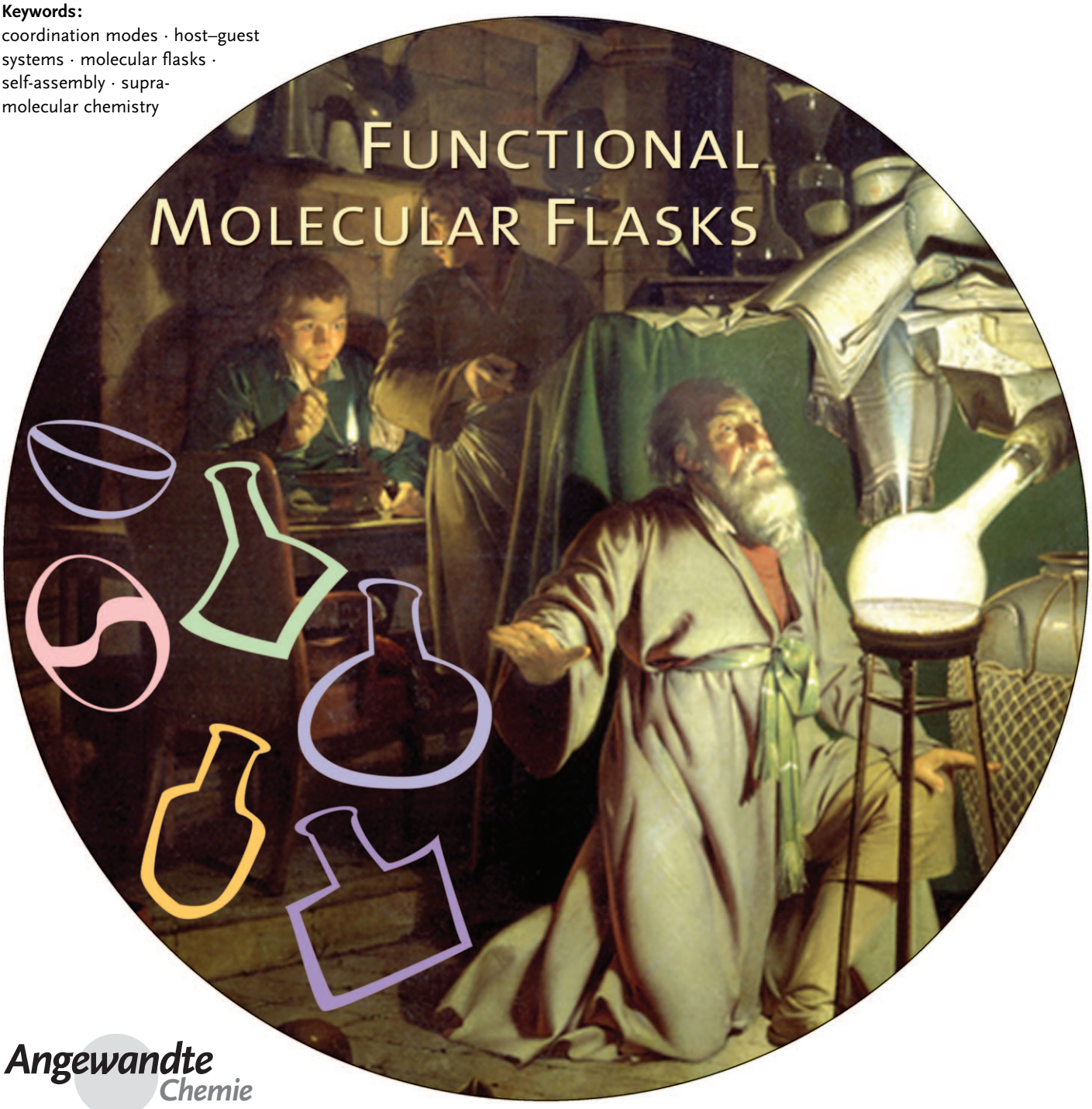
DOI: 10.1002/anie.200805340

Molecular Flasks

Functional Molecular Flasks: New Properties and Reactions within Discrete, Self-Assembled Hosts

*Michito Yoshizawa, Jeremy K. Klosterman, and Makoto Fujita**

Keywords:
coordination modes · host–guest systems · molecular flasks · self-assembly · supramolecular chemistry



The application of self-assembled hosts as "molecular flasks" has precipitated a surge of interest in the reactivity and properties of molecules within well-defined confined spaces. The facile and modular synthesis of self-assembled hosts has enabled a variety of hosts of differing sizes, shapes, and properties to be prepared. This Review briefly highlights the various molecular flasks synthesized before focusing on their use as functional molecular containers—specifically for the encapsulation of guest molecules to either engender unusual reactions or unique chemical phenomena. Such self-assembled cavities now constitute a new phase of chemistry, which cannot be achieved in the conventional solid, liquid, and gas phases.

From the Contents

1. Introduction

> "*The active intellectual powers of man in different times are not so much the cause of the different successes of their labours, as the peculiar nature of the means and artificial resources in their possessions.*"
> Humphrey Davy

From its birth in alchemy, chemistry has always been a practical science, dependent on the instruments and apparatus available. In fact, the evolution of chemistry as a modern science can be traced to the concurrent development of laboratory equipment.[1] Often overlooked in its simplicity, the common flask has remained central to, and emblematic of, chemical research. Originally made of metal or pottery, the flask has undergone many improvements and remains the simplest, and often the best, container in which to prepare and store chemicals. The disparate proportions of the flask compared to the encompassed molecules means that reactions are conducted on a relatively large scale. The size and shape of the container influences the bulk properties, but not the reactions or interactions within. If the reaction were to be performed in a "molecular flask" of comparable scale to the reactants (typically nanometers), the size and shape of the flask would be important parameters, capable of altering the reactivity and properties of the contained molecules.[2]

Molecular flasks are not a recent innovation, but possess a much longer, and often more successful, history than the classical laboratory flask. Enzymes, nature's molecular flasks, provide molecular-sized and -shaped pockets capable of binding substrates and catalyzing unique reactions.[3] While complementary structure is not necessarily the main catalytic driving force,[4] the local microenvironment is paramount to the specific and nonspecific interactions that enhance the efficiency and selectivity of enzymatic reactions under very mild conditions.[5] Similarly, it is the enforced proximity and local microenvironment that enables an efficient electron and energy transfer between organic chromophores and metal clusters in photosynthesis. Such elusive phenomena have yet to be fully imitated within macroscopic flasks and drive the development of artificial molecular flasks.[6]

In this Review we highlight recent developments in the application of artificial, self-assembled molecular hosts as functional molecular flasks. For the sake of brevity, non-self-assembled molecular containers, such as carcerands, cavitands, cyclodextrins, and curcurbiturils,[2,7–9] which can also function as molecular flasks, are not included. Nondiscrete or structurally poorly defined aggregates such as micelles, vesicles, or crystals are beyond the scope of this Review.[10] To stress the similarities of the molecular flasks with their macroscopic counterparts, we focus on systems where the host–guest interactions are well defined or observable. Finally, we emphasize their utility in facilitating unusual chemical reactivity or in isolating molecules and promoting new physical properties.

2. Self-Assembled Molecular Flasks

The initial studies on molecular containers focused on covalent hosts such as cyclodextrins, carcerands, and hemicarcerands.[2,10–12] Over the last two decades the focus has shifted to harness noncovalent, weak interactions, typically hydrogen and coordinative bonds, for the self-assembly of molecular hosts from small components. The simplicity of self-assembly has resulted in a plethora of self-assembled capsules and cages with nanometer-sized cavities.[13–15] While many of these new artificial hosts display interesting molecular recognition properties,[16] the number examined as hosts or for promoting chemical reactions or inducing unique physical properties is small.[10,17] In this section, functional, self-assembled molecular flasks are briefly introduced and their synthesis, structure, and properties are described. Their role in promoting unique chemical phenomena will be described in the following sections.

[*] Dr. J. K. Klosterman, Prof. Dr. M. Fujita
Department of Applied Chemistry, School of Engineering
The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656 (Japan)
E-mail: mfujita@appchem.t.u-tokyo.ac.jp
Dr. M. Yoshizawa
Chemical Resources Laboratory, Tokyo Institute of Technology
4259 Nagatsuta, Midori-ku, Yokohama 226-8503 (Japan)

2.1. Molecular Flasks with Coordination Bonds

The robust, but reversible coordinative bond has played a key role in the self-assembly of supramolecular architectures,[15,18] and the earliest self-assembled host molecules relied on metal–ligand interactions.[19–21] Unlike most weak interactions, coordinative bonds offer a variety of bond strengths and geometries because of the variety of potential metal ions, ligands, and coordination geometries. The Fujita research group has employed an ethylenediamine "capping" ligand to enforce the 90° *cis* geometry around square-planar coordinated Pd^{II} and Pt^{II} ions.[21] The octahedral cage **1** (Figure 1) quantitatively self-assembles by simply mixing end-capped Pd^{II} ions with the tridentate, triangular ligand 1,3,5-tris(4-pyridyl)triazine in a 6:4 ratio,[22] with the six Pd^{II} ions located at the corners of the octahedron. The judicious choice of nitrate counterions endows the cage with high water solubility. The four triazine panels occupy alternate faces of the octahedron and provide a very large, hydrophobic cavity. The cationic cage (overall charge: 12 +) is remarkably stable, encapsulates a variety of organic molecules in aqueous solution, and has demonstrated selective pairwise encapsulation of flexible alkanes and large, planar aromatic molecules.[23] Simply replacing the end-capping ligand with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine or 2,2′-bipyridine results in similar cages, but alters the bulk properties (solubility and crystallinity).[24] The Pd^{II} ions are also exchangeable, and the more robust Pt^{II} analogue of **1** shows a greater tolerance for acidic and basic conditions.[25]

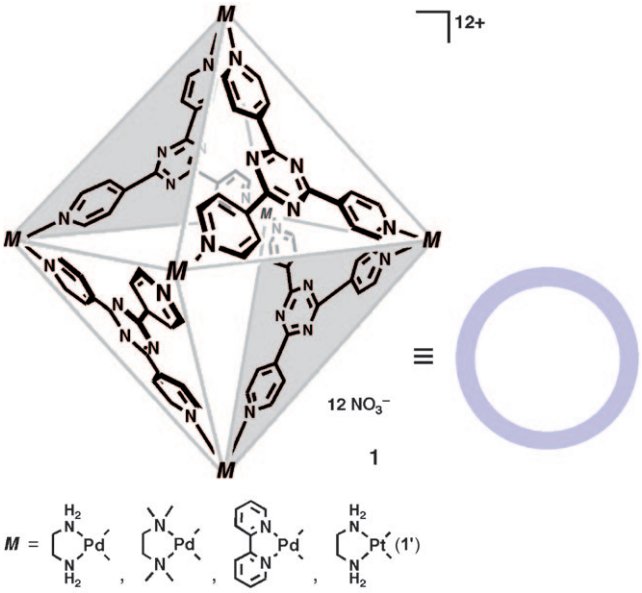


Figure 1. The octahedral coordination cage **1** of Fujita and co-workers.

The template effect of the enforced *cis* geometry is general and exceptionally efficient for the self-assembly of hollow, discrete nanostructures.[14] For example, the triangular tris(3-pyridyl)triazine ligand quantitatively assembles into the bowl-shaped square-pyramidal cage **2** (Figure 2a).[26] Similar to the cavitands developed by Cram et al.,[2] nanobowl **2** has an open hydrophobic pocket capable of binding organic guest molecules. If the sterically demanding tetramethyl-4,4′-bipy-

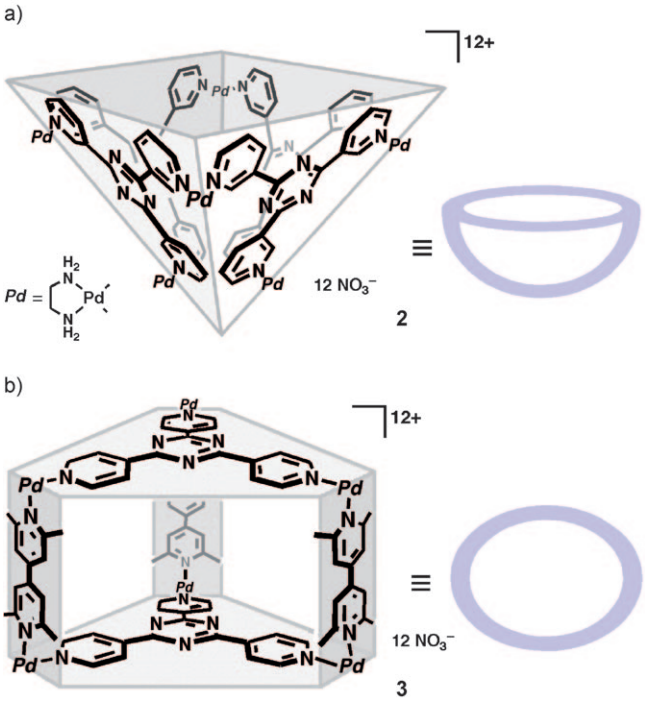


Figure 2. a) Bowl-shaped cage **2** and b) prism-shaped cage **3**.

Jeremy K. Klosterman received his MS in organic chemistry from the University of California, San Diego in 2003 under Prof. Jay S. Siegel. He then moved with Prof. Siegel to the Universität Zürich and, in 2007, completed his PhD research on the development of new ligands for the kinetically driven, stepwise construction of topologically complex, ringed structures. He then joined the Fujita research group as a JSPS postdoctoral fellow, and is currently investigating energy transfer between self-assembled organometallic cages and fluorescent guest molecules.

Michito Yoshizawa received his BS from Tokyo University of Agriculture and Technology in 1997, MS from Tokyo Institute of Technology in 1999, and PhD from Nagoya University in 2002 under Prof. Makoto Fujita. He moved to The University of Tokyo with Prof. Fujita as a JSPS postdoctoral fellow and became Assistant Professor in 2003. He has been a researcher of the PRESTO project of the Japan Science and Technology Agency since 2006. In 2008, he became Associate Professor at the Chemical Resources Laboratory, Tokyo Institute of Technology. His research interests focus on molecular recognition as well as chemical reactions and properties within supramolecular complexes.

didine is added together with the tris(4-pyridyl)triazine panel and *cis*-capped Pd^{II} ions, the prism-shaped cage **3** selectively assembles (Figure 2b).[27] The hydrophobic cavity of cage **3** provides an ideal space for two planar aromatic guest molecules to π stack, and can be expanded by altering the length of the bipyridine pillar ligand.

Improving on the design of Saalfrank et al.,[20] Raymond and co-workers developed the tetrahedral capsule **4** by utilizing four octahedral metal ions (for example, Ga^{3+} or Fe^{3+}) and six naphthalene-linked bis(bidentate) catechol ligands (Figure 3).[28] The environment around the metal

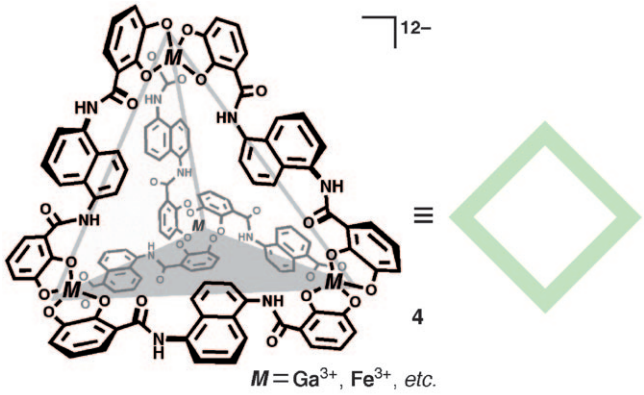


Figure 3. Tetrahedral coordination capsule **4** of Raymond and co-workers.

centers is chiral, and homochiral cages are formed exclusively (Δ,Δ,Δ,Δ or Λ,Λ,Λ,Λ). The anionic capsules (overall charge: 12−) are water soluble and contain a large hydrophobic cavity (300–500 $Å^3$) where monocationic guests such as NMe_4^+, NEt_4^+, PEt_4^+, and a ferrocenium ion are preferentially encapsulated.

A common theme in supramolecular chemistry is the imitation of complex biological processes, such as photosynthesis, and many metallosupramolecular architectures incorporate porphyrin moieties with this goal in mind.[15] In a particularly elegant assembly, Slone and Hupp designed the square-shaped host **5** (R = tetrabutyl) from bis(pyridyl)porphyrinatozinc ligands and octahedral rhenium(I) ions (Figure 4).[29] The cavity is well-suited for the encapsu-

Makoto Fujita received his PhD from the Tokyo Institute of Technology in 1987. Between 1988 and 1997 he worked as Assistant Professor, Lecturer, and then Associate Professor at Chiba University, 1997–1999 as Associate Professor at the Institute for Molecular Science (IMS) at Okazaki, and 1999–2002 as Full Professor at Nagoya University. In 2002 he became a Full Professor at the University of Tokyo. He has been a leader of the CREST project of the Japan Science and Technology Corporation since 1998. His research interests include metal-assembled complexes, molecular recognition, and nanometer-sized molecules.

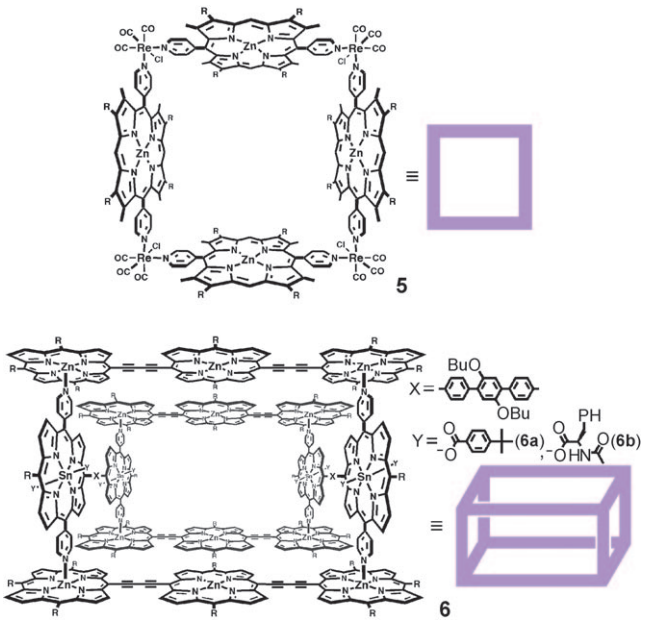


Figure 4. The square zinc porphyrin host **5** and box-shaped multi-porphyrin host **6** of Slone and Hupp.

lation of further pyridylporphyrin molecules, including a manganese(III) porphyrin, a well-known olefin epoxidation catalyst.[30,31] To develop a more rigid box with a tunable cavity, Hupp and co-workers used weaker and more-labile pyridine–zinc bonds to assemble porphyrin box **6** (R = 2,6-dibutoxyphenyl or 2,6-dihexoxyphenyl) from rigid zinc porphyrin trimers and tin porphyrin dimers in toluene.[32] Functionalization of the axial ligands Y of the tin porphyrin unit was used to tailor the properties of the box cavity: **6a** is a sterically bulky ligand, while **6b** produces a chiral cavity. The bulk of the axial substituents on the tin center prevent the tin porphyrin dimers from assuming adjacent positions and keeps up to four zinc binding sites open for the inclusion of less bulky porphyrin dimers. NMR spectroscopy and solution-phase X-ray measurements were used to provide structural evidence for porphyrin box **6**.

2.2. Flasks with Hydrogen Bonds

The hydrogen bond is ubiquitous throughout self-assembled systems in nature[33] and is utilized extensively for controlling molecular self-assembly.[34] Two-dimensional hydrogen-bond arrays are common motifs, but the use of hydrogen bonds for the self-assembly of three-dimensional capsules was initiated by Rebek and co-workers in 1993.[35] The "softball" capsule **7** (Ar = phenyl) and its derivatives assemble from two C-shaped halves, consisting of two glycoluril units connected by a linker (Figure 5a).[36] Complementary hydrogen bonding along the rim ensures that the two molecular halves afford a stable capsule in the presence of smaller guests. The large cavity of **7** (ca. 400 $Å^3$) encapsulates several solvent molecules, which can be smoothly replaced by one medium-sized molecule (for example, adamantane or ferrocene carboxylic acid) through an entropi-

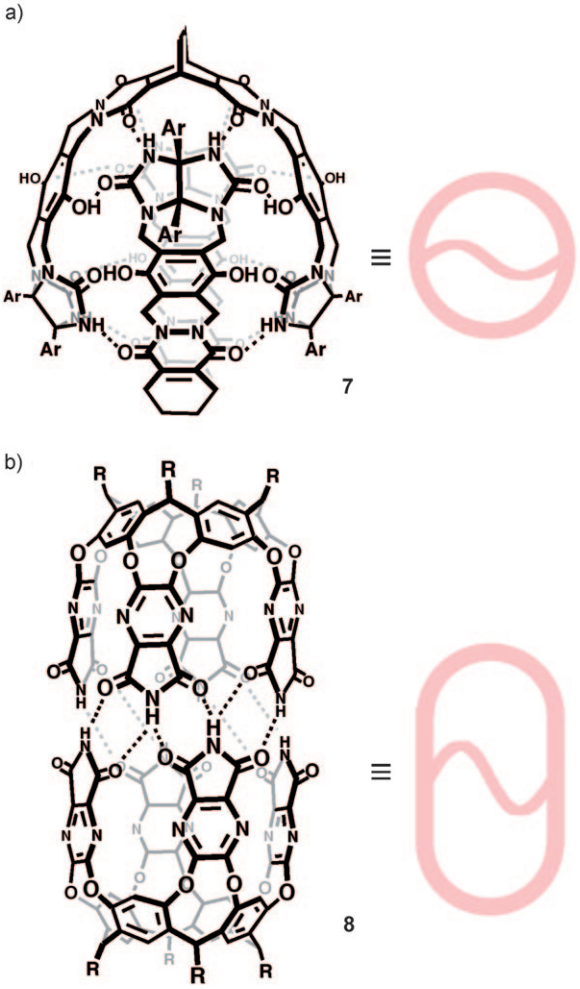


Figure 5. a) The hydrogen-bonding "softball" capsule **7** and b) cylindrical capsule **8** of Rebek and co-workers.

cally driven process. The solvent molecules bound within the capsule are released when a single guest molecule binds within the capsule.

Rebek and co-workers combined the classic, noncovalent bowl-shaped calix[4]resorcinarene with aromatic panels capped by hydrogen-bond donors and acceptors to give dimeric cylindrical capsule **8** ($R = C_{11}H_{23}$); Figure 5b).[37] The deep cavity (ca. 400 Å^3) is large enough to encapsulate two different guest molecules, and has shown utility as a molecular flask. Many other large capsules self-assemble from multiple components through hydrogen bonding, and are under active investigation, but have not yet been applied as functional molecular flasks.[38]

2.3. Hydrophobic Flasks

A recent example by Gibb and Gibb relies on hydrophobic and possibly π–π interactions to form dimeric capsule **9** (Figure 6).[39] Suitably sized hydrophobic guests template the association of the two cavitand halves in aqueous solution. No dimeric capsule forms in the absence of the templating guest. The flask is flexible and the kinetic stability of the

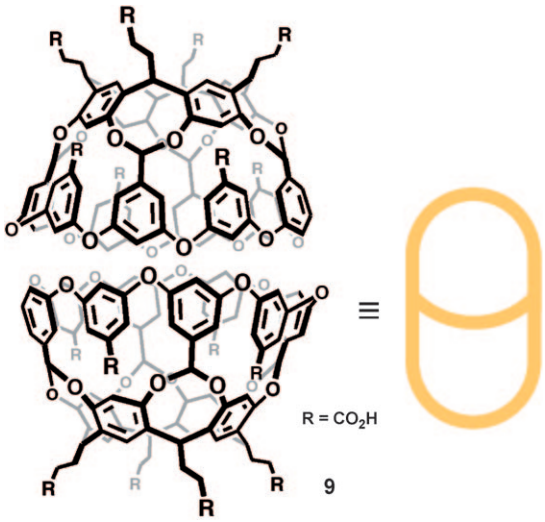


Figure 6. The hydrophobic dimeric capsule **9** of Gibb and Gibb.

dimer depends on the size, shape, and water solubility of the templating guest. The dimeric capsule is roughly 1 nm wide, 2 nm long, and has a volume of approximately 500 Å^3.[40]

3. Molecular Flasks as Reaction Vessels

The study of molecular flasks, and supramolecular catalysis in general, is driven by the ultimate goal of enzyme mimetics.[41] The literature is rife with allusions and direct comparisons,[7,42] yet few "artificial enzymes" achieve the magnificent catalysis of natural enzymes. As a consequence of their self-assembled nature, most self-assembled molecular flasks do not possess specific interactions capable of encapsulating guests and catalyzing their reactions in the covalent manner of enzymes.[5] Several research groups have incorporated catalytically active sites within supramolecular hosts, but these generally interact with substrates as extremely bulky ligands rather than as supramolecular hosts.[30,43]

Self-assembled molecular flasks typically rely on a variety of noncovalent interactions to influence reaction pathways. Of greatest importance for encapsulated bimolecular reactions is the effective molarity (EM) of the two substrates in the cavity.[44] Isolation from the bulk solvent and an increased local concentration results in an accelerated rate of reaction. Molecular hosts can also stabilize unusual guest conformations (preorganization) or transition states that generate accelerated or unusual reactivity. When two or more guest molecules are encapsulated, a particular type of stereoisomers consisting of several noncovalently bound components is formed which arise from their relative spatial positioning and conformation within the host. These stereoisomers are termed "social isomers", and are of vital importance in determining the potential outcome of a reaction.[45]

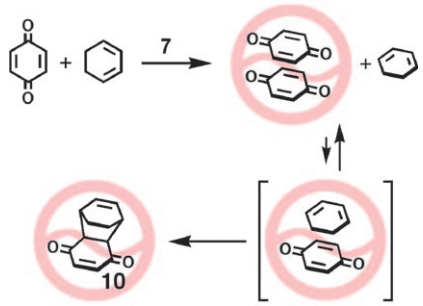
The enhanced concentration and molecular preorganization are the two most important controls of chemical reactions within molecular flasks. Although many of these concepts were initially investigated with robust, covalent hosts, it was unclear if reversibly bound hosts could display similar

behavior. Now established as viable molecular flasks, the simple synthesis and modification of self-assembled hosts has ensured their place at the forefront of functional molecular containers.

3.1. Thermal Cycloadditions

3.1.1. Diels–Alder Reactions

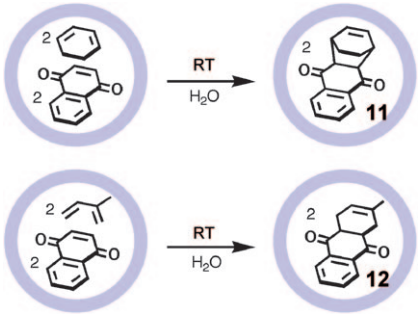
In 1997, Rebek and co-workers demonstrated that reversibly self-assembled hosts also function as molecular flasks.[46] The room temperature Diels–Alder reaction of *p*-benzoquinone and cyclohexadiene at high dilution is significantly accelerated (ca. 200 fold) in the presence of hydrogen-bonded host **7** (Scheme 1). Initially two molecules of the



Scheme 1. Diels–Alder reaction accelerated within hydrogen-bonded host **7** in *p*-xylene.

quinone are encapsulated, but the diene must be able to enter the host as signals for the encapsulated product **10** gradually appear in the NMR spectrum. Once the diene enters the cavity and the heteroleptic host–guest complex is formed, the effective molarity increases and the reaction occurs rapidly.

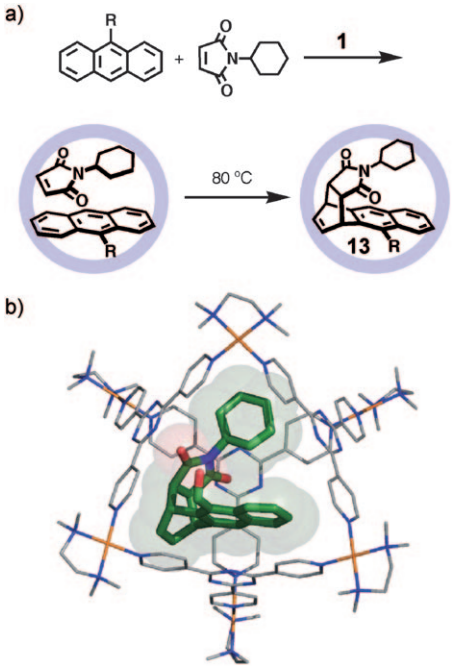
Fujita and co-workers used the water-soluble organometallic cage **1** to accelerate the room-temperature Diels–Alder reaction of 1,4-naphthoquinone and cyclohexadiene.[47] In aqueous solution, two molecules of each substrate are driven into the hydrophobic pocket of **1** and rapidly (ca. 21-fold increase) and quantitatively react to give **11** (Scheme 2). When 2-methyl-1,3-butadiene is employed, the rate of formation of **12** increases 113 fold. As an added benefit, the



Scheme 2. Diels–Alder reactions accelerated within **1**.

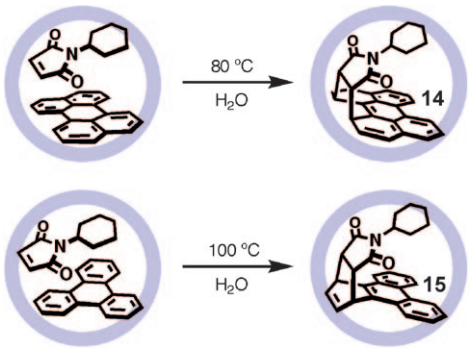
sole Diels–Alder products can be easily extracted with organic solvents, leaving cage **1** intact in the aqueous phase.

In the previous two examples, the rates of reaction are increased because of the increase in the effective molarity, but the steric constriction within the molecular flasks can also initiate unusual regio- and stereoselective Diels–Alder reactions.[48] Typically, anthracene selectively reacts with dienophiles to give the 9,10-adduct.[49] However, once encapsulated with an appropriate dienophile such as *N*-cyclohexylmaleimide only the terminal anthracene rings react to give the *syn* adducts **13** in good yields (for example, 98% yield when R = CH_2OH and 92% yield when R = CO_2H; Scheme 3a). NMR studies and X-ray crystallographic analysis of **1**⊃**13** (R = CH_2OH) unambiguously revealed the unusual 1,4 adduct (Scheme 3b). The particular electronic and spatial characteristics of the hydrophobic pocket determines the initial, selective pairwise recognition and precise orientation of the two substrates within the cavity of **1**.[23] The terminal ring of the anthracene and the maleimide double bond are held in proximity and thus favors the new reaction pathway. The noncovalent interactions (mainly hydrophobic and π-stacking interactions) that preorganize the substrates within the host are general, and a variety of anthracenes display the new 1,4 regioselectivity. The steric bulk of the *N*-alkyl substituent on the maleimide is essential to both the pair-selective recognition and 1,4 regioselectivity. *N*-cyclohexyl- and *N*-cycloheptylmaleimides show pairwise selectivity and 1,4 regioselectivity but the less bulky *N*-propylmaleimide gives the 9,10 adduct.



Scheme 3. a) Unusual regioselectivity of the Diels–Alder reaction of anthracenes and *N*-cyclohexylmaleimide within **1** in water and b) the X-ray crystal structure of **1**⊃**13** (R = CH_2OH); guest: green C, blue N, red O; host: gray C, blue N, orange Pd.

The restricted environment within molecular flasks not only induces new regioselectivity, but new reactivity. The enforced proximity of typically inert arenes and *N*-substituted maleimides within the cavity facilitates their Diels–Alder reactions.[50] Inside cage **1**, perylene and *N*-cyclohexylmaleimide react to give *syn*-Diels–Alder product **14** in good yield (90%) at 80°C (Scheme 4). The product is stable inside cage **1**

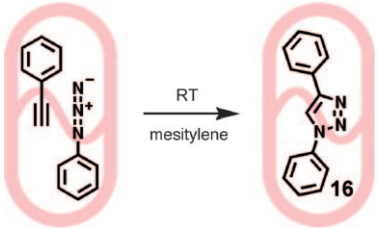


Scheme 4. Diels–Alder reactions of typically inert arenes and maleimides within **1**.

but once removed, it gradually oxidizes in the air. Highly stable triphenylene unexpectedly reacts with the maleimide at 100°C within the cavity of the more robust platinum analogue of **1** to give the unprecedented Diels–Alder adduct **15** in 25% yield (Scheme 4).[50]

3.1.2. 1,3-Dipolar Cycloadditions

Chen and Rebek employed the cylindrical, hydrogen-bonded capsule **8** as a molecular flask for the 1,3-dipolar cycloaddition of phenylacetylene and phenylazide (Scheme 5).[51] In a mesitylene solution, capsule **8** encapsulates two guest molecules as a nearly statistical mixture of homo and hetero combinations under equilibrium. At room temperature, the capsule orients the two substrates and accelerates the cycloaddition 30000 fold. Not only is the reaction accelerated, but the 1,4 regioisomer **16** is also selectively formed within the capsule. In the absence of the capsule, the same reaction yields roughly equal amounts of the 1,2 and 1,4 adducts, with a half-life of several years.

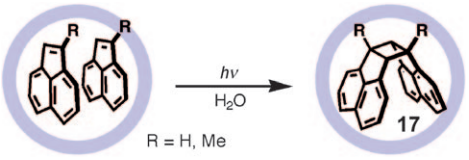


Scheme 5. A regioselective 1,3-dipolar cycloaddition accelerated within capsule **8**.

3.2. Photochemistry

3.2.1. Photochemical [2+2] Dimerizations

Fujita and co-workers utilized self-assembled cages as molecular flasks to accelerate and significantly alter the [2+2] photodimerization of olefins. In 2002, they reported that cage **1** encapsulates two molecules of acenaphthylene and, after photoirradiation, the *syn* dimer **17** (R = H) is selectively obtained in nearly quantitative yield (Scheme 6).[52] Whereas olefin photodimerizations have



Scheme 6. Stereoselective [2+2] photodimerization of acenaphthylenes within **1**.

been found in various media,[53,54] cage **1** sequesters and precisely orients only two substrate molecules in proximity, thereby greatly enhancing the efficacy of the reaction in solution. In the absence of cage **1**, the dimer can only be obtained as a *syn*/*anti* (1:1) mixture in mediocre yields at significantly higher concentrations. As an added benefit, the aromatic framework of **1** prevents the back reaction to the monomer by absorbing wavelengths shorter than 300 nm. When two molecules of the less reactive 1-methylacenaphthylene are encapsulated, dimerization occurs with exclusive formation of the head-to-tail *syn* dimer **17** (R = Me). Karthikeyan and Ramamurthy later investigated the effects of xanthene dyes as photosensitizers for cage **1**, and found that the *syn* dimer is also selectively obtained from the triplet state.[55]

The crystalline nature of cage **1** enabled a detailed analysis of the [2+2] dimerization of acenaphthylene in a single crystal.[56] Before photoirradiation, the two encapsulated substrates interact with the cage framework through π–π interactions and are disordered over three positions (Figure 7a). The molecules are separated by 8.3–9.0 Å, far further than the typical 4.2 Å separation typically observed in

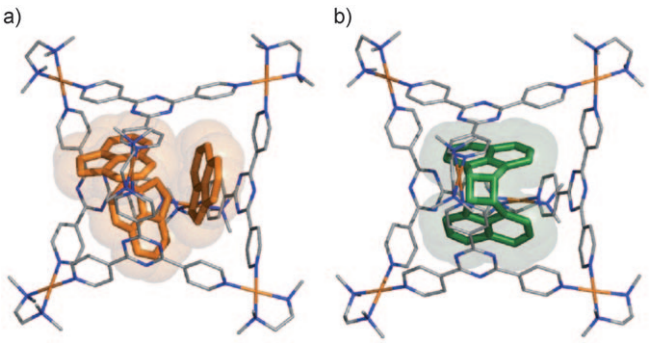
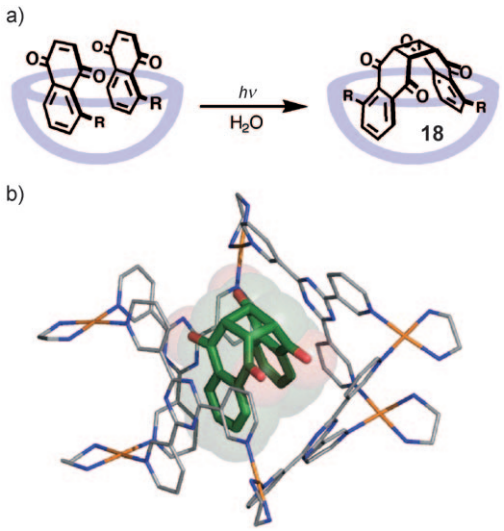


Figure 7. In situ X-ray crystal structures a) before and b) after [2+2] photodimerization of acenaphthylene within **4**; guest: green/orange; host: gray C, blue N, orange Pd.

the crystalline photodimerization of olefins, known as the Schmidt rule.[54] Nevertheless, *syn* dimer **17** (R = H) is quantitatively obtained after irradiation at 240 K, as revealed by crystallographic analysis (Figure 7b). It should be emphasized that, in contrast to the conventional photochemical reactions of organic crystals,[54] the large and rigid cavity of **1** provides a crystalline "molecular flask" capable of hosting non-topochemical reactions involving dynamic molecular motions of the encapsulated substrates.

Hydrophobic capsule **9** assembles and forms a 2:2 host–guest complex in the presence of acenaphthylene and, after photoirradiation, the *syn* dimer **17** (R = H) is selectively obtained.[57] When the photoirradiation is repeated in the presence of eosin-Y, a water-soluble triplet sensitizer, the *syn* dimer is formed, but the *anti* dimer also forms and precipitates from the reaction (*syn*/*anti* 3:2). Given the long lifetime (6 ms) of the acenaphthylene T_1 state, Kaanumalle and Ramamurthy proposed that the dynamic nature of the weakly bound capsule allows the triplet acenaphthylene excimer to exit the capsule, reorient, and form the *anti* dimer.

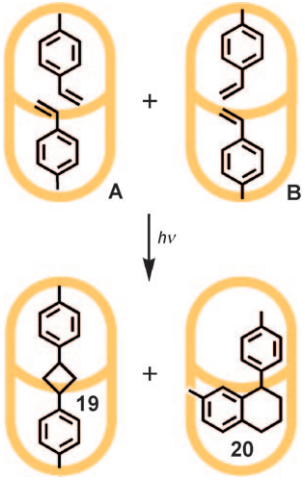
Bowl-shaped cage **2** proved a better flask than **1** for the [2+2] photodimerization of naphthoquinones, and gave *syn* stereoisomer **18** exclusively in greater than 98% yield (Scheme 7a).[52] In the absence of cage **2**, the standard



Scheme 7. a) The stereo- and regioselective [2+2] dimerization of naphthoquinones within **2**. b) X-ray crystal structure of **2**⊃**18** (R = H); guest: green C, red O; host: gray C, blue N, orange Pd.

product distribution is reversed; thus, for example, the typical yields in benzene are 21% *anti* and 2% *syn* dimer. X-ray crystallographic analysis of encapsulated product **2**⊃**18** (R = H) showed a tight, complementary fit between the host and the product (Scheme 7b). The snug fit means that not only is *syn* stereoselectivity favored within cage **2**, but so is head-to-tail regioselectivity. Even though the methoxy substituents are remote, dimerization of 5-methoxy-1,4-naphthoquinone in cage **2** gave the *syn* head-to-tail regioisomer in 79% yield (**18**, R = OMe).

The cavity of hydrophobic capsule **9** preferentially orients "knobbly" alkyl substituents towards the narrow tapered end of each cavitand.[58] When exposed to 4-methylstyrene, for example, the 2:2 host–guest complex forms with the two methyl groups snuggly nestled within the tapered ends of the capsule.[59] The olefins are held in proximity, but exist as two "social isomers", **A** and **B**, in a 55:45 ratio (Scheme 8).



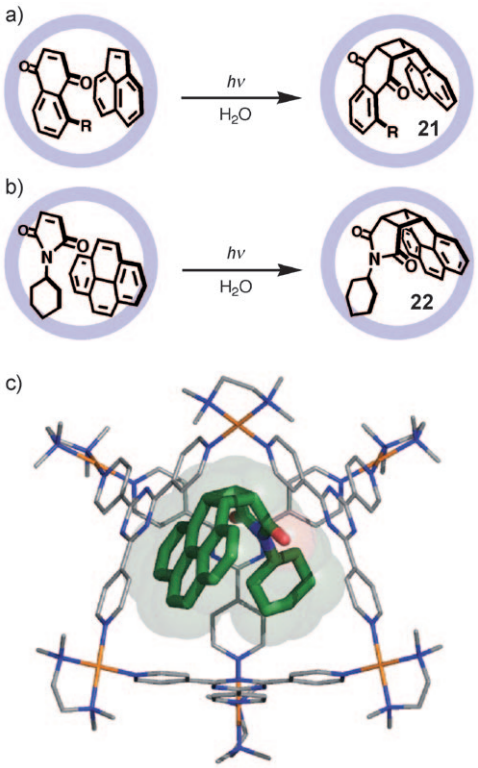
Scheme 8. Photodimerization of 4-methylstyrene within hydrophobic capsule **9** in water.

Photoirradiation of the preorganized olefins gave the two dimers **19** and **20** in the same 55:45 ratio. The authors claim that dimer **19** is most likely formed from isomer **A**, and dimer **20**, known to form in the presence of a triplet photosensitizer, forms from **B**, with capsule **9** acting as a sensitizer.

3.2.2. *[2+2] Cross-Photodimerization*

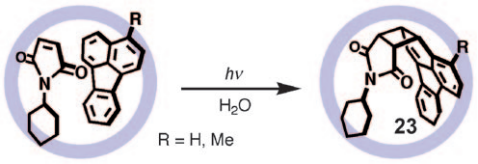
Selective cross-photodimerization of olefins is a challenging and daunting task as both substrates are of comparable reactivity and rarely distinguish between homo and hetero dimers.[54,60] Selective pairwise encapsulation of two substrates within a host cavity can lead to the isolation of the hetero dimer and ensure selective cross-reactivity. Cage **1** preferentially binds acenaphthylene and 5-ethoxy-1,4-naphthoquinone in a 1:1 ratio, and the hetero *syn* dimer **21** (R = OEt) is formed in 92% yield upon photoirradiation (Scheme 9).[61] The key point, as with the previous Diels–Alder reaction in Section 3.1.1, is the co-encapsulation and preorganization of the substrates in the host cavity. The use of bulky *N*-substituted maleimide derivatives affords a selective cross-reaction. Thus, the [2+2] cross-photodimerization with planar arenes, such as acenaphthylene and dibenzosuberenon,[61] give the *syn* hetero dimers in high (>90%) yield.[50] Even typically inert arenes such as pyrene, phenanthrene, and fluoranthene also gives rise to the *syn*-[2+2] adducts under these conditions. Further control experiments showed that no cross-reactions occur in the absence of **1**, even at high concentrations.

Of the many self-assembled molecular flasks synthesized, there are many chiral examples.[13,15,62] Asymmetric synthesis



Scheme 9. [2+2] Cross-photodimerization of a) 5-ethoxy-1,4-naphthoquinone and acenaphthylene and b) *N*-cyclohexylmaleimide and pyrene within **1**. c) X-ray crystal structure of **1**⊃**22**; guest: green C, blue N, red O; host: gray C, blue N, orange Pd

within the chiral cavities, however, remains relatively uncharted because of the difficulties in preparing and isolating optically pure samples of inherently dynamic hosts.[63] Recently, Fujita and co-workers reported the chiral induction of an asymmetric [2+2] cross-photoaddition within a chiral derivative of cage **1** (Scheme 10).[64] Replacement of

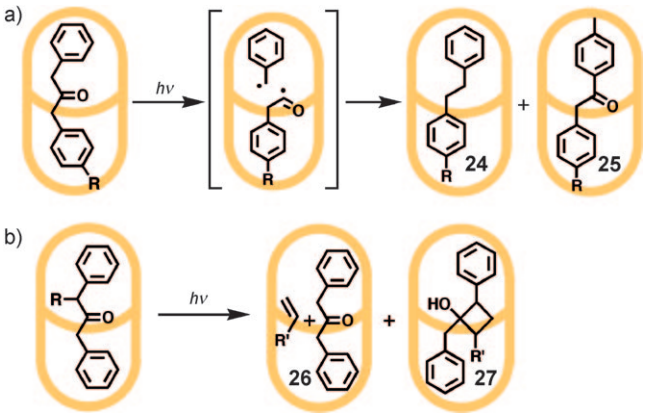


Scheme 10. Asymmetric [2+2] photodimerization of fluoranthenes and *N*-cyclohexylmaleimide within a chiral derivative of **1**.

the ethylenediamine end caps with an enantiopure chiral diamiscine gives the optically pure, chiral cage with only minor structural modifications. Although the chiral auxiliaries are far from the central cavity, the photoreaction of fluoranthene and *N*-cyclohexylmaleimide furnishes the [2+2] adduct **23** (R = H) with an enantiomeric excess of 40% *ee*, and in 50% *ee* when R = Me. The *ee* value of the reaction and the circular dichroism (CD) spectra of the cage are very sensitive to the steric bulk on the chiral auxiliaries; it has been proposed that the chiral auxiliaries induce a minor, chiral deformation in the triazine panels.

3.2.3. Photochemical Rearrangements and Radical Additions

Photoirradiation of asymmetric 1-phenyl-3-*p*-tolyl-2-propanone in solution affords a statistical mixture of the decarbonylation products AA, AB, and BB. When the ketone is encapsulated within hydrophobic capsule **9**, the decarbonylation and radical-recombination processes are faster than cage dissociation and, after less than 50% conversion, the AB decarbonylation product **24** (R = Me) is obtained in 41% (Scheme 11a).[40] Surprisingly, the AB *para*-rearrangement

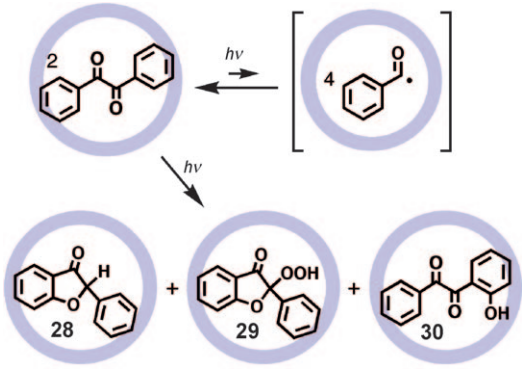


Scheme 11. Unusual photochemical rearrangements of dibenzyl ketones within hydrophobic capsule **9** in an aqueous buffer. a) Norrish type I and b) Norrish type II.

product **25** (R = Me) is also formed in 44% yield. To explain this unusual rearrangement, Gibb et al. proposed that the capsule induces formation of a longer-lived radical pair which allows the benzyl radical to reorient to a thermodynamically favorable conformation before recombination. Here the most favorable conformation orients the methyl groups towards the ends of the capsule and this preference organizes the radical fragments before recombination. When the methyl group is replaced with increasingly longer alkyl chains, the reduced free space within the capsule limits and finally prevents (when R = *n*-pentyl) reorientation of the benzyl radical. Finally, only AB decarbonylation products (**24** and others in a 4:1 ratio) are formed in a yield of 25–35%.[65] NMR studies have indicated that increasing the length of the pendant alkyl chains on encapsulated α-(*n*-alkyl)dibenzylketones further perturbs the guest conformation and opens a new photochemical pathway (Scheme 11b).[66] When R ≥ propyl, the Norrish type II products **26** and **27** are obtained in addition to the Norrish type I decarbonylation and rearrangement products (total conversions: 30–50%). Only decarbonylation and Norrish type II products are formed with hexyl groups as substituents, and dibenzylketone **26** becomes the major product with octyl groups. Similar to zeolites, the hydrophobic cavity of capsule **9** also endows selectivity in the photo-Fries rearrangement of naphthyl esters, presumably by limiting the translational or rotational freedom of the radical pair.[67]

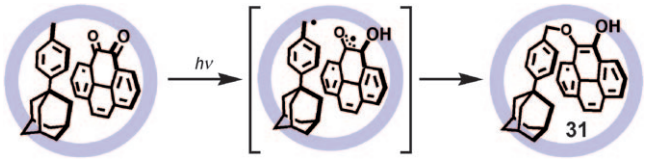
In contrast to the rich photochemistry of ketones,[68] the photochemistry of α-diketones is problematic because the

major reaction pathway is typically homolytic cleavage followed by messy degradations. When two molecules of benzil are encapsulated within coordination cage **1**, the unusual rearrangement products **28**, **29**, and **30** are obtained in a 4.4:1:2 ratio and in 52% overall yield (Scheme 12).[68] Inclusion in cage **1** suppresses homolytic cleavage and opens new, kinetically unfavorable pathways that are unattainable in solution.



Scheme 12. Unusual photochemical rearrangements of benzil within coordination cage **1** in water.

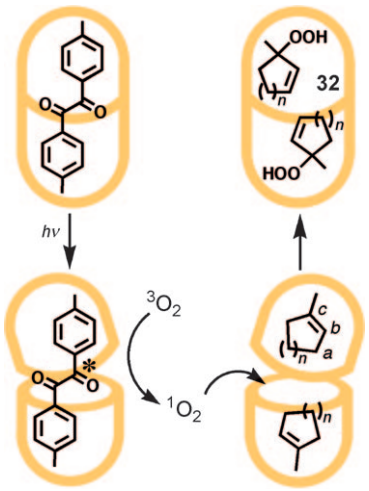
The regio- and stereoselectivity of bimolecular radical reactions is usually quite difficult to control.[68] The well-known pairwise size and shape selectivity of cage **1** was used to preorganize an *o*-quinone and a very bulky toluene derivative.[69] Upon photoexcitation, the quinone abstracts a hydrogen atom from the nearby methyl group. The benzylic and semiquinone radicals then recombine to selectively give 1,4 adduct **31** in 70% yield (Scheme 13). In the absence of cage **1**, a complex mixture was formed, in which the 1,4 adduct was not detected.



Scheme 13. Regio- and stereoselective bimolecular radical addition within **1** in water.

3.2.4. *Photochemical Oxidation*

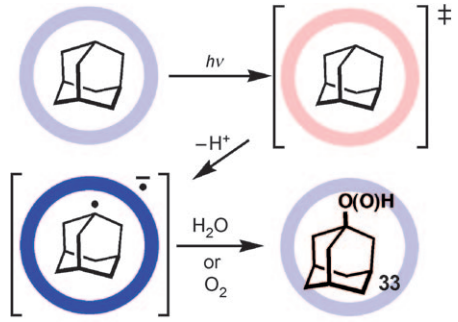
Recently, Gibb and co-workers revealed that dimeric capsule **9** can be used for the oxidation of olefins by singlet oxygen.[70,71] Capsule **9** hosts two molecules of 1-methylcycloalkenes or one molecule of the photosensitizer dimethylbenzile (DMB). When an aqueous solution containing the two host–guest complexes is irradiated, the encapsulated DMB generates singlet oxygen (Scheme 14). The singlet oxygen escapes back into the bulk solution before entering the alkene-containing capsule and attacking the alkene at position *c* with high selectivity ($a:b:c = 5:0:95$) to form



Scheme 14. Regioselective oxidation of 1-methyl cycloalkenes ($n = 1$–3) by singlet oxygen within **9** in an aqueous buffer.

hydroperoxide **32** (for example, $n = 2$). The high regioselectivity is ascribed to the preferred orientation of the methyl groups within capsule **9**. A statistical mixture of the three isomers is found in the absence of **9**.[70]

Typically, self-assembled molecular flasks indirectly influence reaction pathways by raising the effective concentration of the substrates or by preorganization and topochemical stabilization of unusual conformations. However, not all hosts act as mere vessels, and it is possible for the host framework to actively participate in creating new reactivity. For example, coordination cage **1**, typically inert in photochemical reactions, can encapsulate four adamantane molecules, a photochemically inert alkane.[24,72] Photoirradiation of **1** under aerobic conditions affords a mixture of 1-adamantylhydroperoxide and 1-adamantanol (**33**) in 24% yield (96% yield assuming one adamantane is oxidized per cage; Scheme 15). Detailed spectroscopic, electrochemical, and theoretical studies indicate that initially one triazine ring of cage **1** is photochemically excited and electron transfer from an encapsulated adamantane leads to an adamantyl radical and the radical anion of **1**.[73] The reactive radical species are quickly quenched by O_2 and/or H_2O, thus giving rise to oxidation products **33** enclathrated within the regenerated **1**.



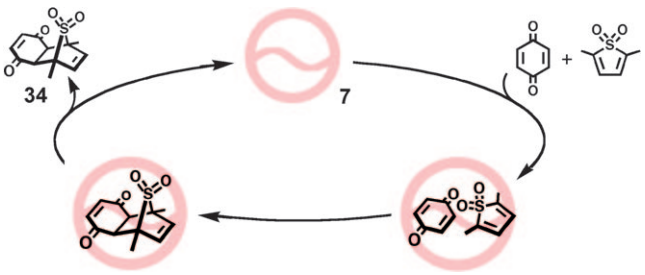
Scheme 15. Photoinduced oxidation of adamantane within **1** in water. Initial photoexcitation of the cage framework is followed by electron transfer from the adamantane to form the adamantyl radical, which is subsequently trapped by water or oxygen.

The photoinduced, radical anion of **1**, clearly observable by UV/Vis and ESR spectroscopy, is formed only with large aliphatic guests, which indicates the synergistic nature of the unusual photoreactivity.

3.3. Catalysis

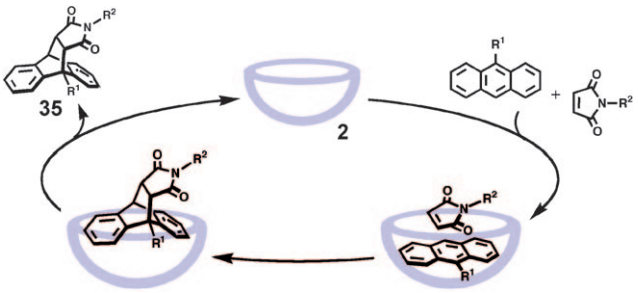
Self-assembled molecular flasks have proven useful for hosting, altering, and accelerating chemical reactions. However, the ultimate goal of creating a true, "artificial enzyme" capable of duplicating the catalysis of natural enzymes remains elusive. In 1946, Pauling introduced the concept that the active sites of enzymes bind by complementing the shapes and characteristics of transition states.[74] Product inhibition can occur when the product is more strongly bound than the reactants.[75] Precise orientation of the reactants within molecular flasks can greatly accelerate reactions; however, as the new product often resembles the preorganized transition state, product inhibition is a significant issue.[46] In other cases, the newly formed product is too large to escape the narrow openings of the flask and prevents further reaction.[76] Prudent selection of the host and substrates so that the host–substrate and the host–product interactions favor product expulsion has enabled the design of catalytic reactions within molecular flasks.

Rebek and co-workers selected 2,5-dimethylthiophene dioxide as the dienophile for the Diels–Alder reaction with *p*-benzoquinone within capsule **7**.[77] The approach called for the loss of SO_2 to alter the shape and binding of the adduct and thus reduce product inhibition.[78] However, SO_2 is not released in the reaction, but adduct **34** does has a significantly smaller association constant than benzoquinone. Thus, the Diels–Alder adduct forms in 75% yield over four days in the presence of capsule **7** (10 mol%; Scheme 16). Only 17% conversion is obtained in the absence of **7**.[77] The catalysis is modest, with a turnover number (TON) of about 7, but it does represent the first example of catalysis within a self-assembled molecular flask.



Scheme 16. Catalytic Diels–Alder reaction of *p*-benzoquinone and 2,5-dimethylthiophene dioxide in the presence of **7** in *p*-xylene.

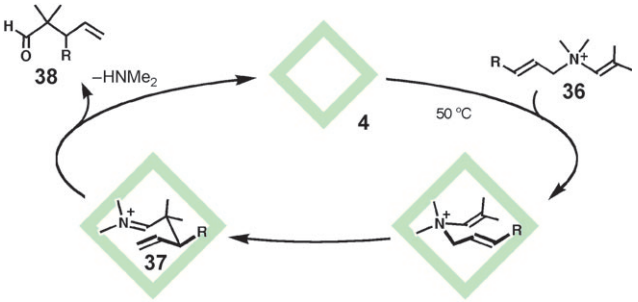
The bowl-shaped coordination cage **2** acts as a catalyst for the Diels–Alder reaction of anthracene and maleimide derivatives in aqueous media (Scheme 17).[48] For example, in the presence of bowl **2** (10 mol%), 9-hydroxymethylanthracene and *N*-phenylmaleimide yield the Diels–Alder



Scheme 17. Catalytic Diels–Alder reaction of anthracene and maleimide derivatives in the presence of **2** in water.

9,10 adduct **35** ($R^1 = CH_2OH$, $R^2 = Ph$) in quantitative yield after five hours (TON ca. 10). The reaction barely occurs (3% yield) in the absence of **2**. Only 1 mol% of **2** will still drive the reaction to near completion (>99%), albeit after 24 hours. Essential for catalysis is the addition of an autoexclusion and subsequent inclusion step in the catalytic cycle. The planar anthracene first enters the hydrophobic pocket and latches onto the interior framework through hydrophobic, π-stacking and/or charge-transfer interactions. After reaction, the anthracene moiety of **35** is bent and can no longer efficiently π stack with the host. Accordingly, further anthracene molecules smoothly displace the destabilized adduct, and the catalytic cycle continues.

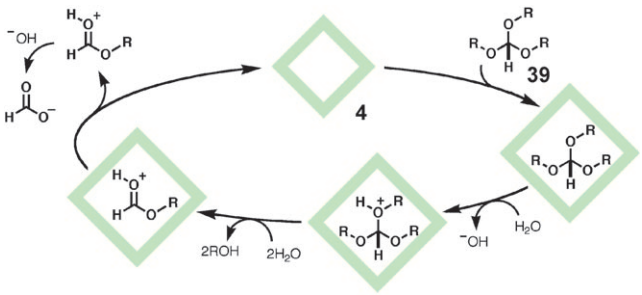
Raymond and co-workers harnessed the preference of the anionic coordination cage **4** ($M = Ga^{3+}$) for cationic guests to catalyze cationic 3-aza-Cope rearrangements (Scheme 18).[79]



Scheme 18. 3-Aza Cope rearrangement of allyl enammonium cations in the presence of anionic cage **4** in water.

Hydrophobic and electrostatic interactions facilitate the aqueous enclathration of enammonium cations **36**. Once inside, the restrictive cavity enforces a minimized, chairlike conformation that closely resembles the transition state, and the reaction is accordingly accelerated up to 850 fold (R = isopropyl).[80] After rearrangement, the iminium cation **37** can dissociate into solution where it is hydrolyzed to the neutral aldehyde. The anionic cage **4** only weakly binds neutral molecules **38**, and product inhibition is avoided (TON ≤ 8). The concept was also successfully applied to the 3-aza Cope rearrangement of the less-reactive allyl enammonium cations.[81]

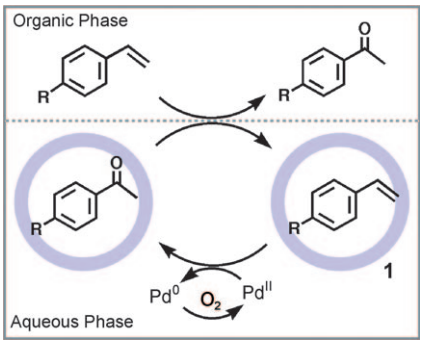
Reasoning that anionic cage **4** would preferentially bind protonated, monocationic guests, Raymond and co-workers exploited the pH difference between the interior and exterior to catalyze the hydrolysis of orthoformates (Scheme 19).[82]



Scheme 19. Catalytic hydrolysis of orthoformates in the presence of **4** in water at 50 °C.

Triethyl orthoformate (**39**, R = Et) is quickly hydrolyzed in the presence of a catalytic amount of **4** (2 mol %) in a basic, aqueous solution (pH 11) to formate. In-depth mechanistic studies showed that neutral guests **39** initially enters the cage, driven by hydrophobic interactions, where it rests until H_3O^+ enters the cavity. Reminiscent of Michaelis–Menton kinetics and enzymatic reactivions, proton transfer is the rate-limiting step. Subsequent hydrolysis releases two equivalents of alcohol before the protonated formate is released into the basic solution where it is finally deprotonated. Similar to competitive inhibition in enzymes, strong binding by an inhibitor, in this case NR_4^+, competes for the cavity space and impedes the reaction. Cage **4** also catalyzes the acidic deprotection of acetals and ketals in basic solution.[83]

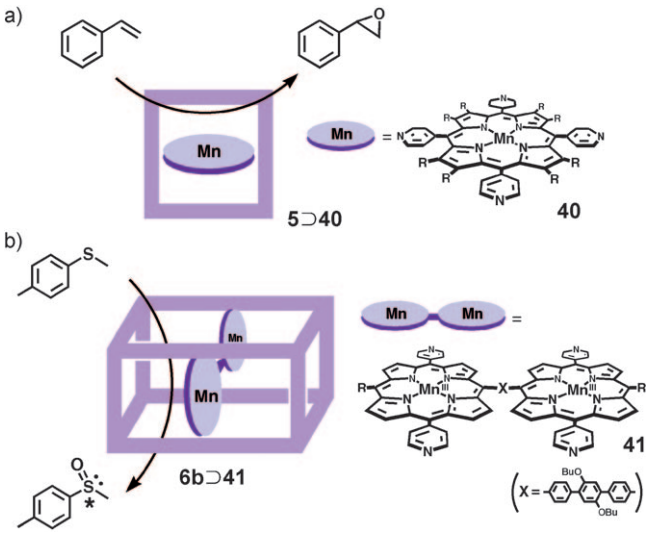
The majority of reactions observed within molecular flasks require no external catalysts. However, combining traditional organometallic catalysts with molecular cages has led to a new class of catalysts, one where reaction parameters are potentially governed by supramolecular host–guest interactions. Coordination cage **1** is ideal for phase-transfer catalysis because of its high water solubility and protected hydrophobic cavity and, in 2000, Fujita and co-workers reported the Wacker-type oxidation of styrenes.[84] Suspension of styrene (R = H) in an aqueous solution containing a catalytic amount of cage **1** and [(en)Pd(NO_3)$_2$] (10 mol % each; en = ethylenediamine) and heating at 80 °C for 24 h led to the styrene being partially transferred into the aqueous phase and encapsulated within the cage. An efficient Wacker oxidation then leads to the formation of acetophenone (82 % yield; TON ca. 8; Scheme 20). Both **1** and free [(en)Pd(NO_3)$_2$] are essential for catalysis: only poor yields are obtained (4 %) if one is absent. Almost no catalytic activity is observed (3 % yield) when the cavity of **1** is blocked with a strongly bound inhibitor. Cage **1** also catalyzes the Wacker oxidation of linear alkenols, such as 8-nonen-1-ol. Only 5 mol % of **1** suffices to give 8-oxononan-1-ol in a good yield (66 % yield; TON ca. 13).[85] The catalytic turnover clearly indicates that product inhibition no longer prevents reaction completion, and that the catalytic cycle now involves inclusion and exclusion steps. The driving force for inclusion of the



Scheme 20. Wacker-type oxidation of styrenes in the presence of **1** and [(en)Pd(NO_3)$_2$].

substrates into the cage is hydrophobic interactions; after oxidation, the slightly water-soluble carbonyl-containing product is extruded and replaced by the more hydrophobic alkenes. The reduced Pd catalyst is reoxidized under the aerobic conditions and recycled.

Many research groups have envisioned an alternative approach—the discrete inclusion of organometallic catalysts within host molecules.[30] The self-assembled host **5** possesses four zinc(II) ions that can strongly bind pyridyl porphyrins through coordinative bonds.[29] Manganese(III) porphyrins are well-known epoxidation catalysts, and Hupp and co-workers trapped tetrapyridylporphyrinatomanganese(III) (**40**) in the box-shaped cavity.[30] Once encapsulated, degradation of the manganese catalyst, typically though formation of μ-oxoporphyrinatomanganese dimer, is suppressed. The turnover numbers for the epoxidation of styrene by catalyst **5**⊃**40** (2×10^{-4} mol %) displayed an impressive increase of up to 21 000 (Scheme 21 a), compared to about 60 for free manganese(III) porphyrin. The restricted space within the

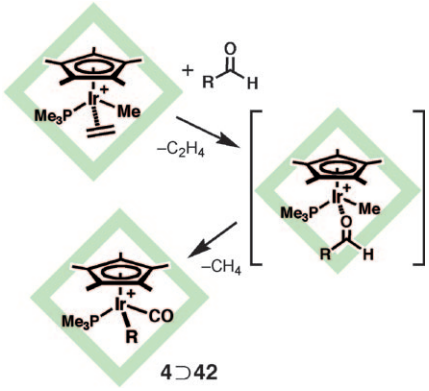


Scheme 21. a) Catalytic epoxidation of styrene with manganese(III) porphyrin **40** within square-shaped porphyrin-based host **5** in CH_2Cl_2. b) Catalytic enantioselective oxidation of methyl *p*-tolyl sulfide by manganese(III) porphyrin dimer **41** within box-shaped porphyrin-based host **6b** in toluene.

cavity, means that the catalyst also displays modest selectivity for the substrate size.

Follow-up theoretical studies highlighted the potential for ligand binding on the outside of the cage, rather than within the cavity as well as the torsional freedom of the porphyrin panels and encapsulated catalyst.[86] Hupp and co-workers designed the larger porphyrin box **6** to provide a rigid box with a tunable cavity.[32] Treatment of box **6** with the catalyst, the manganese porphyrin dimer **41**, generates the new supramolecular organometallic catalyst **6⊃41**.[87] Alternatively, the catalytic box **6⊃41** the can be assembled from the box components in the presence of **41**, thus emphasizing the selectivity of the self-assembly process. As expected, the bulky groups in the cavity of box **6a⊃41** endow the catalyst box with moderate size selectivity in the epoxidation of *cis*-stilbenes. *cis*-Stilbene is about 5.5 times more reactive than the much larger *cis*-3,3′,4,5′-tetra(*tert*-butyl)stilbene. The chiral **6b⊃41** system shows a 12% *ee* for the enantioselective oxidation of methyl *p*-tolyl sulfide. This enantiomeric excess can be reversed by switching the chiral groups in the cavity for their enantiomers (Scheme 21b). This remarkable achiral catalyst **41** displays modest enantioselectivity even on insertion into a surrounding chiral environment.

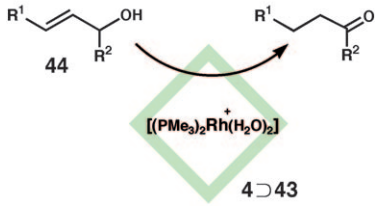
In 2004, Raymond and co-workers successfully trapped the iridium complex $[Cp^*(PMe_3)Ir(Me)(C_2H_4)]^+$ ($Cp^* = C_5Me_5$) within coordination cage **4** (Scheme 22).[88] The free



Scheme 22. Activation of C–H bonds of aldehydes by an iridium complex within **4** in water.

iridium complex can thermally activate the C–H bonds of organic molecules. After encapsulation by host **4**, the complex was found to activate the C–H bonds of aldehydes. A variety of simple aldehydes were examined, and the trapped iridium complex showed a new size and shape selectivity. Also, as the host and iridium complex are both chiral, the formation of insertion complexes **4⊃42** (R = *n*-propyl) showed moderate diastereoselectivity (70:30). The reaction occurs within the molecular flask, since aldehydes that are too large to enter the host cavity do not react, even after weeks at elevated temperatures. Although this is an excellent example of organometallic reactivity within a self-assembled host, the reaction is stoichiometric and not catalytic.

Raymond and co-workers next examined the isomerization of allylic alcohols by entrapped monocationic bisphosphine–rhodium catalysts $[(PMe_3)_2Rh(diene)]$ (Scheme 23).[89] The addition of H_2 to the encapsulated diene precatalyst

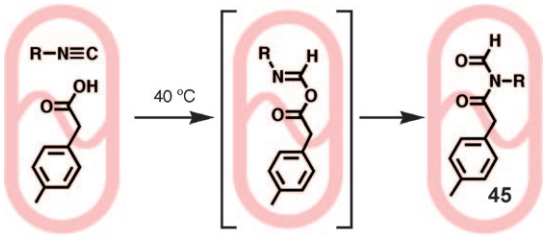


Scheme 23. Selective catalytic isomerization of allylic alcohols by encapsulated rhodium catalyst **4⊃43** in water.

generates the active catalyst **43** within the cavity. Unfortunately, the active catalyst is highly solvated and dissociates into the bulk solvent after 12 h. This limits the application of the catalyst to rapid reactions, such as allylic alcohol isomerization. In contrast to the free catalyst, the encapsulated catalyst selectively isomerizes small and linear alcohols. This selectivity stems not from the catalyst, but from the restricted apertures in the host framework. For example, crotyl alcohol **44** ($R^1 = Me$, $R^2 = H$) inhibits the free catalyst and, in a competition experiment, no reaction occured when allyl ($R^1 = R^2 = H$) and crotyl alcohol were added to the free catalyst. However, when allyl and crotyl alcohol were added to an aqueous solution containing encapsulated catalyst **4⊃43** (10 mol%), the host framework excluded the crotyl alcohol, permited entry of the allyl alcohol, and resulted in the formation of propionaldehyde in 95% yield.

3.4. Miscellaneous Reactions

Reports[90] on the unusual reactions of carboxylic acids with isonitriles prompted Rebek and co-workers to examine the reaction within self-assembled capsule **8**.[91] The preorganization and high effective molarity (4 M) results in the reaction being complete after 20 h at medium temperatures (40 °C), with the desired rearranged product **45** (R = *n*-butyl) and a small amount of the hydrolyzed formamide obtained (Scheme 24). Carrying out the reaction at equivalent concentrations (4 M) without capsule **8** led to only the carboxylic and hydrolyzed formamide being present after two days at 80 °C.



Scheme 24. Reaction of carboxylic acids with isonitriles within **8** in mesitylene.

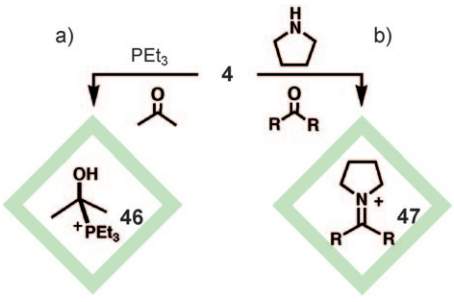
Rearrangement is prevented with bulkier alkyl chains (R = isopropyl), and the addition product reacts with a second equivalent of acid (in the bulk solvent) to form the alkyl formamide and symmetric anhydride.

4. Molecular Flasks as Containers

4.1. Stabilization of Reactive Intermediates within Molecular Flasks

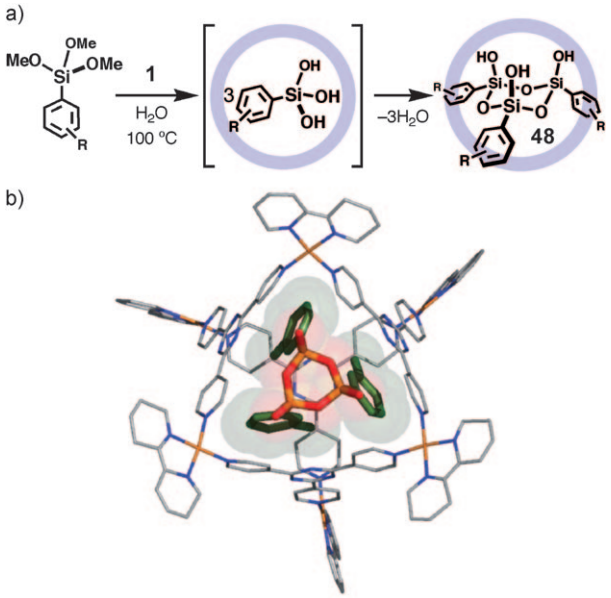
The pioneering work of Cram established molecular container compounds as important tools for probing the fundamental aspects of structural chemistry.[2,12] Within the inner phase of molecular containers and flasks, guest molecules are protected from the bulk phase, and unstable, highly reactive compounds can be stabilized.[9,92] Initial studies utilized covalent hosts, such as carcerands and cavitands, but the increased cavity size of self-assembled molecular flasks has enabled the study of a variety of larger species. Accordingly, the focus here will be on unusual and traditionally unisolable compounds arising from multiple incarcerated guest molecules. Although the conformational regulation and thermal stabilization of single molecules within self-assembled hosts is an alluring display of inner-phase control, they are not discussed in this Review.[93]

Phosphonium ions such as $[Me_2C(OH)PEt_3]^+$ (**46**) are synthesized from phosphines and acetone in acidic conditions, but can only be isolated under anhydrous conditions. In aqueous solutions, the phosphonium ions quickly decompose into their original constituents. In 2000 Raymond and co-workers reported that triethylphosphine and residual acetone combine inside the hydrophobic interior of anionic host **4** to quantitatively form phosphonium ion **46**, which is protected from the aqueous solution (Scheme 25a).[94] More recently, Raymond and co-workers employed the preference of cage **4** for cationic guests to generate and stabilize iminium ions **47** effectively in aqueous solution.[95] The combination of pyrrolidine and acetone in an aqueous solution containing **4** resulted in the formation of the encapsulated iminium ion **47** (R = Me) in 63% yield (Scheme 25b). The concentration of iminium ions in neutral or basic solution is negligible, but could be obtained in the presence of **4**. A wide range of encapsulated iminium cations **47** were formed and the binding efficiencies varied according to the size of the guest molecules.



Scheme 25. Stabilization of a) phosphonium ions and b) iminium ions within **4** in water.

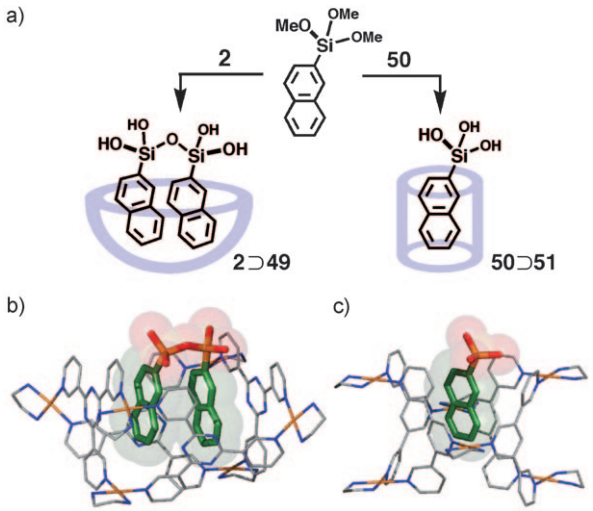
The isolation and identification of the intermediate species during polymerization is a challenging subject as the host must recognize and isolate the target species from the many reactive intermediates present. In 2000, self-assembled cage **1** was found to specifically stabilize the short-lived, cyclic silanol trimers **48** formed in the polycondensation of trialkoxysilanes. Cyclic trimer **48**, formed when phenyltrimethoxysilane is polymerized in the presence of **1** in aqueous solution at 100 °C, is sequestered inside the cavity of **1** (Scheme 26).[76] Encapsulation completely suppresses



Scheme 26. a) Polycondensation of trialkoxysilanes in aqueous solution to form cyclic trimers **48** within **1**. b) X-ray crystal structure of **1**⊃**48** (R = Me); guest: green C, red O, orange Si; host: gray C, blue N, orange Pd.

further condensations. The entrapped trimer **48** (R = H) is very stable in acidic aqueous solutions and can be isolated as a pure clathrate compound in 92% yield. The process is denoted a "ship-in-a-bottle" synthesis, since the reactants can enter and leave the cavity of flask **1**, but once formed, the cyclic product **48** can no longer escape because of its larger size and increased rigidity. Furthermore, the limited cavity size strictly controls the stereochemistry, and only the all-*cis* isomer is formed.

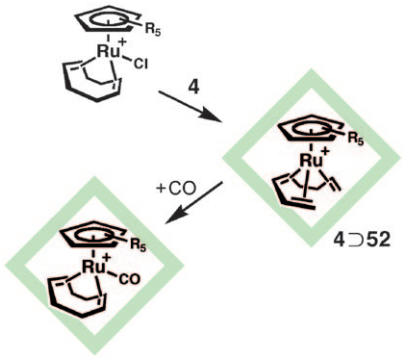
The judicious choice of the molecular flask allows the selective isolation of specific intermediates in the polycondensation of trialkoxysilanes.[96] For example, the bowl-shaped cage **2** has a cavity large enough to accommodate only two molecules of 2-naphthyltrimethoxylsilane, and accordingly the enclathrated dimer **49** is isolated in 88% yield (Scheme 27). The tube-shaped cage **50**,[97] on the other hand, sequesters a single trialkoxysilane molecule, which is then hydrolyzed to give the silanol monomer **51** in 92% yield. Although both the dimer and the monomer are ephemeral intermediates in the polycondensation reaction, because of their highly reactive SiOH groups, they remain remarkably stable within the cages (Scheme 27).[96] Thus, the previously



Scheme 27. a) Isolation of specific intermediates in the polycondensation of trialkoxysilanes within **2** and **50** in water. X-ray crystal structures of b) **2**⊃**49** and c) **50**⊃**51**; guest: green C, red O, orange Si; host: gray C, blue N, orange Pd.

un-isolable silanol monomer, dimer, and cyclic trimer can be selectively enclathrated in the appropriate molecular flask. Therefore, the general concept of "cavity-directed synthesis", where the reactions are directed by the shape, size, and stereoelectronic properties of the host cavities, is not limited to the biological world of enzymes, but is now firmly within the realm of the synthetic chemist.

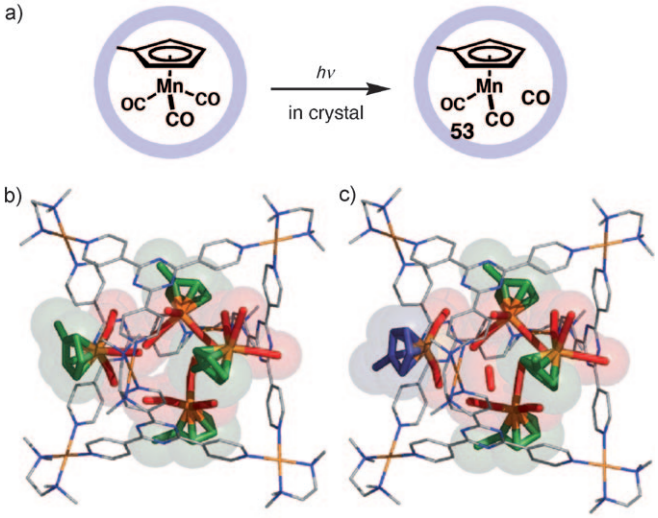
Recently, the Raymond research group demonstrated that reactive organometallic species are also stabilized within the cavity of **4**.[98] Encapsulation of the ruthenium complex [CpRuCl(cod)] (Cp = C_5H_5; cod = 1,5-cyclooctadiene), a catalyst for the formation of C–C bonds, by cage **4** unexpectedly gives a host–guest complex that contains the unusual and very unstable ruthenium complex **52** (Scheme 28). Even though complex **52** decomposes within hours in organic solution and within minutes in water, the host–guest complex **4**⊃**52** is stable in aqueous solution for several weeks. The addition of CO results in the formation of the complex $[CpRu(cod)(CO)]^+$ over several days. While no direct evidence



Scheme 28. a) Preparation and isolation of reactive organometallic species **52** (R = H or Me) within **4** in water.

was obtainable, it is believed that the reaction with CO occurs within the cavity.

The Fujita research group used cage **1** to generate and characterize the coordinatively unsaturated species $[Cp'Mn(CO)_2]$ (Cp′ = methylcyclopentyl) at the atomic level (Scheme 29a).[99] Irradiation of single crystals of the 1:4 host–



Scheme 29. a) Photochemical generation of the coordinatively unsaturated species **53** within **1** in the crystal. b) X-ray crystal structures of **1**⊃$[Cp'Mn(CO)_3]$ b) before and c) after photoirradiation; guest: green C, blue N, red CO, orange Mn; host: gray C, blue N, orange Pd.

guest $[Cp'Mn(CO)_3]$ clathrate at 100 K resulted in the photodissociation of a single CO from one of the four guest complexes. As an answer tothe lengthy debate about the geometry at unsaturated metal centers,[100] the X-ray crystal structure of the 16-electron, unsaturated manganese complex **53** was determined to be pyramidal and not planar. The free CO molecule remains trapped within the cavity and prevents further molecules from dissociating.

4.2. Intermolecular Interactions within Molecular Flasks

Controlling the spatial/temporal relationships of individual molecules in the solid and liquid state is of great importance to the fields of materials science and biomimetics.[101] Self-assembled molecular flasks are a particularly attractive tool, as the lengthy construction of covalent architectures is unnecessary. Simple enclathration suffices to enforce atypical intermolecular interactions and give rise to unusual and unique physical phenomena. The material and bulk properties can then be defined by the properties of the flask rather than by those of the guest molecules.

In 2002, Fujita and co-workers demonstrated that four molecules of the redox active ferrocene were encapsulated by host **1** (Figure 8).[102] Host–guest interactions as well as increased guest–guest interactions, arising from the high local concentration, result in altered electrochemical properties of the ferrocene. The peak potential of Fe^{2+}/Fe^{3+} is

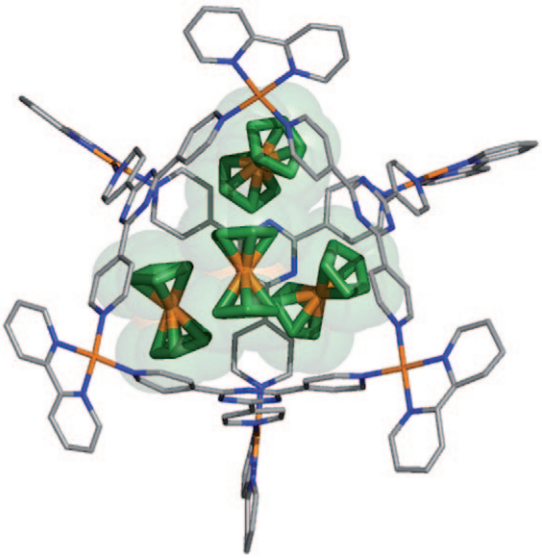
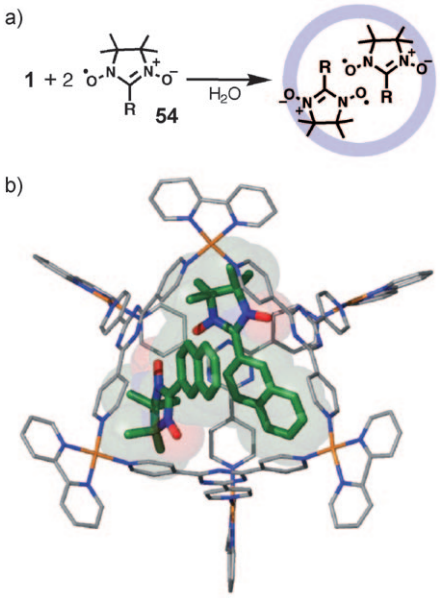


Figure 8. X-ray crystal structures of **1**⊃(ferrocene)$_4$; guest: green C, orange Fe; host: gray C, blue N, orange Pd.

positively shifted by 73 mV, together with an enhanced peak current.

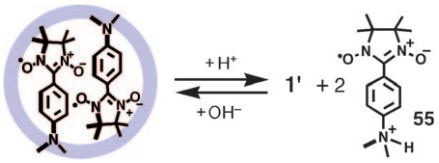
Intermolecular spin–spin interactions are of fundamental importance for the design of magnetic materials, but they are difficult to control and often require the tedious synthesis of covalent frameworks.[103] In an unconventional approach, Fujita and co-workers utilized cage **1** to organize and manipulate the through-space interactions of organic radicals (Scheme 30a).[104] In solution, free nitronyl nitroxides **54** exhibit no particular intermolecular interaction, but the ESR spectrum of the 1:2 host–guest clathrates **1**⊃**54** shows a triplet



Scheme 30. a) Interactions between nitronyl nitroxides **54** within **1**. b) X-ray crystal structure of **1**⊃(**54**)$_2$ (R = 2-naphthyl); guest: green C, blue N, red O; host: gray C, blue N, orange Pd.

state in the solution and solid state. The distance between radical centers (R = 2-naphthyl) was estimated by point–dipole approximation to be 5.9 Å. X-ray crystallographic analysis confirmed that the two radical centers of **54** (R = 2-naphthyl) are held in proximity, with an average intermolecular distance of 5.8 Å (Scheme 30b).

The use of the dimethylamino nitroso radical **55** led to a pH-responsive host–guest system,[25] and the spin–spin interactions could be controlled by adjusting the pH value (Scheme 31).[105] The two guest radicals interact in neutral

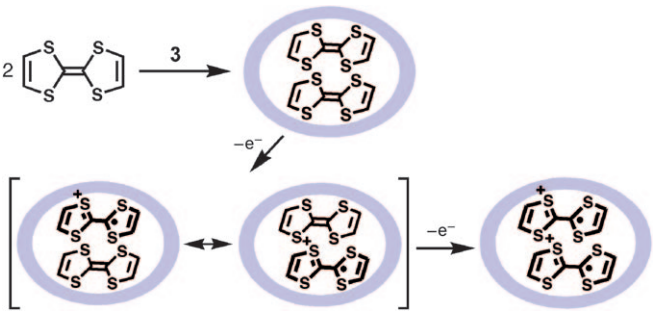


Scheme 31. pH-dependence of interactions between nitroxide radicals **55** within **1′** in water.

solution, and the ESR of **1′**⊃(**55**)$_2$ (**1′** denotes the more robust, platinum analogue of **1**) shows a triplet state. When the pH value is lowered by the addition of acid (HNO_3), the dimethylamino group is protonated and the cationic nitroso radical has a lower affinity for the highly positive cage **1′**. The radical guests exit the host cavity and the ESR triplet signal is replaced by a doublet, which indicates no intermolecular interactions. This process is reversible: neutralization with K_2CO_3 results in re-encapsulation and the reappearance of the triplet signal.

The walls of molecular flasks are not necessarily completely insulating, and interactions between incarcerated guests and external molecules can occur through the phenomenon of superexchange.[106] Ramamurthy and Turro reported that nitroxide radical ions incarcerated within capsule **9** show spin–spin interactions with free nitroxide radicals.[107] The magnitude of the spin coupling can be enhanced by Coulombic interactions between the host and the free radical. In this example, no new host–guest or guest–guest interactions occur, but the host instead facilitates interactions of the enclathrated guest with the outside environment. It is an important reminder that compartmentalization on the molecular scale is not as black and white as it might seem.

π-Conjugated planar molecules are fascinating compounds from the standpoint of functional materials, particularly when they form orderly stacks.[101,108] Fujita co-workers used the confined spaces of molecular flasks to precisely assemble specific aromatic stacks and induce new intermolecular interactions and chemical phenomena.[27,109] The key to success is the prism-shaped cage **3**, which has a cavity ideally sized to accommodate two stacked planar aromatic molecules.[27] When cage **3** is treated with excess tetrathiafulvalene (TTF) in an anaerobic, aqueous solution, the colorless solution quickly turns dark green as **3**⊃(TTF)$_2$ is selectively formed (Scheme 32).[110] Electrochemical studies revealed that an initial one-electron reduction occurs at 152 mV to give the mixed valence dimer $[(TTF)_2]^{+\cdot}$ and this is

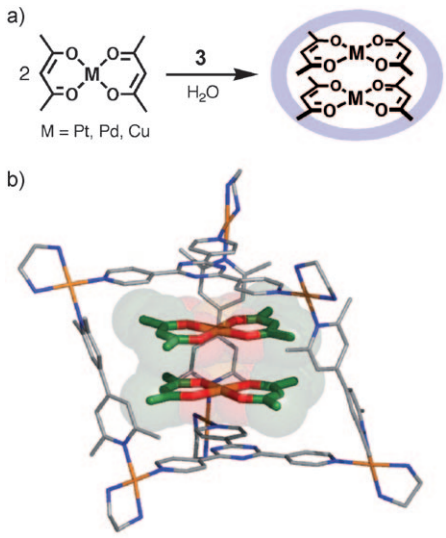


Scheme 32. Formation of unstable mixed-valence dimer $[(TTF)_2]^{+\bullet}$ and cation radical dimer $(TTF^{+\bullet})_2$ within prism-shaped cage **3** in water.

followed by a second one-electron reduction at 304 mV to give the cation radical dimer $(TTF^{+\bullet})_2$. A broad absorption band in the near-IR ($\lambda_{max} \approx 2000$ nm) appears in the UV/Vis spectra at a constant voltage of 180 mV, which is indicative of the mixed-valence dimer $[(TTF)_2]^{+\bullet}$. The cage framework holds the two TTF guests in proximity and protects the mixed-valence dimer $[(TTF)_2]^{+\bullet}$ from oxygen and solvent. Thus, the dimer has unusually high stability, even under aerobic conditions ($t_{1/2} \approx 1$ day). Further oxidation to the dication TTF^{2+} occurs at 552 mV and results in guest expulsion, most likely because of cationic repulsions.

The encapsulation and isolation of planar aromatic compounds can also be used to alter and control interactions in the excited state. When capsule **9** assembles in the presence of two molecules of naphthalene, the excimer emission increases as a result of the effective molarity (ca. 3 M). However, the cavity is large enough that monomer emission is also observed.[111] Two molecules of anthracene are also encapsulated, but in this case only the excimer emission is observed. In the absence of capsule **9**, anthracene immediately and quantitatively photodimerizes. Only one molecule of the larger tetracene is isolated; photodimerization is thus suppressed and only monomer emission is observed.

Strict control over the spatial distribution in arrays of metal ions has been the basis for the development of a new class of molecular-based materials,[112] and, in a similar fashion, interactions between the d orbitals of metal centers can lead to the stacking of metal complexes within the cavity of cage **3**.[113] Bisacetylacetonato–metal complexes $[M(acac)_2]$ are classic coordination compounds, but intermolecular metal–metal interactions have never before been observed. The addition of excess $[M(acac)_2]$ ($M = Pt^{II}$, Pd^{II}, or Cu^{II}) to an aqueous solution of cage **3** results in two molecules of the planar M^{II} complexes entering the cavity of **3**, thereby forming a dimeric stack, which has led to the observation of the characteristic metal–metal interactions (Scheme 33). The UV/Vis spectra of the Pd and Pt complexes showed transitions at 450 and 500 nm, respectively, distinctive of interactions between the d orbitals of two metal centers. X-ray analysis of the host–guest complex **3**⊃$[\{Pt(acac)_2\}_2]$ revealed the two Pt atoms are separated by 3.32 Å, typical for interactions between the d orbitals of Pt^{II} ions (< 3.5 Å). ESR analysis of the 1:2 complex of **3** and $[Cu(acac)_2]$ revealed spin–spin coupling between the two Cu^{II} centers.



Scheme 33. a) Metal–metal d–d interactions through the stacking of metal complexes within **3**. b) X-ray crystal structure of **3**⊃$[Pt\{(acac)_2\}_2]$; guest: green C, red CO, orange M; host: gray C, blue N, orange Pd.

Insertingly, the introduction of an extra phenyl group in the side pillar gives the extended prism cage **3′** in which three stacked aromatic compounds, such as tetraazaporphine **56**, can easily be accommodated (Figure 9).[114] In the presence of excess copper(II) azaporphine **56** (M = Cu), a Cu^{II}-Cu^{II}-Cu^{II} array is formed within the prism-shaped cage **3′**. Exciton coupling is clearly apparent in the UV/Vis spectrum, and ESR

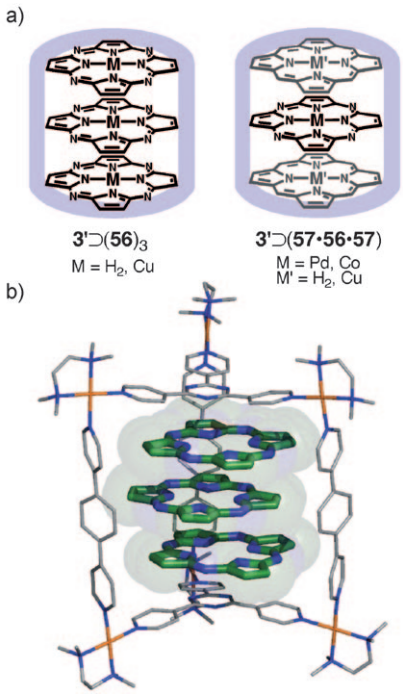


Figure 9. a) Homo and hetero triple stacks of metal azaporphine **56** and metal porphine **57** within prism-shaped cage **3′**. b) X-ray crystal structure of **3′**⊃$(\mathbf{56})_3$ ($M = H_2$); guest: green C, blue N; host: gray C, blue N, orange Pd.

spectroscopic analysis revealed the quartet state of the three metal centers, despite the lack of covalent or noncovalent bonds between the azaporphine rings. Surprisingly, the $\Delta m_s = 3$ forbidden transition was also observed at a field strength of 100 mT and a temperature of 113 K. This was the first time this transition has been observed in an inorganic system. Treatment of cage **3′** with excess electron-rich porphine **57** and electron-deficient azaporphine affords the D-A-D triple-stacked complex **3′**⊃(**57**·**56**·**57**) consisting of two metal-free donor molecules and one metal-free acceptor molecule in 31% yield. The preference for alternating D-A-D stacking was then used to arrange hetero-metal triple stacks containing two copper(II) porphines and a single palladium(II) or cobalt(II) azaporphine. Although the hyperfine structures in the ESR spectra are smeared, they indicate that the two Cu^{II} centers do not interact through the Pd^{II} center, but that the Co^{II} center propagates the coupling of electron spin.

5. Conclusions and Outlook

In the mere 30 years since Cram and co-workers defined artificial molecular hosts, guests, and their complexes,[115] the field of molecular containers has actively advanced towards the elusive goal of enzyme mimetics. The advent of self-assembled molecular flasks has offered significant new opportunities, and the last ten years has seen a rapid growth in new self-assembled hosts and, more importantly, in functional molecular flasks. The simplicity of self-assembly has facilitated the engineering of molecular flasks with specific sizes, shapes, and properties. As a result, specific host–guest and guest–guest interactions can be better manipulated on the molecular level to generate new chemical phenomena.

Quo Vadis?

The field of functional, self-assembled molecular flasks is relatively new but productive, and has the potential for significant growth. The innate modularity of self-assembled flasks lends itself to further application such as enzyme mimetics, artificial photosynthesis, molecular magnets, chemosensors, and delivery systems. The molecular flasks presented here are no longer esoteric and of limited application, but represent the next step in nanoscale laboratory equipment. Some of them are already commercially available, and we expect that not only chemists but also biologists, physicists, and material scientists will find new uses for functional molecular flasks. Ultimately, the value and utility of any tool depends on the ingenuity and productivity of the user.

We hope that this Review will serve as the inspiration for newcomers to the field, and several areas that warrant further investigation should be emphasized. Foremost is a better structural characterization of both the host and host–guest complex. When discussing the effects of the shape and size of molecular flasks, NMR spectroscopy is certainly informative, but X-ray crystallography provides the clearest structural evidence of the often subtle intermolecular interactions. Solution-state methods (NMR spectroscopy, mass spectrometry) and solid-state methods (X-ray structure analysis) should be coupled for an overall understanding of the host–guest behavior. Similarly, mechanisms of guest inclusion, guest exchange, and host–guest interactions are not simple since self-assembled hosts are, by their very nature, dynamic, flexible systems. Better understanding of the structures of the hosts and host–guest systems in combination with detailed kinetic data is necessary. For example, following reactions in situ by X-ray diffraction, namely single-crystal to single-crystal reactions, is a direct and a powerful method for understanding the effects of preorganization and the paths of reactions in molecular flasks.

Received: November 1, 2008

[1] *Instruments and Experimentation in the History of Chemistry*, 1st ed. (Eds.: F. L. Holmes, T. H. Levere), MIT Press, Cambridge, **2000**; C. Reinhardt, *Shifting and Rearranging: Physical Methods and the Transformation of Modern Chemistry*, Science History Publications, USA, **2006**.
[2] D. J. Cram, J. M. Cram, *Container Molecules and Their Guests*, Royal Society of Chemistry, Cambridge, **1994**.
[3] W. P. Jencks, *Catalysis in Chemistry and Enzymology*, McGraw-Hill, New York, **1969**.
[4] L. Pauling, *Nature* **1948**, *161*, 707–709.
[5] X. Zhang, K. N. Houk, *Acc. Chem. Res.* **2005**, *38*, 379–385.
[6] J. W. Steed, J. L. Atwood, *Supramolecular Chemistry*, 1st ed., Wiley, Chichester, **2000**.
[7] R. Breslow, S. D. Dong, *Chem. Rev.* **1998**, *98*, 1997–2011.
[8] D. M. Rudkevich, *Bull. Chem. Soc. Jpn.* **2002**, *75*, 393–413.
[9] R. Warmuth, *Eur. J. Org. Chem.* **2001**, 423–437.
[10] D. M. Vriezema, M. C. Aragones, J. A. A. W. Elemans, J. J. L. M. Cornelissen, A. E. Rowan, R. J. M. Nolte, *Chem. Rev.* **2005**, *105*, 1445–1489.
[11] D. J. Cram, *Science* **1983**, *219*, 1177–1183.
[12] D. J. Cram, *Nature* **1992**, *356*, 29–36.
[13] D. L. Caulder, K. N. Raymond, *Acc. Chem. Res.* **1999**, *32*, 975–982.
[14] M. Fujita, M. Tominaga, A. Hori, B. Therrien, *Acc. Chem. Res.* **2005**, *38*, 371–380.
[15] S. Leininger, B. Olenyuk, P. J. Stang, *Chem. Rev.* **2000**, *100*, 853–908.
[16] F. Hof, S. L. Craig, C. Nuckolls, J. Rebek, Jr., *Angew. Chem.* **2002**, *114*, 1556–1578; *Angew. Chem. Int. Ed.* **2002**, *41*, 1488–1508; J. Rebek, Jr., *Angew. Chem.* **2005**, *117*, 2104–2115; *Angew. Chem. Int. Ed.* **2005**, *44*, 2068–2078.
[17] D. Fiedler, D. H. Leung, R. G. Bergman, K. N. Raymond, *Acc. Chem. Res.* **2005**, *38*, 351–360.
[18] C. H. M. Amijs, G. P. M. van Klink, G. van Koten, *Dalton Trans.* **2006**, 308–327; G. F. Swiegers, T. J. Malefetse, *Chem. Rev.* **2000**, *100*, 3483–3537.
[19] A. W. Maverick, S. C. Buckingham, Q. Yao, J. R. Bradbury, G. G. Stanley, *J. Am. Chem. Soc.* **1986**, *108*, 7430–7431; A. W. Maverick, F. E. Klavetter, *Inorg. Chem.* **1984**, *23*, 4129–4130; J. R. Bradbury, J. L. Hampton, D. P. Martone, A. W. Maverick, *Inorg. Chem.* **1989**, *28*, 2392–2399; A. W. Maverick, M. L. Ivie, J. H. Waggenspack, F. R. Fronczek, *Inorg. Chem.* **1990**, *29*, 2403–2409.
[20] R. W. Saalfrank, A. Stark, K. Peters, H. G. von Schnering, *Angew. Chem.* **1988**, *100*, 878–880; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 851–853; R. W. Saalfrank, B. Horner, D. Stalke, J. Salbeck, *Angew. Chem.* **1993**, *105*, 1223–1225; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1179–1182; R. W. Saalfrank, A. Stark,

M. Bremer, H.-U. Hummel, *Angew. Chem.* **1990**, *102*, 292 – 295; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 311 – 314; R. W. Saalfrank, R. Burak, A. Breit, D. Stalke, R. Herbst-Irmer, J. Daub, M. Porsch, E. Bill, M. Müther, A. X. Trautwein, *Angew. Chem.* **1994**, *106*, 1697 – 1699; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1621 – 1623.

[21] M. Fujita, J. Yazaki, K. Ogura, *J. Am. Chem. Soc.* **1990**, *112*, 5645 – 5646.

[22] M. Fujita, D. Oguro, M. Miyazawa, H. Oka, K. Yamaguchi, K. Ogura, *Nature* **1995**, *378*, 469 – 471.

[23] M. Yoshizawa, M. Tamura, M. Fujita, *J. Am. Chem. Soc.* **2004**, *126*, 6846 – 6847.

[24] T. Kusukawa, M. Fujita, *J. Am. Chem. Soc.* **2002**, *124*, 13576 – 13582.

[25] F. Ibukuro, T. Kusukawa, M. Fujita, *J. Am. Chem. Soc.* **1998**, *120*, 8561 – 8562.

[26] M. Fujita, S.-Y. Yu, T. Kusukawa, H. Funaki, K. Ogura, K. Yamaguchi, *Angew. Chem.* **1998**, *110*, 2192 – 2196; *Angew. Chem. Int. Ed.* **1998**, *37*, 2082 – 2085; S.-Y. Yu, T. Kusukawa, K. Biradha, M. Fujita, *J. Am. Chem. Soc.* **2000**, *122*, 2665 – 2666.

[27] M. Yoshizawa, J. Nakagawa, K. Kumazawa, M. Nagao, M. Kawano, T. Ozeki, M. Fujita, *Angew. Chem.* **2005**, *117*, 1844 – 1847; *Angew. Chem. Int. Ed.* **2005**, *44*, 1810 – 1813; M. Yoshizawa, M. Nagao, K. Kumazawa, M. Fujita, *J. Organomet. Chem.* **2005**, *690*, 5383 – 5388.

[28] D. L. Caulder, R. E. Powers, T. N. Parac, K. N. Raymond, *Angew. Chem.* **1998**, *110*, 1940 – 1943; *Angew. Chem. Int. Ed.* **1998**, *37*, 1840 – 1842.

[29] R. V. Slone, J. T. Hupp, *Inorg. Chem.* **1997**, *36*, 5422 – 5423.

[30] M. L. Merlau, M. del Pilar Mejia, S. T. Nguyen, J. T. Hupp, *Angew. Chem.* **2001**, *113*, 4369 – 4372; *Angew. Chem. Int. Ed.* **2001**, *40*, 4239 – 4242.

[31] S. Bélanger, J. T. Hupp, *Angew. Chem.* **1999**, *111*, 2360 – 2362; *Angew. Chem. Int. Ed.* **1999**, *38*, 2222 – 2224.

[32] S. J. Lee, K. L. Mulfort, X. Zuo, A. J. Goshe, P. J. Wesson, S. T. Nguyen, J. T. Hupp, D. M. Tiede, *J. Am. Chem. Soc.* **2008**, *130*, 836 – 838.

[33] G. A. Jeffery, *Hydrogen Bonding in Biological Structures*, Springer, Berlin, **1991**.

[34] *Supramolecular Assembly via Hydrogen Bonds I*, *Vol. 1*, Springer, Berlin, **2004**.

[35] R. Wyler, J. de Mendoza, J. Rebek, Jr., *Angew. Chem.* **1993**, *105*, 1820 – 1821; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1699 – 1701.

[36] X. Garcías, J. Rebek, Jr., *Angew. Chem.* **1996**, *108*, 1328 – 1330; *Angew. Chem. Int. Ed. Eng.* **1996**, *35*, 1225 – 1228; R. S. Meissner, J. Rebek, Jr., J. de Mendoza, *Science* **1995**, *270*, 1485 – 1488; C. Valdés, U. P. Spitz, L. M. Toledo, S. W. Kubik, J. Rebek, Jr., *J. Am. Chem. Soc.* **1995**, *117*, 12733 – 12745; J. Kang, J. Rebek, Jr., *Nature* **1996**, *382*, 239 – 241.

[37] T. Heinz, D. M. Rudkevich, J. Rebek, Jr., *Nature* **1998**, *394*, 764 – 766.

[38] G. W. V. Cave, J. Antesberger, L. J. Barbour, R. M. McKinlay, J. L. Atwood, *Angew. Chem.* **2004**, *116*, 5375 – 5378; *Angew. Chem. Int. Ed.* **2004**, *43*, 5263 – 5266; L. R. McGillivray, J. L. Atwood, *Nature* **1997**, *389*, 469 – 472; L. J. Prins, J. Huskens, F. de Jong, P. Timmerman, D. N. Reinhoudt, *Nature* **1999**, *398*, 498 – 504; L. J. Prins, F. de Jong, P. Timmerman, D. N. Reinhoudt, *Nature* **2000**, *408*, 181 – 184; S. C. Zimmerman, F. Zeng, D. E. C. Reichert, S. V. Kolotuchin, *Science* **1996**, *271*, 1095 – 1098.

[39] C. L. D. Gibb, B. C. Gibb, *J. Am. Chem. Soc.* **2004**, *126*, 11408 – 11409.

[40] L. S. Kaanumalle, C. L. D. Gibb, B. C. Gibb, V. Ramamurthy, *J. Am. Chem. Soc.* **2004**, *126*, 14366 – 14367.

[41] R. Breslow, *Acc. Chem. Res.* **1995**, *28*, 146 – 153; A. Kirby, *Angew. Chem.* **1996**, *108*, 770 – 790; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 706 – 724.

[42] J.-M. Lehn, *Angew. Chem.* **1988**, *100*, 91 – 116; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 89 – 112; D. J. Cram, *Angew. Chem.* **1988**, *100*, 1041 – 1052; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1009 – 1112; K. Takahashi, *Chem. Rev.* **1998**, *98*, 2013 – 2033.

[43] A. W. Kleij, J. N. H. Reek, *Chem. Eur. J.* **2006**, *12*, 4218 – 4227.

[44] R. Cacciapaglia, S. Di Stefano, L. Mandolini, *Acc. Chem. Res.* **2004**, *37*, 113 – 122; A. Kirby, *Adv. Phys. Org. Chem.* **1980**, *17*, 183 – 278.

[45] A. Shivanyuk, J. Rebek, Jr., *J. Am. Chem. Soc.* **2002**, *124*, 12074 – 12075; P. Timmerman, W. Verboom, F. C. J. M. van Veggel, J. P. M. van Duynhoven, D. N. Reinhoudt, *Angew. Chem.* **1994**, *106*, 2437 – 2440; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 2345 – 2348.

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

[47] T. Kusukawa, T. Nakai, T. Okano, M. Fujita, *Chem. Lett.* **2003**, *32*, 284 – 285.

[48] M. Yoshizawa, M. Tamura, M. Fujita, *Science* **2006**, *312*, 251 – 254.

[49] P. von R. Schleyer, M. Manoharan, H. Jiao, F. Stahl, *Org. Lett.* **2001**, *3*, 3643 – 3646; M.-F. Cheng, W.-K. Li, *Chem. Phys. Lett.* **2003**, *368*, 630 – 638.

[50] Y. Nishioka, T. Yamaguchi, M. Yoshizawa, M. Fujita, *J. Am. Chem. Soc.* **2007**, *129*, 7000 – 7001.

[51] J. Chen, J. Rebek, Jr., *Org. Lett.* **2002**, *4*, 327 – 329.

[52] M. Yoshizawa, Y. Takeyama, T. Kusukawa, M. Fujita, *Angew. Chem.* **2002**, *114*, 1403 – 1405; *Angew. Chem. Int. Ed.* **2002**, *41*, 1347 – 1349.

[53] R. S. Liu, G. S. Hammond, *Acc. Chem. Res.* **2004**, *39*, 396 – 403; *Solid State and Surface Photochemistry. Molecular and Supramolecular Photochemistry*, *Vol. 5* (Eds.: V. Ramamurthy, K. S. Schanze), Marcel Dekker, New York, **2000**; M. N. Chrétien, *Pure Appl. Chem.* **2007**, *79*, 1 – 20; V. Ramamurthy, D. Eaton, *Acc. Chem. Res.* **1988**, *21*, 300 – 306; N. J. Turro, G. S. Cox, M. A. Paczkowski, *Top. Curr. Chem.* **1985**, *129*, 57 – 97.

[54] V. Ramamurthy, K. Venkatesan, *Chem. Rev.* **1987**, *87*, 433 – 481.

[55] S. Karthikeyan, V. Ramamurthy, *Tetrahedron Lett.* **2005**, *46*, 4495 – 4498.

[56] K. Takaoka, M. Kawano, T. Ozeki, M. Fujita, *Chem. Commun.* **2006**, 1625 – 1627.

[57] L. S. Kaanumalle, V. Ramamurthy, *Chem. Commun.* **2007**, 1062 – 1064.

[58] Z. R. Laughrey, C. L. D. Gibb, T. Senechal, B. C. Gibb, *Chem. Eur. J.* **2003**, *9*, 130 – 138.

[59] A. Parthasarathy, L. S. Kaanumalle, V. Ramamurthy, *Org. Lett.* **2007**, *9*, 5059 – 5062.

[60] N. Haga, H. Nakajima, H. Takayanagi, K. Tokumaru, *J. Org. Chem.* **1998**, *63*, 5372 – 5384; N. Haga, H. Takayanagi, K. Tokumaru, *J. Chem. Soc. Perkin Trans. 2* **2002**, 734 – 745.

[61] M. Yoshizawa, Y. Takeyama, T. Okano, M. Fujita, *J. Am. Chem. Soc.* **2003**, *125*, 3243 – 3247.

[62] P. J. Stang, B. Olenyuk, D. C. Muddiman, R. D. Smith, *Organometallics Organomet.* **1997**, *16*, 3094 – 3096.

[63] A. V. Davis, D. Fiedler, M. Ziegler, A. Terpin, K. N. Raymond, *J. Am. Chem. Soc.* **2007**, *129*, 15354 – 15363; A. Terpin, M. Ziegler, D. W. Johnson, K. N. Raymond, *Angew. Chem.* **2001**, *113*, 161 – 164; *Angew. Chem. Int. Ed.* **2001**, *40*, 157 – 160; M. Ziegler, A. V. Davis, D. W. Johnson, K. N. Raymond, *Angew. Chem.* **2003**, *115*, 689 – 692; *Angew. Chem. Int. Ed.* **2003**, *42*, 665 – 668.

[64] Y. Nishioka, T. Yamaguchi, M. Kawano, M. Fujita, *J. Am. Chem. Soc.* **2008**, *130*, 8160 – 8161.

[65] A. K. Sundaresan, V. Ramamurthy, *Org. Lett.* **2007**, *9*, 3575 – 3578.

[66] C. L. D. Gibb, A. K. Sundaresan, V. Ramamurthy, B. C. Gibb, *J. Am. Chem. Soc.* **2008**, *130*, 4069 – 5080.
[67] L. S. Kaanumalle, C. L. D. Gibb, B. C. Gibb, V. Ramamurthy, *Org. Biomol. Chem.* **2007**, *5*, 236 – 238.
[68] N. J. Turro, *Modern Molecular Photochemistry*, University Science Books, Sausalito, **1991**; T. Furusawa, M. Kawano, M. Fujita, *Angew. Chem.* **2007**, *119*, 5819 – 5821; *Angew. Chem. Int. Ed.* **2007**, *46*, 5717 – 5719.
[69] T. Yamaguchi, M. Fujita, *Angew. Chem.* **2008**, *120*, 2097 – 2099; *Angew. Chem. Int. Ed.* **2008**, *47*, 2067 – 2069.
[70] A. Greer, *Nature* **2007**, *447*, 273 – 274.
[71] A. Natarajan, L. S. Kaanumalle, S. Jockusch, C. L. D. Gibb, B. C. Gibb, N. J. Turro, V. Ramamurthy, *J. Am. Chem. Soc.* **2007**, *129*, 4132 – 4133.
[72] M. Yoshizawa, S. Miyagi, M. Kawano, K. Ishiguro, M. Fujita, *J. Am. Chem. Soc.* **2004**, *126*, 9172 – 9173.
[73] Y. Furutani, H. Kandori, M. Kawano, K. Nakabayashi, M. Yoshizawa, M. Fujita, *J. Am. Chem. Soc.* **2009**, *131*, 4764 – 4768.
[74] L. Pauling, *Chem. Eng. News* **1946**, *24*(10), 1375 – 1377.
[75] *Templated Organic Synthesis* (Eds.: F. Diederich, P. J. Stang), Wiley-VCH, Weiheim, **2000**.
[76] M. Yoshizawa, T. Kusukawa, M. Fujita, K. Yamaguchi, *J. Am. Chem. Soc.* **2000**, *122*, 6311 – 6312.
[77] J. Kang, J. Santamaría, G. Hilmersson, J. Rebek, Jr., *J. Am. Chem. Soc.* **1998**, *120*, 7389 – 7390.
[78] D. Hilvert, K. W. Hill, K. D. Nared, M.-T. M. Auditor, *J. Am. Chem. Soc.* **1989**, *111*, 9261 – 9263.
[79] D. Fiedler, R. G. Bergman, K. N. Raymond, *Angew. Chem.* **2004**, *116*, 6916 – 6919; *Angew. Chem. Int. Ed.* **2004**, *43*, 6748 – 6751.
[80] D. Fiedler, H. Van Halbeek, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2006**, *128*, 10240 – 20252.
[81] C. J. Hastings, D. Fiedler, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2008**, *130*, 10977 – 10983.
[82] M. D. Pluth, R. G. Bergman, K. N. Raymond, *Science* **2007**, *316*, 85 – 88.
[83] M. D. Pluth, R. G. Bergman, K. N. Raymond, *Angew. Chem.* **2007**, *119*, 8741 – 8743; *Angew. Chem. Int. Ed.* **2007**, *46*, 8587 – 8589.
[84] H. Ito, T. Kusukawa, M. Fujita, *Chem. Lett.* **2000**, 598 – 599.
[85] M. Yoshizawa, N. Sato, M. Fujita, *Chem. Lett.* **2005**, *34*, 1392 – 1393.
[86] L. Miljacic, L. Sarkisov, D. E. Ellis, R. Q. Snurr, *J. Chem. Phys.* **2004**, *121*, 7228 – 7236.
[87] S. J. Lee, S.-H. Cho, K. L. Mulfort, D. M. Tiede, J. T. Hupp, S. T. Nguyen, *J. Am. Chem. Soc.* **2008**, *130*, 16828 – 16829.
[88] D. H. Leung, D. Fiedler, R. G. Bergman, K. N. Raymond, *Angew. Chem.* **2004**, *116*, 981 – 984; *Angew. Chem. Int. Ed.* **2004**, *43*, 963 – 966.
[89] D. H. Leung, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2007**, *129*, 2746 – 2747.
[90] A. Shaabani, E. Soleimani, A. H. Rezayan, *Tetrahedron Lett.* **2007**, *48*, 6137 – 6141; X. Li, S. J. Danishefsky, *J. Am. Chem. Soc.* **2008**, *130*, 5446 – 5448.
[91] J.-L. Hou, D. Ajami, J. Rebek Jr. , *J. Am. Chem. Soc.* **2008**, *130*, 7810 – 7811.
[92] D. J. Cram, M. E. Tanner, R. Thomas, *Angew. Chem.* **1991**, *103*, 1048 – 1051; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1024 – 1027; 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; D. A. Makeiff, K. Vishnumurthy, J. C. Sherman, *J. Am. Chem. Soc.* **2003**, *125*, 9558 – 9559; P. Roach, R. Warmuth, *Angew. Chem.* **2003**, *115*, 3147 – 3150; *Angew. Chem. Int. Ed.* **2003**, *42*, 3039 – 3042; R. Warmuth, *Angew. Chem.* **1997**, *109*, 1406 – 1409; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1347 – 1350; R. Warmuth, M. A. Marvel, *Angew. Chem.* **2000**, *112*, 1168 – 1171; *Angew. Chem. Int. Ed.* **2000**, *39*, 1117 – 1119; R. Warmuth, M. A. Marvel, *Chem. Eur. J.* **2001**, *7*, 1209 – 1220; T. Sawada, M. Yoshizawa, S. Sato, M. Fujita, *Nature Chem.* **2009**, *1*, 53 – 56; K. Ono, M. Yoshizawa, M. Akita, T. Kato, Y. Tsunobuchi, S. Ohkoshi, M. Fujita, *J. Am. Chem. Soc.* **2009**, *131*, 2782 – 2783.
[93] S. K. Körner, F. C. Tucci, D. M. Rudkevich, T. Heinz, J. Rebek, Jr., *Chem. Eur. J.* **2000**, *6*, 187 – 195; K. Kumazawa, K. Biradha, T. Kusukawa, M. Kawano, T. Okano, M. Fujita, *Angew. Chem.* **2003**, *115*, 4039 – 4043; *Angew. Chem. Int. Ed.* **2003**, *42*, 3909 – 3913; T. Kusukawa, M. Fujita, *J. Am. Chem. Soc.* **1999**, *121*, 1397 – 1398; A. Scarso, J. Rebek, Jr., *J. Am. Chem. Soc.* **2004**, *126*, 8956 – 8960; S. Tashiro, M. Tominaga, M. Kawano, B. Therrien, T. Ozeki, M. Fujita, *J. Am. Chem. Soc.* **2005**, *127*, 4546 – 4547; S. Tashiro, M. Tominaga, Y. Yamaguchi, K. Kato, M. Fujita, *Angew. Chem.* **2006**, *118*, 247 – 250; *Angew. Chem. Int. Ed.* **2006**, *45*, 241 – 244; S. Tashiro, M. Kobayashi, M. Fujita, *J. Am. Chem. Soc.* **2006**, *128*, 9280 – 9281; L. Trembleau, J. Rebek, Jr., *Science* **2003**, *301*, 1219 – 1220; M. Yoshizawa, T. Kusukawa, M. Kawano, T. Okano, I. Tanaka, K. Kurihara, N. Niimura, M. Fujita, *J. Am. Chem. Soc.* **2005**, *127*, 2798 – 2799; B. Therrien, G. Süss-Fink, P. Govindaswamy, A. K. Renfrew, P. J. Dyson, *Angew. Chem.* **2008**, *120*, 3833 – 3836; *Angew. Chem. Int. Ed.* **2008**, *47*, 3773 – 3776.
[94] M. Ziegler, J. L. Brumaghim, K. N. Raymond, *Angew. Chem.* **2000**, *112*, 4285 – 4287; *Angew. Chem. Int. Ed.* **2000**, *39*, 4119 – 4121.
[95] V. M. Dong, D. Fiedler, B. Carl, R. G. Bergman, K. N. Raymond, *J. Am. Chem. Soc.* **2006**, *128*, 14464 – 14465.
[96] M. Yoshizawa, T. Kusukawa, S. Sakamoto, K. Yamaguchi, *J. Am. Chem. Soc.* **2001**, *123*, 10454 – 10459.
[97] M. Aoyagi, K. Biradha, M. Fujita, *J. Am. Chem. Soc.* **1999**, *121*, 7457 – 7458.
[98] D. Fiedler, R. G. Bergman, K. N. Raymond, *Angew. Chem.* **2006**, *118*, 759 – 762; *Angew. Chem. Int. Ed.* **2006**, *45*, 745 – 748.
[99] M. Kawano, Y. Kobayashi, T. Ozeki, M. Fujita, *J. Am. Chem. Soc.* **2006**, *128*, 6558 – 6559.
[100] R. Poli, *Chem. Rev.* **1996**, *96*, 2135 – 2204.
[101] E. A. Meyer, R. K. Castellano, F. Diederich, *Angew. Chem.* **2003**, *115*, 1244 – 1287; *Angew. Chem. Int. Ed.* **2003**, *42*, 1210 – 1250.
[102] W.-Y. Sun, T. Kusukawa, M. Fujita, *J. Am. Chem. Soc.* **2002**, *124*, 11570 – 11571.
[103] *Molecular Magnets: Recent Highlights* (Eds.: W. Linert, M. Verdaguer), Springer, Vienna, **2003**; *Molecular Magnetism: From Molecular Assemblies to the Devices*, *Vol. 321* (Eds.: E. Coronado, P. Dalhaès, D. Gatteschi, J. S. Miller), Kluwer, Dordrecht, **1996**; O. Kahn, *Molecular Magnetism*, Wiley-VCH, New York, **1993**.
[104] K. Nakabayashi, M. Kawano, M. Yoshizawa, S.-i. Ohkoshi, M. Fujita, *J. Am. Chem. Soc.* **2004**, *126*, 16694 – 16695.
[105] K. Nakabayashi, M. Kawano, M. Fujita, *Angew. Chem.* **2005**, *117*, 5456 – 5459; *Angew. Chem. Int. Ed.* **2005**, *44*, 5322 – 5325; K. Nakabayashi, M. Kawano, T. Kato, K. Furukawa, S.-i. Ohkoshi, T. Hozumi, M. Fujita, *Chem. Asian J.* **2007**, *2*, 164 – 170.
[106] P. Piotrowiak in *Electron Transfer in Chemistry*, *Vol. 1* (Ed.: V. Balzani), Wiley-VCH, Weinheim, **2001**, p. 3992; P. Piotrowiak, K. Deshayes, Z. S. Romanova, C. Pagba, S. Hore, G. Zordan, I. Place, A. Farrán, *Pure Appl. Chem.* **2003**, *75*, 1061 – 1068.
[107] J. Y.-C. Chen, N. Jayaraj, S. Jockusch, M. F. Ottaviani, V. Ramamurthy, N. J. Turro, *J. Am. Chem. Soc.* **2008**, *130*, 7206 – 7207.
[108] T. Yamamoto, T. Fukushima, A. Kosaka, W. Jin, Y. Yamamoto, N. Ishii, T. Aida, *Angew. Chem.* **2008**, *120*, 1696 – 1699; *Angew. Chem. Int. Ed.* **2008**, *47*, 1672 – 1675; A. P. H. J. Schenning, F. B. G. Benneker, H. P. M. Geurts, X. Y. Liu, R. J. M. Nolte, *J. Am. Chem. Soc.* **1996**, *118*, 8549 – 8552; S.-i. Kawano, S.-i. Tamaru, N. Fujita, S. Shinkai, *Chem. Eur. J.* **2004**, *10*, 343 – 351;

H. Engelkamp, S. Middelbeek, R. J. M. Nolte, *Science* **1999**, *284*, 785 – 788; R. J. Bushby, O. R. Lozman, *Curr. Opin. Colloid Interface Sci.* **2002**, *7*, 343 – 354.
[109] M. Yoshizawa, J. Nakagawa, K. Kumazawa, M. Nagao, M. Kawano, T. Ozeki, M. Fujita, *Angew. Chem.* **2005**, *117*, 1844 – 1847; *Angew. Chem. Int. Ed.* **2005**, *44*, 1810 – 1813; Y. Yamauchi, M. Yoshizawa, M. Fujita, *J. Am. Chem. Soc.* **2008**, *130*, 5832 – 5833; Y. Yamauchi, M. Yoshizawa, M. Akita, M. Fujita, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, in press.
[110] M. Yoshizawa, K. Kumazawa, M. Fujita, *J. Am. Chem. Soc.* **2005**, *127*, 13456 – 13457.
[111] L. S. Kaanumalle, C. L. D. Gibb, B. C. Gibb, V. Ramamurthy, *J. Am. Chem. Soc.* **2005**, *127*, 3674 – 3675.
[112] M. C. Böhn, *One-Dimensional Organometallic Materials*, Springer, New York, **1987**; D. Braga, L. Maini, M. Polito, L. Scaccianoce, G. Cojazzi, F. Grepioni, *Coord. Chem. Rev.* **2001**, *216–217*, 225 – 248; F. A. Cotton, R. A. Walton, *Multiple Bonds Between Metal Atoms*, 2nd ed., Clarendon Press, Oxford, **1993**; J. K. Bera, K. R. Dunbar, *Angew. Chem.* **2001**, *113*, 4585 – 4588; *Angew. Chem. Int. Ed.* **2001**, *40*, 4453 – 4457.
[113] M. Yoshizawa, K. Ono, K. Kumazawa, T. Kato, M. Fujita, *J. Am. Chem. Soc.* **2005**, *127*, 10800 – 10801.
[114] K. Ono, M. Yoshizawa, T. Kato, K. Watanabe, M. Fujita, *Angew. Chem.* **2007**, *119*, 1835 – 1838; *Angew. Chem. Int. Ed.* **2007**, *46*, 1803 – 1806; K. Ono, M. Yoshizawa, T. Kato, M. Fujita, *Chem. Commun.* **2008**, 2328 – 2330.
[115] E. P. Kyba, R. C. Helgeson, K. Madan, G. W. Gokel, T. L. Tarnowski, S. S. Moore, D. J. Cram, *J. Am. Chem. Soc.* **1977**, *99*, 2564 – 2571.

