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Guest Encapsulation within Self-Assembled Molecular Containers

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Molecules can behave quite differently when they are isolated from their surrounding and are restrained within a molecular container with a defined shape, volume, and chemical environment. Since the pioneering work by Cram et al. on covalent hemicarcerands,[1] in the last years also self-assembled capsules based on the reversible aggregation of smaller building blocks have received broad attention. Different kinds of molecular containers have been developed, for example, on the basis of metal–ligand interactions,[2] H-bonds,[3] ion pairing,[4] or hydrophobic interactions.[5] This Highlight will focus on some recent achievements in the field of guest encapsulation within self-assembled molecular containers. For earlier work up to 2005, some excellent review articles are recommended.[6] We will show how molecular containers can be used 1) to selectively bind specific guests, 2) to force guest molecules to adopt otherwise unstable conformations, 3) to stabilize reactive intermediates, and 4) to control chemical reactions.

Fabris and co-workers very recently presented a new H-bonded capsule based on trisoxime **1** (Figure 1 a).[7] In chloroform solution, **1** forms dimers that selectively encapsulate small guests such as methane, O_2, N_2, or Ar whereas larger molecules such as cyclohexane are not bound. Guest binding can be followed by using NMR spectroscopy. On the one hand, the bound guest experiences a high-field shift owing to the anisotropy of the benzene ring current. For example, bound methane gives a ^{1}H NMR signal at $\delta = -2.64$ ppm (a downfield shift of $\Delta\delta = -2.85$ ppm). On the other hand, oxygen as a guest also affects the NMR signals of the host. Its paramagnetic triplet state changes the relaxation times of the nuclei of the host that are in close proximity of the bound oxygen. Hence, the selective broadening of some signals of host **1** in the presence of oxygen can be used to probe its position within the capsule.

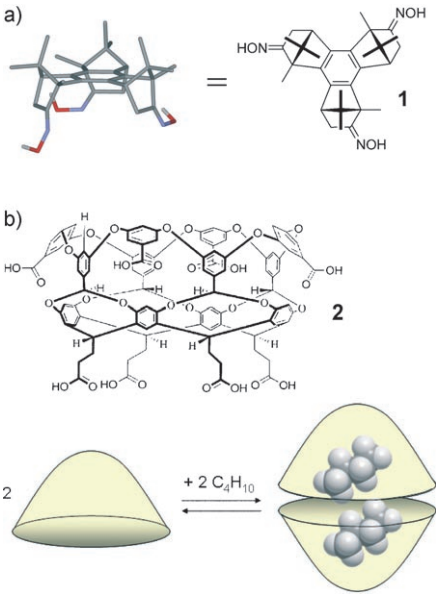

Figure 1. a) The trisoxime **1** forms H-bonded dimeric capsules that bind small gas molecules (O_2, N_2, CH_4, Ar) in organic solution; C dark gray, N blue, O red, H light gray. b) Butane induces the solvophobic dimerization of cavitand **2** in water, whereas smaller hydrocarbons are bound less efficiently.

The capsule preferentially binds cylindrical guests such as O_2, N_2, or CO over spherical guests (Ar, methane). The optimal packing coefficient for gaseous guests is in the range 0.40–0.55.

Sometimes more than one guest molecule fits into a capsule. The deep-cavity host **2** with a hydrophobic rim takes up gaseous butane in aqueous solution to form a 2:2 complex (Figure 1 b).[8] In this case, capsule formation is templated by guest encapsulation. Without the guest, only monomeric **2** is present in solution, as could be shown with DOSY NMR spectroscopy. Spontaneous gas uptake occurs on a time scale of several hours and depends on the partial pressure of the guest in the gas phase. Propane also forms a similar but weaker 2:2 complex. Its affinity is only $^1/_{12}$ of that of butane. Hence, an aqueous solution of host **2** selectively takes up butane from a 1:1 mixture of butane and propane. Ethane is too small to induce capsule formation, therefore only a weak 1:1 complex between **2** and ethane is formed. Such a selective guest encapsulation within a molecular container might find applications for gas separation and storage. The bound guest can be easily removed by increasing the temperature of the solution or by purging with an inert gas.

When the noncovalent interactions between the building blocks of the capsule are strong enough, also guests that are too large can be bound if they can be forced to adopt a folded and hence more compact conformation. For example, Rebek, Jr. et al. could show that within a resorcinol-based self-assembled capsule **3** (Figure 2), alkanes up to *n*-decane are bound in an extended conformation which is also the energeti-

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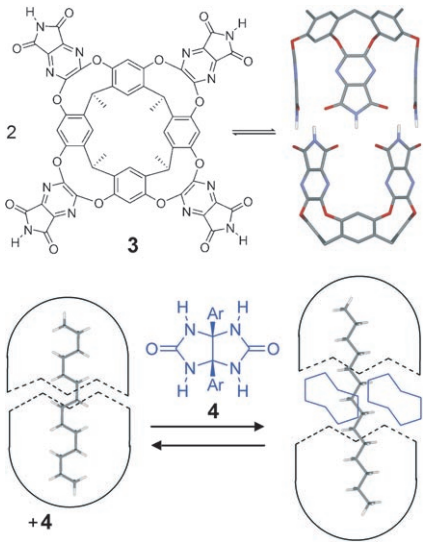

Figure 2. Cavitand **3** forms a H-bonded dimer, which encapsulates tetradecane in a compressed conformation. Upon addition of glycouril **4**, the capsule expands and allows the guest to relax to its more stable extended conformation.

cally most stable conformation for the free molecule.[9] However, tetradecane is too long to fit into the cavity of the capsule; nevertheless, it is bound but forced to adopt a compressed, helical conformation that contains at least eight unfavorable *gauche* interactions. This coiled conformation therefore exerts a pressure onto the self-assembled capsule as the tetradecane molecule tries to uncoil. The system is in a sort of mechanically excited state, representing a molecular "spring-loaded" device.

Glycourils such as **4** can be incorporated into the H-bond network at the dimerization rim, thereby extending the capsule and allowing the tetradecane to relax to an extended conformation. The glycouril spacer can then be removed again by the addition of acid (HCl), thereby causing the precipitation of its insoluble hydrochloride salt. The tetradecane molecule is then forced back into the coiled conformation within the once again smaller capsule. These coiling/extension cycles can be repeated several times, thus representing a model for a molecular machine that is controlled by an external stimulus (acid/base, in this case).

The amount of "stress" that can be forced onto a guest of course depends on the strength of the noncovalent interactions that hold the self-assembled capsule together. Therefore, the spring-loaded device **3** only works in nonpolar organic solvents as it relies on H-bonds. Metal–ligand interactions are much stronger, approaching the strength of covalent bonds. Metallo-supramolecular capsules are therefore also stable in water in contrast to purely H-bonded assemblies.

Fujita has used a prismlike porphyrin cage self-assembled from a pyridyl-substituted porphyrin and {Pd^{II}(en)} to bind the tripeptide Ac-Ala-Ala-Ala-NH_2 (Ac = acetyl, Ala = alanine) in water.[10] The guest is bound within the cage through extensive hydrophobic interactions ($K_{ass} = 10^6\,M^{-1}$). However, NOESY experiments showed that the tripeptide adopts a β-turn conformation. Distinct NOE signals were observed between the *N*-acetyl group and the C-terminal alanine residue. In contrast, in free solution the tripeptide is present in an extended conformation. A β-turn is normally only stable within a folded conformation of more than nine amino acids. So here again, the bound guest is forced into a conformation that is not the most stable one of the free guest. However, this strained conformation provides the best spatial fitting within the cavity and allows for the most extensive interactions between the guest and host (CH–π interactions, as indicated by modelling data). Similarly, a nine-residue peptide was folded into an α-helical conformation upon encapsulation within the dimeric capsule of a metal-linked $[M_6L_4]$ (M = {Pt^{II}(en)}, L = tris(3-pyridyl)triazine) bowl-shaped host.[11]

The geometric requirements within a self-assembled capsule can thus force a molecule to fold into a specific conformation. Furthermore, within the capsule, the guest is isolated from the surrounding, which significantly affects its chemical reactivity. In this way, also otherwise unstable molecules can be efficiently trapped and isolated within such capsules. Compared to the stabilization of reactive intermediates within covalent hemicarcerands, as developed by Cram et al. and now continued by Warmuth et al.,[12] the use of self-assembled capsules makes this approach synthetically much easier. One just has to mix the building blocks of the capsule as well as the guest in solution, and the complex forms spontaneously.

However, the entrapped guest can exchange with its surrounding even though its lifetime within the capsule can vary from milliseconds to weeks (the latter especially for very stable metallo-supramolecular cages). This process of course limits the lifetime of any reactive intermediate trapped within a self-assembled capsule.

In the crystalline state, guest exchange is more or less impossible. Therefore, Fujita and co-workers were able to generate the coordinatively unsaturated complex $[Cp'Mn(CO)_2]$ (**6**; $Cp' = C_5H_4Me$) within a self-assembled $[M_6L_6]$ coordination cage **5** (Figure 3).[13] Initially, the stable precursor

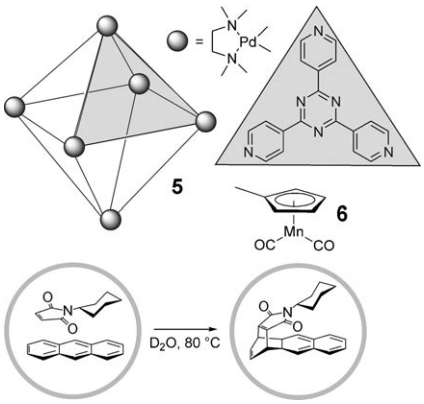

Figure 3. Fujita et al. used a self-assembled $[M_6L_6]$ cage **5** to encapsulate and stabilize reactive organometallic intermediates such as **6** or to impose geometric constraints onto the [4+2] cycloaddition of anthracene and maleimide to give an unexpected regioselectivity.

$[Cp'Mn(CO)_3]$ was encapsulated. The reactive intermediate was then generated upon photoirradiation of the crystal, which led to the dissociation of one CO molecule. The X-ray structure analysis showed that the unstable $[Cp'Mn(CO)_2]$ fragment adopts a pyramidal geometry.

Raymond et al. were able to isolate the highly reactive ion [Cp(Ru(*cis*-1,3,7-octatriene)]$^+$ (**8**; Cp = C_5H_5) within a tetrahedral $[M_4L_6]$ self-assembled cage **7** (Figure 4).[14] This reactive organometallic intermediate is stable within the capsule for weeks in aqueous solution even though it otherwise decomposes within minutes in water. Nevertheless, it can still react within the cage, for

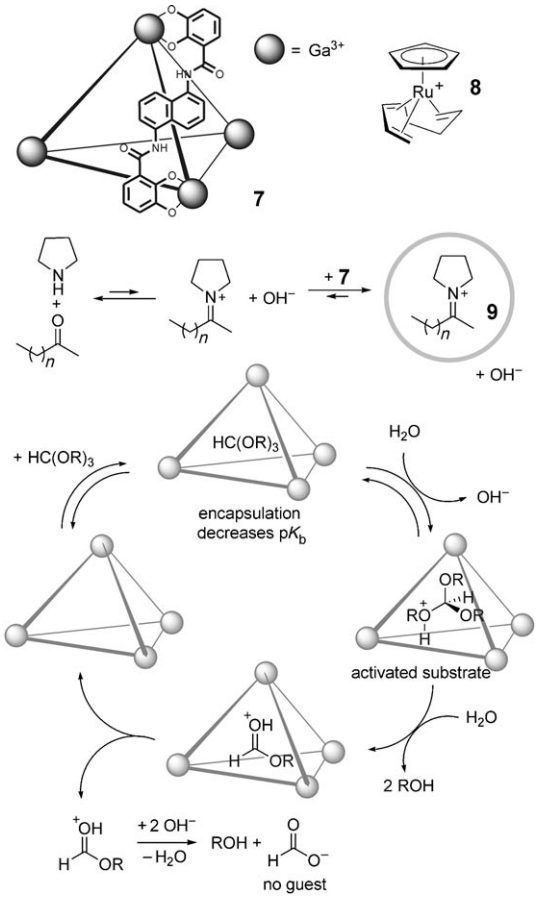

Figure 4. The self-assembled $[M_4L_6]$ cage **7**, developed by Raymond et al., preferentially binds cationic substrates such as **8** or iminium ions **9** that are otherwise unstable in aqueous solution. Even acid catalysis in basic solution (pH 11) becomes possible, as shown for the hydrolysis of an orthoester.

example, with CO which is present in the solution.

Also unstable organic species can be stabilized within the same capsule.[15] The self-assembled $[M_4L_6]$ cage preferentially hosts cationic guests over neutral ones as the cage is negatively charged. For example, iminium ions are formed from the condensation of a secondary amine with an aldehyde or ketone. This is an equilibrium reaction that, in the presence of water, normally lies completely on the side of the reactants. The concentration of iminium ions is negligible in neutral or basic aqueous solution. The cage **7**, however, efficiently traps and stabilizes the iminium ions within the capsule (Figure 4). Once encapsulated, the iminium ions are stable for months at room temperature even in water at pH > 7. However, the shape of the capsule dictates which iminium ions can be entrapped. The binding efficiency depends on the size, shape, and hydrophobic character of the iminium ion. For example, for iminium ions formed from pyrrolidine and 2-alkanones, the encapsulation efficiency first increases until an optimum is reached for 2-pentanone before it decreases again with longer alkyl chains. Finally, no iminium ion could be observed for 2-undecanone, which is obviously too large as a guest to be accommodated within the cavity of the host.

Guest encapsulation within a self-assembled molecular container can also significantly change the chemical properties of the bound guest. The preference of **7** for cationic guests over neutral ones affects the basicity of encapsulated guests (amines become more basic by about four orders of magnitude). As Raymond et al. just recently showed,[16] this pK_a shift allows also for acid catalysis in basic solution (Figure 4). Upon encapsulation within the cage, orthoformates $HC(OR)_3$ (R = C1–C5 alkyl groups) are easily protonated by water even at pH 11. The protonated orthoester within the cage is then hydrolyzed to give the protonated ester. After release from the cage, the ester is immediately converted into the carboxylate. As the carboxylate is no guest for the cage anymore, no product inhibition occurs: The self-assembled host acts as a real supramolecular catalyst, accelerating the hydrolysis of orthoformates up to a factor of 890 over the uncatalyzed reaction. Of course, only those orthoformates that fit into the capsule are hydrolyzed. Triphenylorthoformate is too large and does not react. Furthermore, similarly to enzymes, a better binding guest such as NPr_4^+ also effectively prevents hydrolysis owing to competitive inhibition.

In this case, the molecular container first enables the reaction under the specific conditions. However, the capsule can also change the selectivity of a reaction as a result of the geometric constraints it imposes on the bound guests. Rebek, Jr. and Kang showed some years ago that a H-bonded capsule promotes Diels–Alder reactions by bringing the two reactants into close proximity upon coencapsulation.[17] Fujita and co-workers have now used **5** to impose an unusual regioselectivity upon the Diels–Alder reaction between anthracene and *N*-cyclohexyl maleimide.[18] Within the capsule, the two reactants are orientated in a way that only allows cycloaddition to the 1,4-position of the anthracene molecule (Figure 3). The usual 9,10-adduct can not be formed owing to geometric constraints. The large *N*-cyclohexyl substituent on the maleimide forces the double bond over the terminal ring of the anthracene molecule. However, this reaction is not catalytic, as the product is bound even better than the two starting materials for entropic reasons. However, this product inhibition allowed Fujita and co-workers to obtain the crystal structure of the reaction product bound inside the cage, thus illustrating its orientation within the capsule.[18b] The scope of this reaction was very recently extended by Fujita et al. to other aromatic compounds besides anthracene. Also arenes such as triphenylene give efficient formation of Diels–Alder adducts through coencapsulation with *N*-cyclohexyl maleimide, even though in free solution they are not substrates for [4+2] cycloadditions.[18c] Similar geometric constraints in reactions have also been observed for guests encapsulated in dimeric capsules of host **2**.[19]

These examples show that the field of guest encapsulation within self-assembled containers has matured in recent years. Such nanovessels provide a very specific environment in terms of size, shape, and chemical properties around a bound guest, which not only dictates the selectivity of guest binding but can also be exploited to control the structure or the chemical reactivity of encapsulated species. At the moment, the choice of capsules still dictates which species are bound and which reactions can be performed within. But as our knowledge of these phenomena improves, the more likely tailor-made

nanovessels for specific purposes will become available. Perhaps we will even see self-assembled minienzymes in the future?

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[1] a) D. J. Cram, M. E. Tanner, R. Thomas, *Angew. Chem.* **1991**, *103*, 1048 – 1051; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1024 – 1027; b) R. Warmuth, J. Yoon, *Acc. Chem. Res.* **2001**, *34*, 95 – 105.

[2] a) S. Russel-Seidel, P. J. Stang, *Acc. Chem. Res.* **2002**, *35*, 972 – 983; b) M. Fujita, M. Tominaga, A. Hori, B. Therrien, *Acc. Chem. Res.* **2005**, *38*, 369 – 380.

[3] a) J. Rebek, Jr., *Angew. Chem.* **2005**, *117*, 2104 – 2115; *Angew. Chem. Int. Ed.* **2005**, *44*, 2068 – 2078; b) F. Hof, S. L. Craig, C. Nuckolls, J. Rebek, Jr., *Angew. Chem.* **2002**, *114*, 1556 – 1578; *Angew. Chem. Int. Ed.* **2002**, *41*, 1488 – 1508.

[4] a) F. Corbellini, R. M. A. Knegtel, P. D. J. Grootenhuis, M. Crego-Calama, D. N. Reinhoudt, *Chem. Eur. J.* **2005**, *11*, 298 – 307; b) G. V. Oshovsky, D. N. Reinhoudt, W. Verboom, *J. Am. Chem. Soc.* **2006**, *128*, 5270 – 5278.

[5] C. L. D. Gibb, B. C. Gibb, *J. Am. Chem. Soc.* **2004**, *126*, 11 408 – 11 409.

[6] a) A. Lützen, *Angew. Chem.* **2005**, *117*, 1022 – 1025; *Angew. Chem. Int. Ed.* **2005**, *44*, 1000 – 1002; b) M. Yoshizawa, M. Fujita, *Pure Appl. Chem.* **2005**, *77*, 1107 – 1112; c) V. Maurizot, M. Yoshizawa, M. Kawano, M. Fujita, *Dalton Trans.* **2006**, 2750 – 2756; d) S. M. Biros, J. Rebek, Jr., *Chem. Soc. Rev.* **2007**, *36*, 93 – 104.

[7] A. Scarso, L. Pellizzaro, O. De Lucchi, A. Linden, F. Fabris, *Angew. Chem.* **2007**, *119*, 5060-5063; *Angew. Chem. Int. Ed.* **2007**, *46*, 4972 – 4975.

[8] C. L. D. Gibb, B. C. Gibb, *J. Am. Chem. Soc.* **2006**, *128*, 16 498 – 16 499.

[9] a) D. Ajami, J. Rebek, Jr., *J. Am. Chem. Soc.* **2006**, *128*, 15 038 – 15 039; b) M. P. Schramm, J. Rebek, Jr., *Chem. Eur. J.* **2006**, *12*, 5924 – 5933.

[10] S. Tashiro, M. Kobayashi, M. Fujita, *J. Am. Chem. Soc.* **2006**, *128*, 9280 – 9281.

[11] a) S. Tashiro, M. Tominaga, Y. Yamaguchi, K. Kato, M. Fujita, *Angew. Chem.* **2006**, *118*, 247 – 250; *Angew. Chem. Int. Ed.* **2006**, *45*, 241 – 244; b) S. Tashiro, M. Tominaga, Y. Yamaguchi, K. Kato, M. Fujita, *Chem. Eur. J.* **2006**, *12*, 3211 – 3217.

[12] Some recent examples: a) R. Warmuth, S. Makowiec, *J. Am. Chem. Soc.* **2007**, *129*, 1233 – 1241; b) X. Liu, G. Chu, R. A. Moss, R. R. Sauers, R. Warmuth, *Angew. Chem.* **2005**, *117*, 2030 – 2033; *Angew. Chem. Int. Ed.* **2005**, *44*, 1994 – 1997.

[13] M. Kawano, Y, Kobayashi, T. Ozeki, M. Fujita, *J. Am. Chem. Soc.* **2006**, *128*, 6558 – 6559.

[14] D. Fiedler, R. B. Bergman, K. N. Raymond, *Angew. Chem.* **2006**, *118*, 759 – 762; *Angew. Chem. Int. Ed.* **2006**, *45*, 745 – 748.

[15] V. M. Dong, D. Fielder, B. Carl, R. B. Berg, K. N. Raymond, *J. Am. Chem. Soc.* **2006**, *128*, 14 464 – 14 465.

[16] M Pluth, R. B. Bergman, K. N. Raymond, *Science* **2007**, *316*, 85 – 88.

[17] J. Kang, J. Rebek, Jr., *Nature* **1997**, *385*, 50 – 52.

[18] a) M. Yoshizawa, M. Tamura, M. Fujita, *Science* **2006**, *312*, 251 – 254; b) K. Takaoka, M. Kawano, T. Ozeki, M. Fujita, *Chem. Commun.* **2006**, 1625 – 1627; c) Y. Nishioka, T. Yamaguchi, M. Yoshizawa, M. Fujita, *J. Am. Chem. Soc.* **2007**, *129*, 7000 – 7001.

[19] a) A. Natarajan, L. S. Kaanumalle, S. Jokusch, C. L. D. Gibb, B. C. Gibb, N. J. Turro, V. Ramamurthy, *J. Am. Chem. Soc.* **2007**, *129*, 4132 – 4133; b) L. S. Kaanumalle, C. L. D. Gibb, B. C. Gibb, V. Ramamurthy, *Org. Biomol. Chem.* **2007**, *5*, 236 – 238.

