although the strongly high field-shifted guest signals (−0.10 to −0.15 ppm) indicated some form of capsular assembly. DOSY spectroscopy has proven to be the ideal tool to probe the size of the resorcinarene assembly as demonstrated by the Cohen group.[7,9a−d,10b] Therefore, this technique was used to determine the size of the respective species. The

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observed diffusion value ($0.24 \pm 0.01 \times 10^{-5}$ cm^2s^{-1}; see SI Figure 5) for a sample containing 1.4 equiv of triethylamine (Figure 2, spectrum h; complete deprotonation of **I**) is in very good agreement with the literature values of the hexamer **I** reported by the Cohen group.[7,9a−d,10b] Therefore, a smaller assembly—for instance a dimer, which was observed in crystal structures—[15] can be ruled out.

Taken together, the collected evidence is consistent with the encapsulation of the amine **3** as a protonated species inside the negatively charged capsule **I**—denoted here as $HNEt_3^+@I^-$ (Figure 3). To some extent, a pairwise encapsulation of a

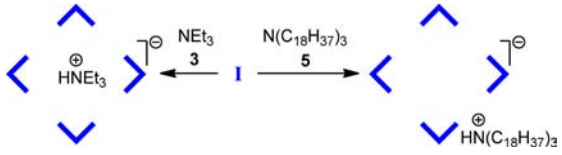

Figure 3. Schematic representation of the protonation and encapsulation of NEt_3 (**3**) by **I**. The larger trioctadecylamine (**5**) is protonated by **I** but cannot be accommodated inside the cavity.

protonated amine and regular amine—interacting via the proton—is likely, since we observe complete uptake of 1 equiv of NEt_3 but not complete disappearance of the original phenolic capsule **I** signals (e.g., Figure 2f). The pairwise encapsulation of amines could also explain the splitting of the aromatic signal at 7.20 ppm (Figure 2): The peak highlighted in green corresponds to the original capsule **I**; the red arrow marks the peak of $HNEt_3^+@I^-$; and the yellow arrow refers to assembly $Et_3N{\cdot}HNEt_3^+@I^-$. Such a pairwise encapsulation of amines was also observed in metal–ligand based capsules by the groups of Bergman and Raymond.[4j]

To corroborate these findings, we tried to obtain direct evidence for the protonation of the tertiary amine: The affected methylene groups of NEt_3 (**3**) next to the nitrogen atom were strongly high field-shifted due to encapsulation—concealing any possible low field shift caused by protonation. Therefore, we studied the protonation using trioctadecylamine (**5**), which is too large for encapsulation[8f] and where we therefore could easily observe possible low field shifts of the affected methylene groups in the ^1H NMR spectrum. Consistent with protonation of the amine, we observed a shift of the adjacent methylene groups from 2.37 to 2.84 ppm—a value which is in good agreement with the separately synthesized trifluoroacetic acid salt (see SI Figure 7).

After having collected evidence that protonation of tertiary amines is indeed occurring, we wanted to estimate the acidity of assembly **I**. Therefore, we investigated its behavior toward amines of decreasing basicity[16] (Figure 4). Addition of 0.5 equiv of bases with pK_a values ranging from 11−6.1 to a solution of **I** in water-saturated $CDCl_3$ (3.3 mM) resulted in approximately 80% of protonation (as revealed by the residual OH peak at 9.75−9.31 ppm, cf. Figure 2). As discussed before, complete protonation is not observed, since a pairwise encapsulation of a protonated and a regular amine is also observed ($Et_3N{\cdot}HNEt_3^+@I^-$). Beginning with pyridine (pK_a = 5.2), we observed a lower degree of protonation (53 ± 1%), which is further decreased to 23 ± 2% in the case of aniline (pK_a = 4.6). Amines of lower basicity did not show any degree of protonation as evidenced by ^1H NMR spectroscopy. From these results, we estimated the pK_a of hexamer **I** as approximately 5.5−6 (for calculations, see SI).[17]

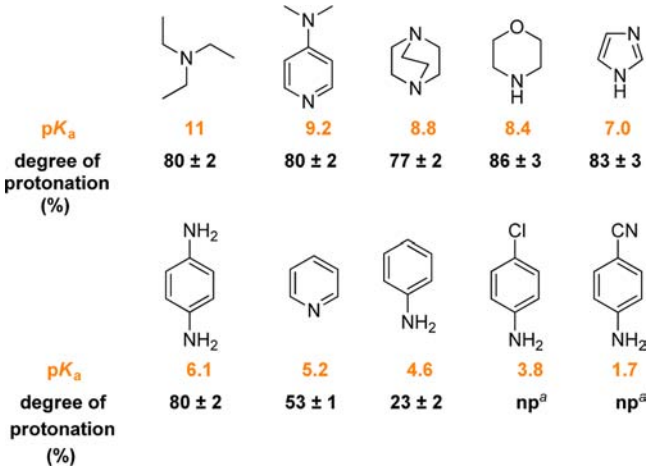

Figure 4. Estimation of the pK_a value of **I** by addition of 0.5 equiv of base to a solution of **I** in water-saturated $CDCl_3$ (3.3 mM); pK_a values (measured in water) were taken from literature.[16] [a]No protonation was observed.

Why is the hexameric capsule **I** acting as a relatively strong acid? (1) The protonation leads to thermodynamically more stable complexes due to cation-π interactions. (2) The anion formed is stabilized well by delocalization. The negative charge can be freely shifted between the 48 phenolic groups and the eight water molecules of assembly **I** via proton migration (see Figure 5). (3) Additionally, attractive Coulomb interactions between the ammonium guest and the negatively charged capsule could be involved.

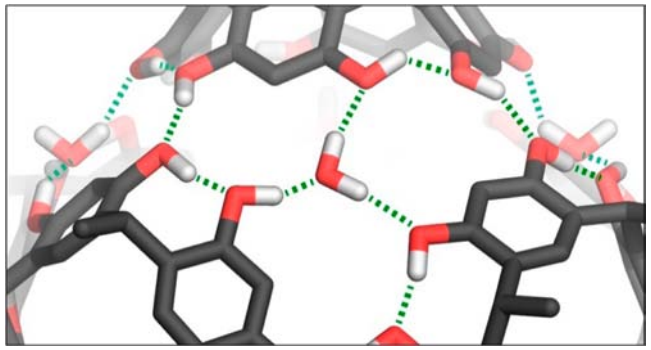

Figure 5. Section of the hydrogen bond seam of capsule **I**.

We next investigated if encapsulation of an ammonium guest influences the acidity of **I**. We chose to synthesize the large dialkyl aniline **6** (Figure 6) as a probe, which due to its pK_a (cf., Figure 4) should not be protonated to a high extent and therefore should allow the observation of increased and decreased protonation. Additionally, due to its size it cannot be encapsulated, and therefore, the addition of the ammonium guest cannot change the encapsulation ratio (which could alter the protonation equilibrium). While we observed 15 ± 1% protonation when adding 1 equiv of **6** to **I** in water-saturated $CDCl_3$ (3.3 mM), the degree of protonation was increased to 22 ± 1% when the capsule was occupied by a tetrabutylammonium guest (1.0 equiv of Bu_4NBr was added to the solution of **I**) under otherwise identical conditions. The increased acidity of **I** in this case could stem from the energy gain from Coulomb interactions between the tetrabutylammonium guest and the negatively charged capsule. This observation was interesting in

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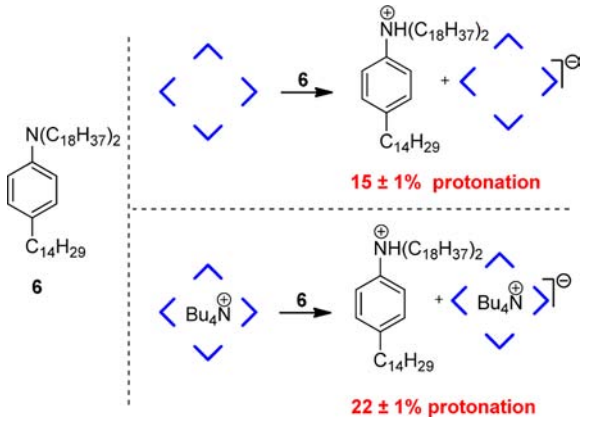

Figure 6. The protonation of aniline **6** by **I** was explored in the presence and absence of the encapsulated tetrabutylammonium salt.

light of potential applications of **I** as an acidic catalyst, since blocking the cavity with the ammonium guest could result in an increased background reaction outside of the capsule during a control reaction.

Synthetic Application via Size-Selective Protonation. After having revealed the acidity of assembly **I**, we next tried to translate these findings into first synthetic applications. We explored the possibility of protonating a stabilized Wittig ylide, which should have an appropriate pK_a value of approximately 8–9.[18] Indeed, the addition of 0.85 equiv of Wittig ethyl ester **7** (Figure 7a) to a solution of **I** (1.0 equiv) in water-saturated $CDCl_3$ (8.0 mM) resulted in complete protonation of the ylide (as evidenced by the integral of the original phenolic OH signals in the ^{1}H NMR spectrum) and complete encapsulation.

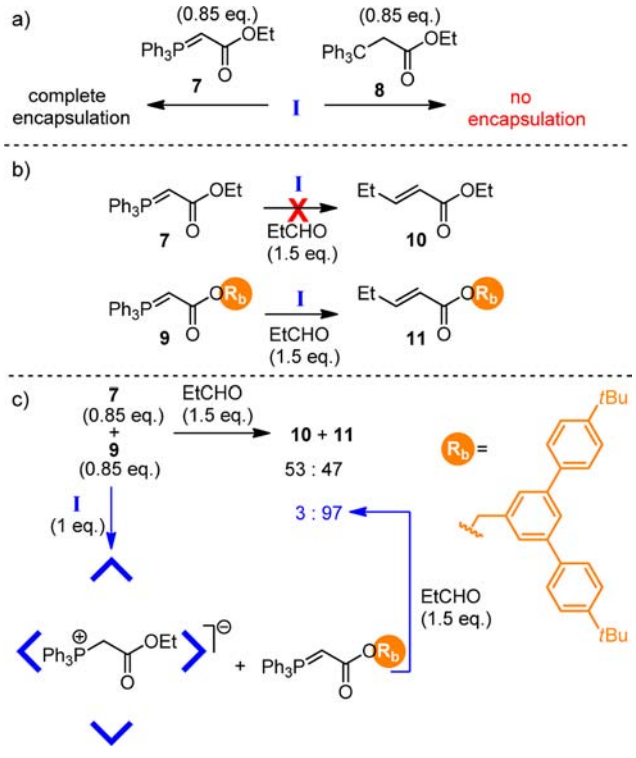

Figure 7. (a) Encapsulation experiments with Wittig ylide **7** and carbon analog **8**; (b) reactivity test of Wittig ylides **7** and **9** in the presence of **I** and EtCHO; and (c) comparison of the selective Wittig reaction in the presence of **I** and the regular reaction in solution.

For comparison, the carbon analog of **7**, namely ethyl 3,3,3-triphenylpropanoate (**8**, Figure 7a), which lacks the ability to accept a proton, was also investigated: It did not yield any detectable amounts of encapsulated species under similar conditions, again emphasizing the role of protonation in the binding of basic compounds. The encapsulated protonated Wittig ylide **7** was tested for its reactivity toward aldehydes. Even the addition of excess propanal (10 equiv) did not produce any alkene product, although the uptake of propanal into the capsule could be observed by the appearance of characteristic signals (SI Figure 10). This lack of reactivity further corroborates our understanding of the acid base chemistry in this system.

We next synthesized a large Wittig ester **9** (Figure 7b), which is not able to fit inside **I**. When 0.85 equiv of **9** were added to a solution of **I** (1.0 equiv) in water-saturated $CDCl_3$ (8.0 mM), as expected, a high degree of protonation (approximately 90%) and no encapsulation was observed via ^{1}H NMR spectroscopy. Addition of 1.5 equiv of propanal to this solution resulted in formation of alkene **11** (66% yield after 16 h), indicating that the protonation of the Wittig ylide outside of **I** was reversible and did not prevent conversion to the alkene. Finally, we tested if capsule **I** can act as a selector in the Wittig reaction of a mixture of ylides **7** and **9** (Figure 7c): Addition of a ylide mixture (0.85 equiv of **7**, 0.85 equiv of **9**) to a solution of **I** in water-saturated $CDCl_3$ (8.0 mM), followed by the addition of propanal (1.5 equiv), led to the highly selective formation of alkene **11** (74% isolated yield, E/Z = 14: 1). Only traces of alkene **10** could be detected by ^{1}H NMR spectroscopy and 72% of ylide **7** could be recovered by basic column chromatography. The selectivity imposed by capsule **I** (ratio of **10: 11** = 3: 97) was in stark contrast to the unselective reaction without **I** under otherwise identical conditions, which led to a 53:47-mixture of **10** and **11**.

Catalytic Size-Selective Hydrolysis of Acetals. After having demonstrated that the acidity of assembly **I** can be efficiently used to impose substrate selectivity on a stoichiometric reaction, we wanted to explore the potential use of **I** as a selective enzyme-like catalyst. We decided to investigate the hydrolysis of acetals, and after screening several different acetal groups found that 1,1-diethoxyethane (**12**, R = methyl, Figure 8) was a suitable substrate: Addition of 10 equiv of acetal to a solution of **I** in water-saturated $CDCl_3$ (3.3 mM) resulted in good conversion (85%) after 1 h at 25 °C. The control experiment with inhibited catalyst (adding 2.4 equiv of the guest Bu_4NBr to the catalyst solution before addition of substrate) only showed a slow background reaction (1% after 1 h). A second control experiment in water-saturated $CDCl_3$ without added catalyst did not show any detectable conversion. These first results were interesting, since they demonstrated that a catalytic conversion is indeed possible with **I** and that the reaction is taking place inside the cavity. Additionally, the successful hydrolysis implies that water is able to enter the cavity of **I**. It is likely that the eight water molecules that are already bound at the surface of **I** (Figure 5) are enabling hydrolysis.

We next investigated the substrate selectivity of the catalytic diethyl acetal hydrolysis by varying the alkyl group R (Figure 8). 1,1-Diethoxypropane **13** (R = ethyl) showed comparable results to 1,1-diethoxyethane **12** (R = methyl), giving approximately 86% conversion after 60 min. When catalyst **I** was blocked with a good guest (Bu_4NBr), the hydrolysis of **13** was efficiently slowed down, giving only a weak background

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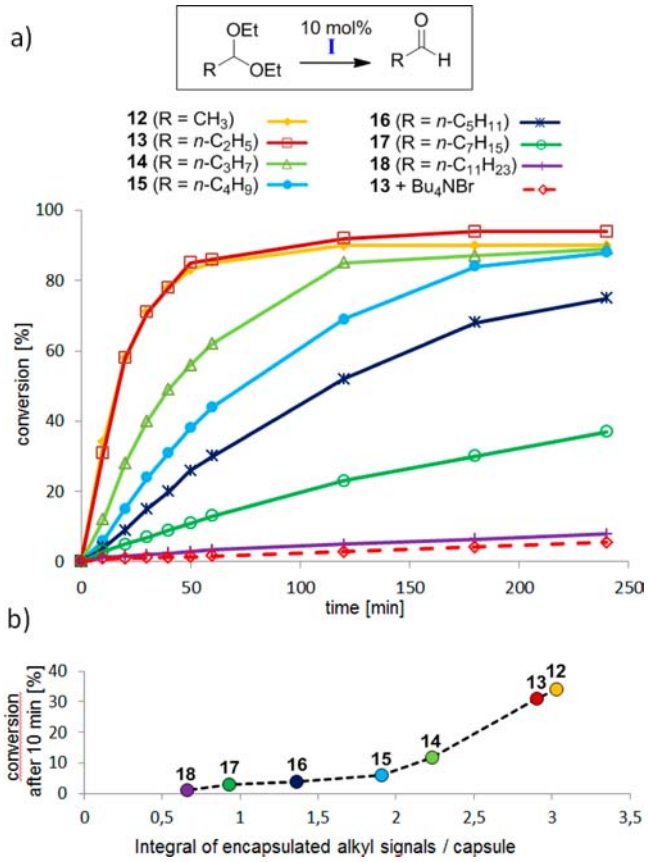
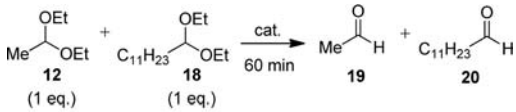


Figure 8. (a) Catalytic hydrolysis of various diethyl acetals inside **I** and (b) comparison of the conversion after 10 min to encapsulated alkyl signals (^{1}H NMR region: 0.6 to −2 ppm).

reaction (dotted line in Figure 8), although we observed increased acidity of **I** when occupied by the ammonium guest (see Figure 6). This further demonstrates that the reaction is indeed greatly accelerated *inside* the cavity of **I**. Interestingly, the reaction rate slowed down considerably with longer alkyl groups: 1,1-diethoxybutane **14** (R = propyl) gave 62%, 1,1-diethoxypentane **15** (R = butyl) gave 44%, 1,1-diethoxyhexane **16** (R = pentyl) gave 30%, 1,1-diethoxyoctane **17** (R = heptyl) gave 13% and 1,1-diethoxydodecane **18** (R = undecyl) gave only 3.4% conversion after 60 min. The decreased hydrolysis rate of the longer alkyl acetals cannot be explained by size exclusion arguments. All of the tested acetals can be accommodated well inside the cavity of **I**, as evidenced by the occupation ratio. Even the largest tested acetal (1,1-diethoxydodecane) only occupies 22% of the available space, much less than the optimum of approximately 55%[19] (see SI Table 2). The remaining space would be filled with solvent molecules. To explain the selectivity, we turned to the extent of encapsulation of the different acetals. Unfortunately, we could not determine the encapsulation ratio, since the characteristic acetal-guest signals are not observable after encapsulation, due to signal overlap. We therefore tried to utilize the encapsulated alkyl signals of the acetal, which were shifted to the region of 0.6 to −2 ppm as measure of encapsulation. Since the acetals utilized differ greatly in the number of alkyl protons, and more importantly, it is not known which of the respective alkyl protons are shifted into the observable region due to the anisotropy of the capsule walls, the encapsulation ratio remained elusive. We could only compare the integral of the encapsulated aliphatic signals (characteristically shifted to the region 0.6 to −2 ppm) in the various experiments. In Figure 8b, these values are plotted versus the respective conversion after 10 min (initial rate). Although the larger acetals (especially **17** and **18**) have more aliphatic protons (which potentially could shift to the high field-region mentioned), we observe a negative correlation of acetal size and alkyl integral. These findings point to a faster encapsulation of the smaller guests, a phenomenon which has been observed in other systems[20] but has not been translated into synthetic applications before. It seems that the smaller acetals are cleaved much more rapidly due to more efficient encapsulation.

Finally we explored the possibility of selectively hydrolyzing one acetal in the presence of another. Indeed, the hydrolysis of a mixture of **12** and **18** (10 equiv each) proceeded in a highly selective fashion (Figure 9): After 60 min, the smaller acetal



cat.	conv.	ratio 19 : 20
400 mol% TFA	65%	37 : 63
10 mol% **I**	85%	98 : 2

Figure 9. Selective hydrolysis of acetal **12** in the presence of acetal **18** within catalyst **I**.

was hydrolyzed to a large extent (83%), while the other acetal showed only 2% conversion—resulting in a selectivity of 98:2 at 85% combined conversion. As a control experiment, we wanted to replace capsule **I** with a regular acid of comparable acidity. When utilizing acetic acid (pK_a = 4.8)[16] instead of **I** under otherwise identical conditions, no conversion was observed (monitored for 15 h), although its acidity is approximately one magnitude higher than **I**. This observation indicated the fundamental role of the cavity space in the hydrolysis: We believe that it enables reactions under mild conditions that are not possible in the solution phase by stabilizing cationic intermediates and transition states in the hydrolysis process. To reach comparable hydrolysis rates in solution, we had to turn to the much stronger trifluoroacetic acid (pK_a = 0.2)[16] and use it in large excess (4 equiv per acetal as compared to 10 mol % **I**!). Not surprisingly, the hydrolysis led to mixtures—giving 24% of **19** and 41% of **20** after 60 min (ratio of 37:63). Thus, we could demonstrate selectivity imposed by catalyst **I** in a reaction that is very hard to control in the solution phase.

■ CONCLUSIONS

We have provided evidence that the hexameric capsule **I** is acting as a reasonable strong acid ($pK_a \approx 5.5–6$). This finding explains its good binding of tertiary amines, which are protonated to give ammonium ions and then encounter strong cation-π interactions inside the cavity. Further, we demonstrated that the acidity of **I** can be translated into first synthetic and even catalytic applications.[21] The catalytic example presented mimics the basic principle of operation in enzymes: A suitable substrate is selectively isolated inside the reaction pocket, its reactivity is enhanced by protonation, and the cationic transition states likely stabilized by cation-π interactions with the aromatic cavity. Finally, the product is released, since it does not bind strongly to **I**, to complete the catalytic

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cycle. We are convinced that our findings will fuel further applications of **I** as a reaction chamber and as an enzyme-like catalyst.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures, characterization data for new compounds and relevant NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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