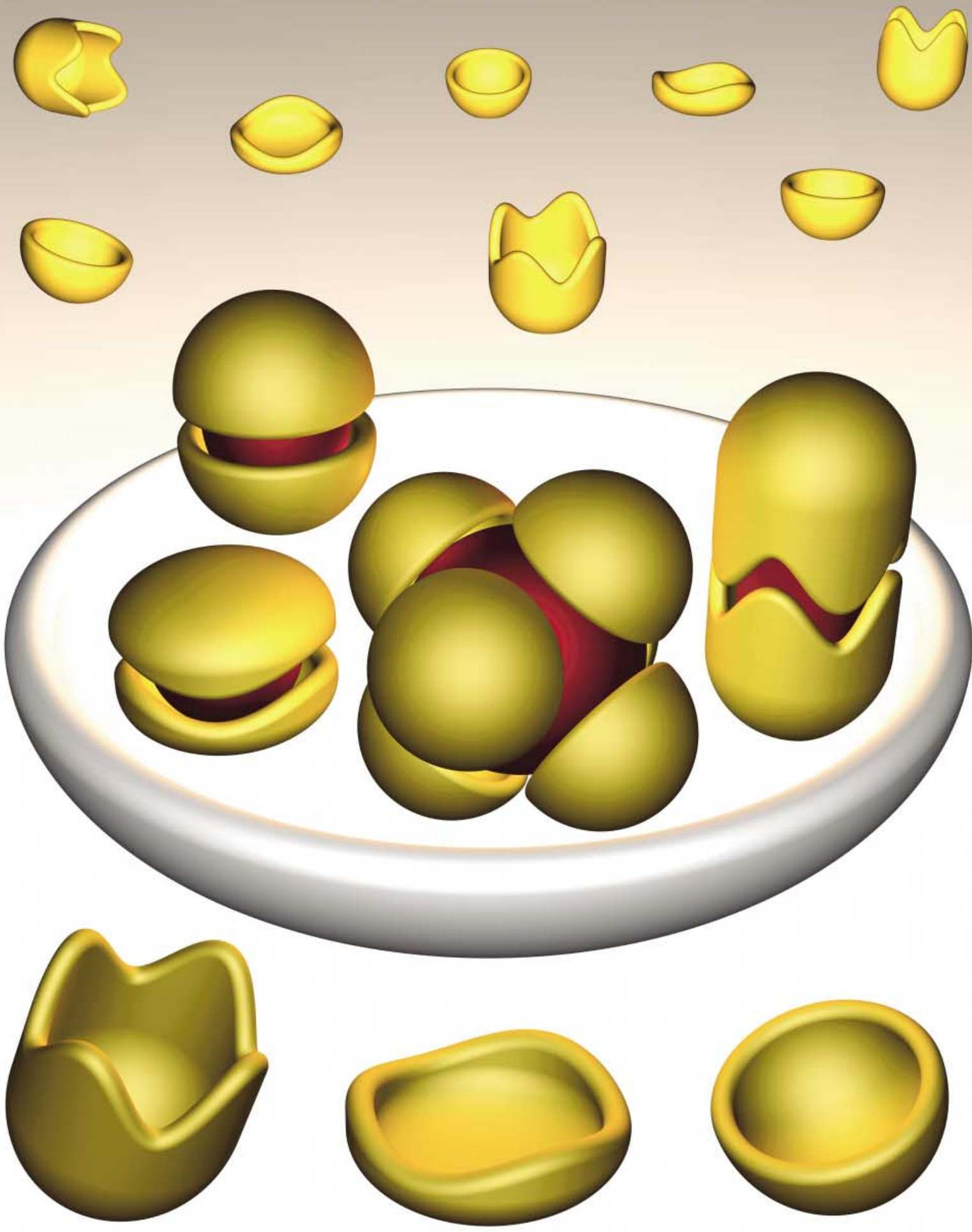

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Molecular Encapsulation

Fraser Hof, Stephen L. Craig, Colin Nuckolls, and Julius Rebek, Jr.*

Dedicated to Ivar Ugi

Louis Kahn, architect of the Salk Institute in La Jolla, said[1] "even a common, ordinary brick wants to be something more than it is." Suppose that were also true of molecules. We know that they can and do aggregate; they give complex structures, and by doing so they acquire new properties—functions that may not be apparent from a study of the individual components. This review is about molecular aggregates of a certain sort, namely, those that assemble and more or less completely surround other molecules. Taking part in this intimacy imparts unique properties to the participants, and new functions emerge from the aggregate as a whole. For the most part, we emphasize self-complementary structures. Their ability to assemble—an expression of the molecule's desire to be something more than it is—results from instructions engineered into the molecules during their creation.

Keywords: host–guest systems · molecular capsules · molecular recognition · self-assembly

1. Introduction

In the 1980s, most of the publications on molecular recognition dealt with the selectivity of synthetic receptors and the energetics of intermolecular forces, and were confined for the most part to bimolecular systems. Termolecular systems would show up in a desultory way, such as in models for allosteric effects,[2] but there was much less work in pursuit of, for example, binding cooperativity.[3] There were rare cases in which a third molecule would interact with a weakly held bimolecular complex, and their beauty was exhilarating—like hitting a moving target.[4]

Studies of termolecular systems spread quickly during the 1990s in the form of template effects.[5–7] Interest in molecular self-replication had been ignited by von Kiedrowski[8] using nucleic acid components and the fire leapt to modified nucleic acids[9, 10] and entirely synthetic systems.[11–14] Even peptides now fan these flames.[15, 16] Elsewhere, other bimolecular reaction templates were devised[17] and more complex systems were contrived. This is engineering (or is it art?)[18] at the molecular level.[19] It did not matter that these systems weren't particularly efficient, what mattered was that they improved the understanding of three-component systems.

Synthetic receptors became more sophisticated and concave surfaces such as clefts,[20] armatures,[21] tweezers,[22, 23] bowls,[24] and other shapes[25] emerged for the study of reversible interactions. We thought that a receptor could be created that could completely surround the target by using only the weak intermolecular forces of molecular recognition. These systems would be capsular assemblies, the reversible counterparts of the carcerands and cryptophanes—the covalently bound "molecules within molecules" crafted by Cram et al.[26] and Collet and co-workers.[27] The synthetic economy of using aggregates of self-complementary compounds[28–30][31] rather than one large molecule as a receptor proved irresistible. These structures have been termed "encapsulation complexes" and they are now tools of physical organic chemistry on the nanoscale.

At the outset, most of the assemblies—spectacular as they were in the number of components, the intricacies, and sheer molecular weight—did little more than fill space. More sophisticated properties quickly emerged, and these will be the focus of this review. The complexes are used today as probes of isolated molecules and of the intrinsic characteristics of the liquid state, and are capable of enantioselective recognition, reversible polymerization, isolation of reactive species, and promoting reactions within their interiors.

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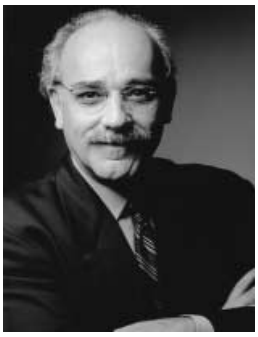
Solvent-free environments provide an undiluted, often intensified interaction between the host and guest or between multiple guests themselves. Groups of molecules residing in the channels of zeolites, the pores of polymers, active sites of enzymes, and within globular micelles or dendrimers display behavior that is amplified by their environment. Encapsulation is a means by which the environment and encounters of a *single* molecule can be rigorously controlled. What can be learned about them in their isolated states, either alone or, as we shall relate, grouped in pairs? Much effort has been expended on isolation tactics in the chemical sciences. In the solid state or glassy states, inert matrices are used at low temperatures to isolate and stabilize reactive intermediates. In the gas phase, isolation can be achieved by subjecting a molecule to such low pressure that collisions with other molecules are essentially zero.[32] In the encapsulation complexes presented in this review, molecules are isolated from solvent encounters at ambient temperatures in the liquid phase.

Other supramolecular structures are also capable of surrounding guest molecules. The differences here are those of topology and timing. Supramolecular rings, tubes, and cavitands are able to briefly bind one or more guest molecules within a restricted environment, while still allowing varying amounts of solvent access to the secluded guests. We will not dwell on these here; rather, this review focuses on hosts that self-assemble and encapsulate molecules within a closed-shell topology.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Julius Rebek, Jr. was born in Hungary in 1944 and lived in Austria from 1945–1949. He and his family then settled in the USA in Kansas. He received his undergraduate education at the University of Kansas in 1966, and obtained his Ph.D. degree from the Massachusetts Institute of Technology (1970) for studies in peptide chemistry with Professor D. S. Kemp. As an Assistant Professor at the University of California at Los Angeles (1970–1976) he developed the "three-phase test" for reactive intermediates. In 1976 he moved to the University of Pittsburgh where he rose to the rank of Professor of Chemistry and developed cleftlike structures for studies in molecular recognition. In 1989 he returned to the Massachusetts Institute of Technology, where he was the Camille Dreyfus Professor of Chemistry, and devised synthetic, self-replicating molecules. In July of 1996, he moved his research group to The Scripps Research Institute to become the Director of The Skaggs Institute for Chemical Biology, where he continues to work in molecular recognition and self-assembling systems.

Fraser Hof was born in Medicine Hat, Alberta, Canada. He obtained a B.Sc. in chemistry at the University of Alberta in 1998, and is currently pursuing a Ph.D. under the direction of Professor Julius Rebek, Jr. at the Scripps Research Institute in La Jolla, California. He has been awarded postgraduate fellowships by the Natural Sciences and Engineering Research Council of Canada and the Skaggs Institute for Chemical Biology. His research focuses on the rational design of novel emergent properties through supramolecular chemistry.

Stephen Craig received his undergraduate degree in chemistry at Duke University, Durham (1991) and obtained an M.Phil. degree from Cambridge (1992) and a Ph.D. from Stanford University (1997). After two years as a Research Chemist in DuPont Central Research, he went to Scripps Research Institute in 1999 where he was an NIH postdoctoral fellow in the lab of Professor Julius Rebek. He joined the Duke chemistry department in 2000 as an Assistant Professor, where his research interests center around the physical organic chemistry of materials.

Colin Nuckolls joined the faculty of Columbia University as an Assistant Professor of organic chemistry in July 2000. His group is studying the properties of materials that form through self-assembly. Previously, he was a National Institutes of Health post-doctoral fellow in the laboratory of Professor Julius Rebek, Jr. at the Scripps Research Institute. His undergraduate degree was awarded from The University of Texas, Austin where he worked with Professor Marye Anne Fox. He obtained his doctoral degree from Columbia University where he studied under the tutelage of Professor Thomas Katz.

Molecules that form supramolecular capsules are defined by two fundamental emergent properties: self-assembly and the encapsulation of guest molecules. Self-assembly is based on capsule components bearing complementary functional groups capable of reversible, noncovalent interactions. The noncovalent forces that are useful in constructing capsules are primarily hydrogen bonds and metal–ligand interactions. Both enjoy facile reversibility and reliable directionality, but hydrogen bonds offer greater plasticity and faster equilibration, while metal–ligand bonds typically offer greater strength and more rigidity. High-symmetry designs are used to multiply these individually weak and reversible interactions into coherent structures with lifetimes that range from microseconds to hours. The subsequent encapsulation of guest molecules is dependent on the complementarity of the guest's size, shape, and chemical surface with the cavity of the host. The filling of space within the host is of utmost importance: nature abhors a vacuum, and this would seemingly include even those vacuums that measure only 10^{-25} liters![33]

Although these capsules are constructed with the express purpose of isolating guest molecules from the bulk solvent, the role of solvent in the formation of the capsules cannot be ignored. The medium must not disrupt the interactions that hold the components of the capsule together. Capsules constructed through metal–ligand interactions are typically disrupted by strongly ligating solvents, while they may remain stable in water. In contrast, solvent competition for hydrogen bonds prevents capsules constructed using these forces from being stable in aqueous media. The space-filling properties of the solvent must also be considered when dealing with encapsulation complexes. While the encapsulation of the solvent itself is sometimes desirable, the use of a large solvent that is physically excluded from the cavity can be an important tactic when encapsulating other guest molecules.[34]

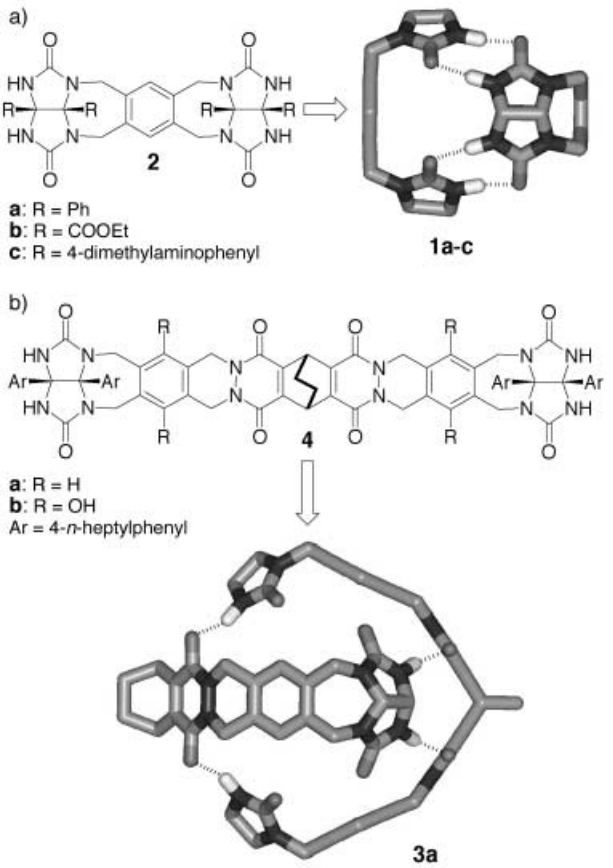

Figure 1. Self-assembling glycoluril-based dimeric capsules: a) the "tennis ball" and b) the "softball". As in most hydrogen-bonded capsules, curved monomers and self-complementary hydrogen-bonding seams are necessary components of the capsule geometry. (Some substituents and hydrogen atoms have been omitted for clarity.)

2. Structural Motifs for Encapsulation

2.1. Glycoluril-Derived Hydrogen-Bonded Capsules

Glycoluril has been used to spectacular effect in the construction of supramolecular systems.[35] A more detailed discussion of the guest-binding properties of self-assembling glycoluril-based capsules than that which follows can be found in a recent review.[36]

Reversibly formed molecular capsules began with the "tennis ball", **1** (Figure 1a). The monomer (**2**) consists of two glycoluril subunits appended to a central aromatic skeleton; the glycoluril units provide curvature and a self-complementary hydrogen-bonding motif. The tennis ball is held together by eight hydrogen bonds, and as a host structure has a tiny cavity capable of housing guests with a volume of about 50 Å^3. Accordingly, the tennis ball includes methane, ethane, ethylene, and the noble gases, while larger guests such as propane, allene, and isobutylene are excluded.[37, 38] Variation in the spacer leads to smaller[39] and larger capsules ("softballs", **3**, Figure 1b).[40–42] The same general symmetry remains, but apart from binding larger guests, the "softballs" (their internal volumes lie between 240 and 320 Å^3) are also capable of simultaneously binding *two* copies of moderately sized guests such as benzene.[41] Glycolurils were also appended to spacers of threefold symmetry to form small, rigid (**6**, Figure 2a)[43] and large, flexible capsules(**8a** and **b**, Figure 2b).[44]

Cyclic sulfamides share the self-complementary hydrogen-bonding patterns of glycolurils. However, given the opportunity, sulfonamides and glycolurils prefer heteromeric hydrogen bonds. That is, they attract each other rather than themselves. A monomer such as **9** that contains both functional groups is programmed for self-assembly: if the groups appear at the ends of a suitably curved structure, assembly proceeds in a head-to-tail manner, with the best hydrogen donors and acceptors in contact.[45] The result is a capsule (**10**) made up of four subunits surrounding a cavity with a volume of about 160 Å^3 (Figure 3a).[46] The entropic penalty of bringing together four monomers and one guest in a single, discrete complex is forfeited by the enthalpic gains provided by the formation of 16 hydrogen bonds and whatever host–guest interactions are on offer. As with the dimers, the tetrameric capsules bind molecules on the basis of size, shape, and chemical functionality. The larger monomer **11** assembles into the tetrameric capsule **12** (Figure 3b) that encapsulates

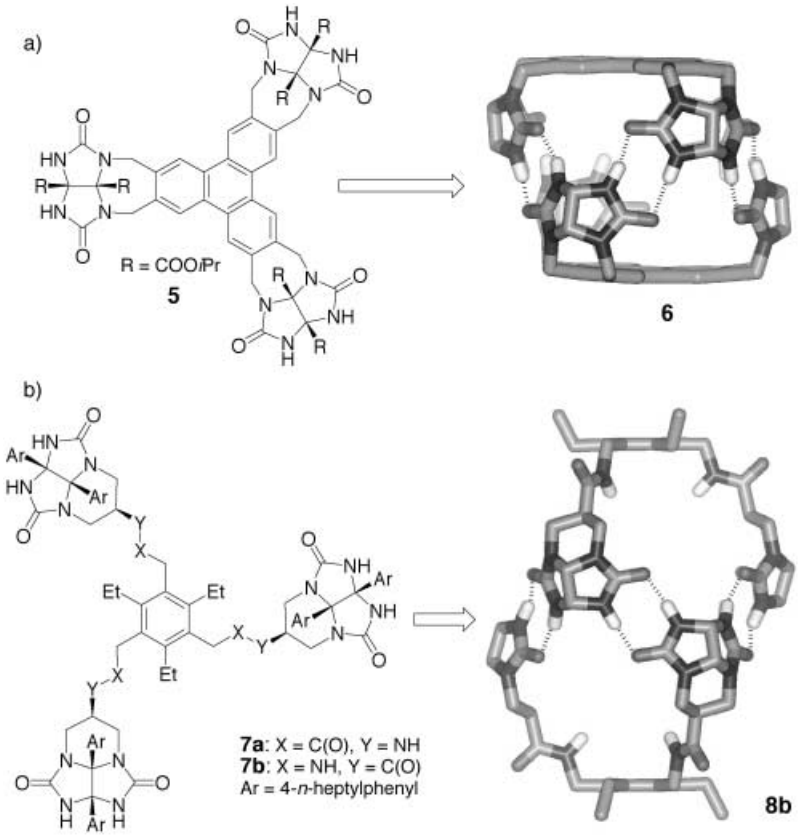

Figure 2. C_3-symmetric self-assembling glycoluril-based dimers: a) the "jelly donut" describes a flattened cavity. b) Capsule **8b** contains holes through which small guests may pass freely. (For clarity here and in the following Figures, only hydrogen bonds in the foreground are depicted and some substituents and hydrogen atoms have been omitted.)

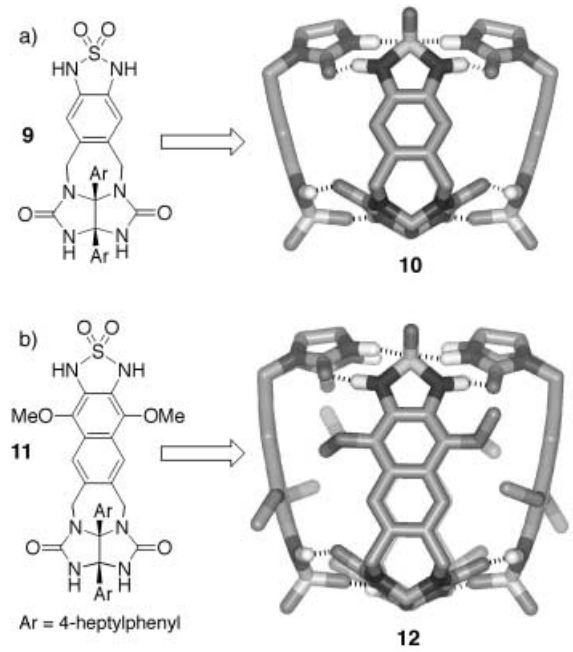

Figure 3. Self-assembling tetrameric capsules. Two seams, each comprised of eight hydrogen bonds, stitch together a total of four identical monomers in a head-to-tail manner.

guests as large as the natural product longifolene within its expanded cavity (about 270 Å^3).[47]

2.2. Cyclophane-Based Hydrogen-Bonded Supramolecular Capsules

Calix[4]arene and resorcin[4]arene are much admired, even standard subunits of self-assembled capsules. Both molecules exhibit variable conformations that can, through appropriate derivatization, be fixed into a single bowl-shaped conformation. The concave face of a bowl represents one half of a closed-shell topology, and a variety of functional groups mediate the corresponding dimerization. We refer the reader to a recent review[48] for a more detailed discussion of calixarenes than that which follows.

Secondary ureas were installed on the upper, wider rim of a calix[4]arene. In the presence of an appropriate guest molecule the ureas from two such calixarene monomers interdigitate and organize a directional seam of 16 hydrogen bonds around the equator of a dimeric capsule (**14**, Figure 4).[49] A variety of aromatic, aliphatic, and cationic guests are held within the twisted, bipyramidal cavity of approximately 180 Å^3. The distal urea nitrogen atoms can be easily adorned with a variety of functional groups that alter the self-organizing behavior of the calix[4]arene monomer.[50, 51] This modularity programs heterodimeric assemblies (**13a**,**b**),[52] kinetic stability (**13c**,**d**),[53] and chirality (**13e**)[54, 55] into the monomers. Larger calix[6]arene capsules have also recently been reported.[56]

The bowl shape of calixarenes and resorcinarenes led to other versions, inspired by the report by MacGillivray and Atwood of a spectacular hexameric capsule in the solid state.[57] The structure shows a chiral arrangement of six resorcinarene subunits (**15a**) enclosing an

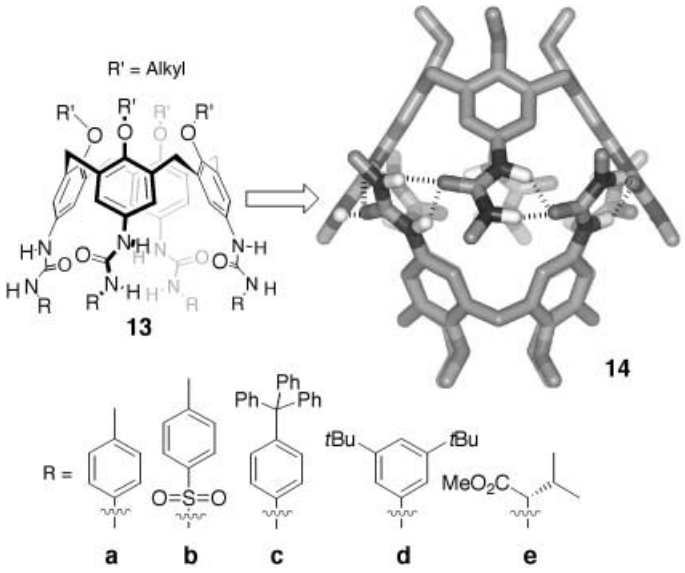

Figure 4. Self-assembling calix[4]arene tetraureas. The formation of homodimers (for example, **13a**·**13a** = **14a**) and heterodimers (for example, **13a**·**13b**) is determined by the identity of the urea substituents on the basis of electronic or steric properties.

enormous cavity of about 1375 Å^3 (Figure 5). The hexameric capsule **16a** features a total of 60 hydrogen bonds, in which 8 ordered water molecules are recruited to integrate the architecture. A similar water-bridged spherical structure was indicated by the ^{1}H NMR spectrum of **15b** in benzene, but no evidence of specific guest encapsulation by the cubic hexamer **16b** was reported. A hydroxy derivative, also a hexameric assembly in the solid state, also did not give any clues as to what was trapped inside.[58]

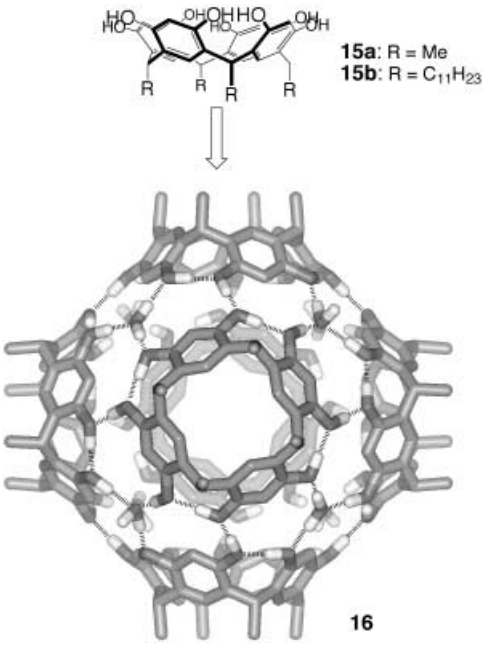

Figure 5. Hexameric structure observed in the solid state for methyl-substituted resorcin[4]arene **15a**. Eight water molecules are included in the hydrogen-bonding seam. Soluble monomer **15b** also forms this structure in solution in the presence of appropriate guests.

We revisited the solution characteristics of the resorcinarene monomer **15b** (Figure 5) more than a decade after Aoyama et al. had described the formation of 1:1 complexes of **15b** with dicarboxylic acids in $CDCl_3$ solution and subsequently with ribose, terpenes, and even steroids.[59] We found kinetically stable complexes of **15b** formed in wet $CDCl_3$ when suitable guests were available.[60] Guests such as large tetraalkylammonium and tetraalkylphosphonium salts reveal complexes with a host:guest ratio of 6:1. The dependence on the guest size correlates nicely with the expected cubic hexameric structure observed by MacGillivray and Atwood in the solid state. Additional evidence suggests that the charged guests are encapsulated as ion pairs. When tetrabutylammonium bromide acts as the guest, enough space remains to concomitantly encapsulate a secondary neutral guest such as 4-phenyltoluene, thus three different species occupy the cavity. In the solid state, water-bridged dimeric capsules of **15** with small alkyl ammonium guests were characterized by Murayama and Aoki[61] as well as Rissanen and co-workers.[62, 63]

Following the synthetic and structural work of Cram et al.[26] and Dalcanale and co-workers,[64, 65] we devised and synthesized **17**, in which a vase-shaped cavitand structure presents four imide functions around its rim (Figure 6). The molecule dimerizes through bifurcated hydrogen bonds to form a capsule (**18**) about the size of a can of tennis balls (the molecular sort, see Figure 1a).[66] The nonspherical shape of the cavity accommodates elongated guests and also promotes

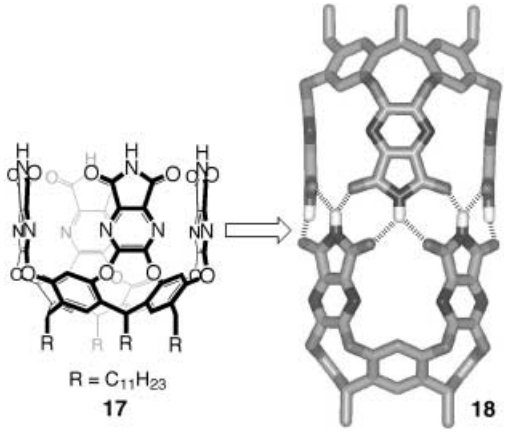

Figure 6. Self-assembly of an imide-substituted cavitand into a dimeric capsule capable of binding elongated guests.

the pairwise selection of two simple aromatic compounds in an edge-to-edge manner. The selection depends strongly on the shape and size of each guest. Two molecules of benzene or two molecules of toluene are encapsulated simultaneously, while two molecules of *p*-xylene are not. In the presence of benzene, toluene, and *p*-xylene the capsule shows a strong (about 20:1) bias for the simultaneous binding of a benzene:*p*-xylene guest pair over the constitutionally isomeric toluene:toluene pair. Although the origin of this preference is not known, it demonstrates the stunning selectivity of molecular capsules.

Other resorcinarene platforms have also been developed. Chapman and Sherman explored the use of ionic hydrogen bonds in the generation of self-assembled capsules using a partially deprotonated hydroxy-substituted resorcinarene (**19**, Figure 7a).[67] Kobayashi et al. have constructed a similar methylene-bridged resorcinarene scaffold functionalized with four carboxylic acids (Figure 7b).[68] Here, 2-aminopyrimidine is used as a wedge-shaped hydrogen-bonding bridge that forms two hydrogen bonds with each of two carboxylic acids on neighboring molecules (**20**). Resorcinarene **21**, which employs hydroxy and ester functional groups as hydrogen-bonding donors and acceptors, respectively, allows the assembly of supramolecular capsule **22** (Figure 7c).[69] Flexible electron-rich walls are able to collapse and form good contacts with a π-acceptor guest, which results in a dimeric capsule that binds a tropylium cation within its cavity. The glycoluril module[44] and resorcinarene module have been hybridized in the supramolecular capsule **24** (Figure 8).[70] The large interior volume (about 950 Å^3) allows for the "host within a host" supramolecular encapsulation of ionic cryptate complexes, an arrangement analogous to Russian matryoshka dolls.

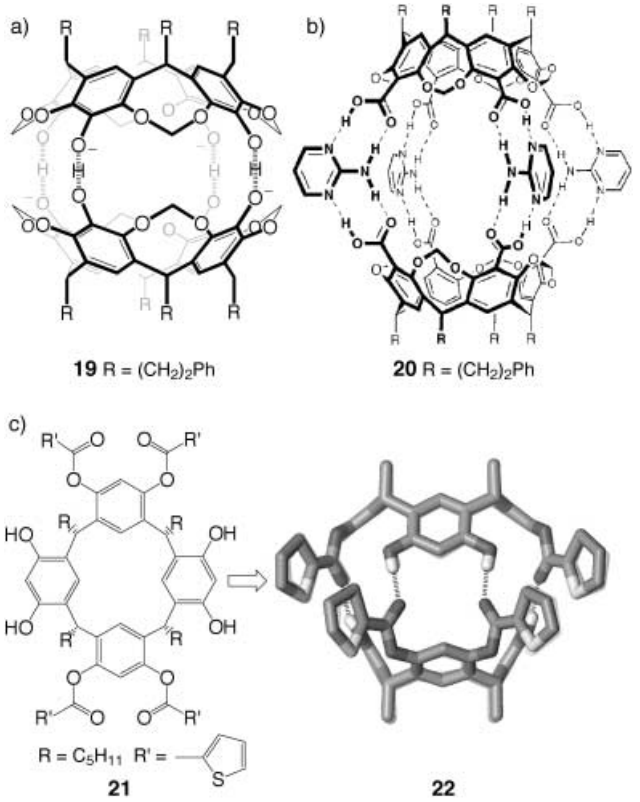

Figure 7. Dimeric molecular capsules based on resorcin[4]arene building blocks: a) a dimeric capsule stitched together by charged hydrogen bonds, b) a capsule utilizing 2-aminopyridine as a hydrogen-bonding wedge (reprinted with permission from ref. [69]), c) the flexible walls of this resorcinarene collapse to give π contacts with encapsulated guest.

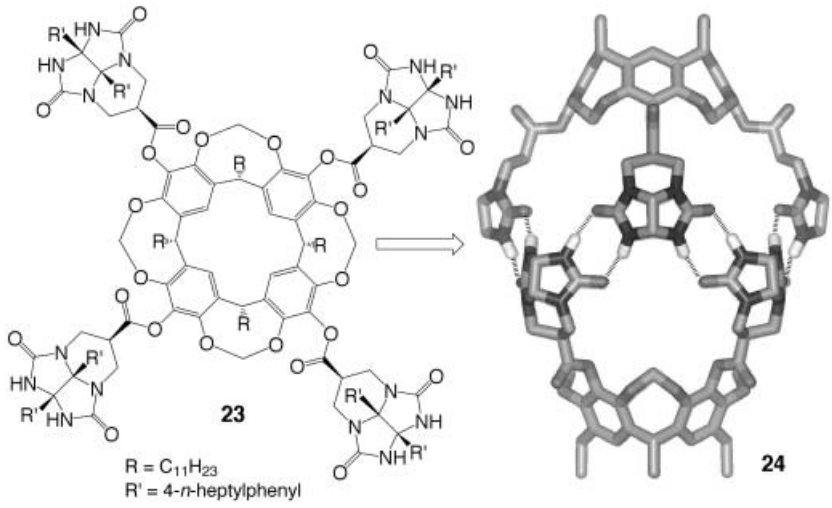

Figure 8. Self-assembly of a resorcin[4]arene – glycoluril hybrid capable of encapsulating ion – cryptate complexes.

2.3. Cyclophane-Derived Metal – Ligand-Based Supramolecular Capsules

Hydrogen bonds do not have exclusive rights to the assembly of supramolecular capsules, and molecular housings built by using metal – ligand interactions have their own architectural style.[71] Whereas the rectilinear arrangement of ideal hydrogen bonds requires molecules with curvature elsewhere, in the metal – ligand assemblies metal hinges can be installed in the corners while the walls are constructed from flat ligand panels. Dalcanale and co-workers have created a variety of bridged resorcinarenes functionalized with four nitrile groups for the purposes of metal – ligand-directed self-assembly.[72–74] Square-planar palladium or platinum complexes having two labile ligands in adjacent positions can act as coordinating corner units for the self-assembly of such nitrogenous ligands. The resulting metal – ligand interactions (and the assemblies that they generate) are reversible and robust in a variety of solvents. The combination of a C_{4v}-symmetric resorcinarene – nitrile ligand and a right-angle metal subunit in a 1:2 ratio leads to the formation of a self-assembled supramolecular cage complex **25** (Figure 9a). The complex bears a total +8 charge, and the cavity is found to encapsulate one of the eight counterions. The assembled structure is stable in water, but is subject to decomposition by competing ligands such as triethylamine or acetate.

Shinkai and co-workers have demonstrated that the substitution of pyridines into calix[4]arenes also results in the self-assembly of supramolecular capsules. A rigidified calixarene monomer displaying four pyridine ligands undergoes metal-directed self-assembly to produce capsule **26** (Figure 9b) in a manner analogous to that of **25**.[75] The bridging glycol substituents at the lower rim stabilize the C_{4v}-symmetric cone conformation necessary for assembly. Modification of a homooxacalix[3]arene derivative to include 4-pyridyl groups gives a species that undergoes metal-directed self-assembly to form a supramolecular capsule (Figure 9c).[76] This assembly (**27**) even encapsulates [60]fullerene ($K_a = 54\,M^{-1}$).

The list of metal ions useful for directing encapsulation continues to grow. Harrison and co-workers introduced tridentate chelating ligands as structural elements. A resorcinarene functionalized with four iminodiacetate groups (**28**) shows an affinity for binding Co^{II}, Cu^{II}, and Fe^{II} salts. The result is the complexation of each metal in a chelated pseudo-octahedral environment and the generation of supramolecular capsules **29** (Figure 10).[77–80] They are stable in water and encapsulate a wide variety of organic compounds, such as cyclic and acyclic aliphatic alcohols, ethers, ketones, esters, and halides, within a cavity of approximately 215 $Å^3$. Compounds held in close contact with the metals that line the cavity experience enormous paramagnetic shifts. Guests encapsulated within the Co^{II} complex show upfield chemical shifts of 18 to 40 ppm upon complexation.[80]

The water-soluble *p*-sulfonatocalix[4]arene **30** is even more impressive in its response to small ligands and metals. It is coaxed to assemble by the presence of 1 equivalent of pyridine *N*-oxide and 0.5 equivalents of $La(NO_3)_3$.[81] The resulting spherical cluster (**31**, Figure 11) has a delicate balance of hydrogen bonds, van der Waals forces, metal – ligand interactions, and electrostatic contacts that work in

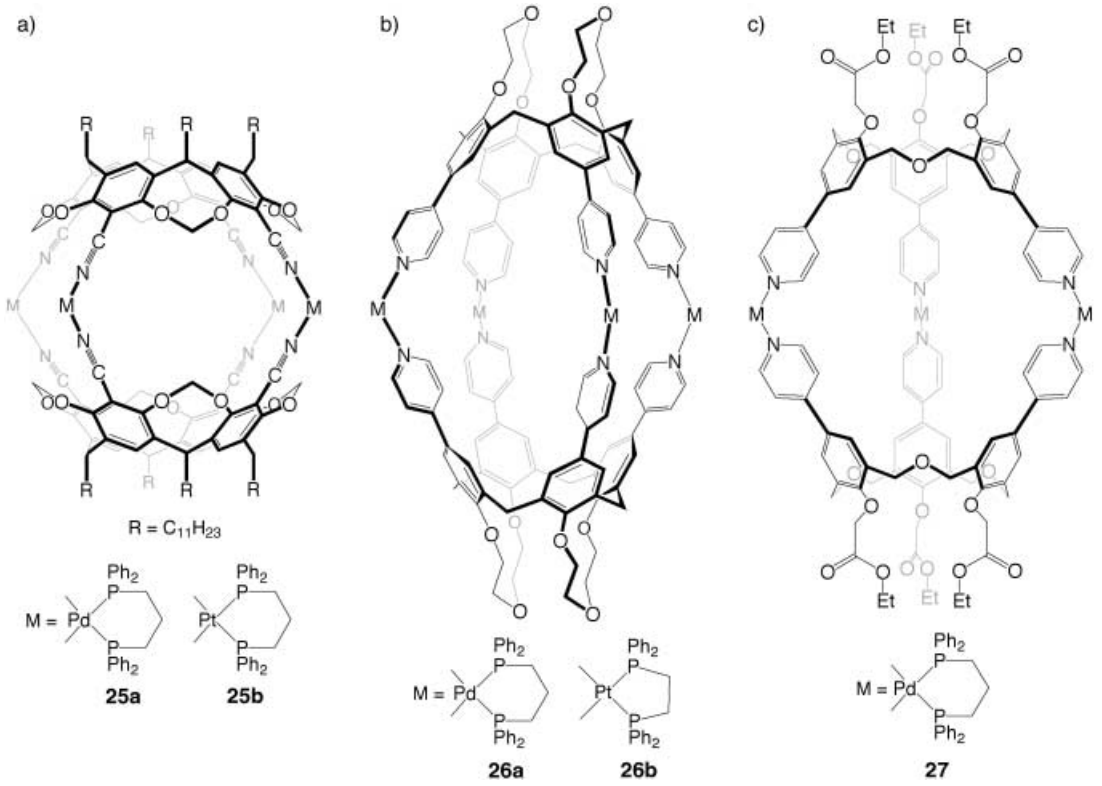

Figure 9. Metal-mediated dimerization of cyclophane-based ligands to form supramolecular capsules.

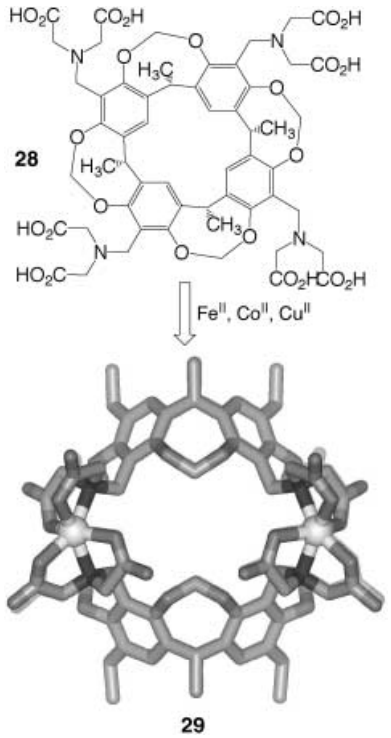

Figure 10. Dimerization of a cyclophane bearing four tridentate ligands mediated by four metal ions in pseudo-octahedral environments.

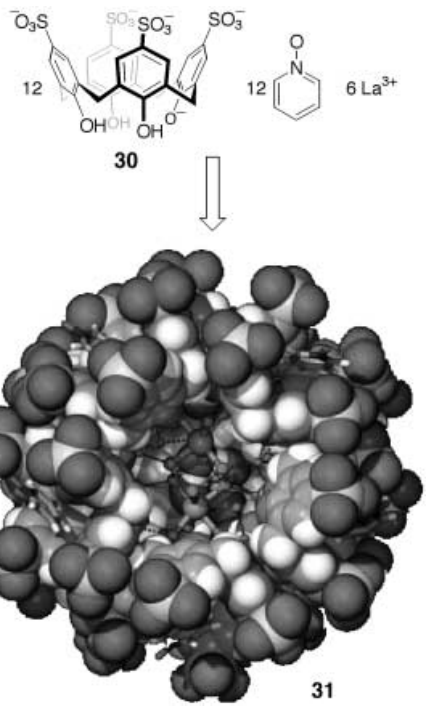

Figure 11. Colossal supramolecular capsule arising from self-assembly of 12 calix[4]arene subunits, 12 copies of pyridine *N*-oxide, and 6 La^{3+} ions. One calix[4]arene subunit has been omitted to allow visualization of the capsule interior, which is occupied by 2 Na^{+} ions and 30 ordered water molecules. (Reprinted with permission from ref. [81].)

concert to create an ordered supramolecular capsule. X-ray crystallographic analysis shows: 1) 12 calixarene units functioning as pyramidal wedges, 2) a pyridine *N*-oxide molecule filling the cavity of each calixarene, and 3) the lanthanide ions acting as coordinating hinges between calixarenes of adjacent clusters. The internal cavity of this spherical assembly has a prodigious volume of about 1700 $Å^3$, and is occupied by an

ordered cluster of 2 sodium ions and 30 water molecules. On the scale of the other capsules, this resembles a soccer ball. Under a different stoichiometry, the same three subunits can also form open-ended helical tubes in the solid state.[81]

2.4. Complexes Based on Tris(pyridine) and Tris(pyrimidine) Ligands

In a dramatic departure from cyclophane-based capsules, Fujita et al. have used simple triangular heterocyclic ligands (Figure 12) in combination with *cis*-enforced square-planar Pd and Pt complexes for the construction of highly symmetric supramolecular capsules.[82] The positively charged metal centers impart water solubility on the complexes, and their relatively hydrophobic cavities bind a variety of organic guest molecules. A brief overview of the striking structures born of this motif is now given. For a more detailed discussion we refer the reader to a recent review.[82]

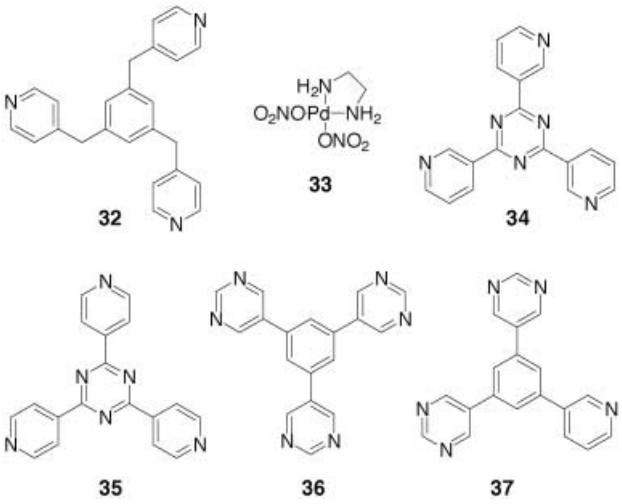

Figure 12. Triangular pyridine/pyrimidine ligands for the construction of supramolecular capsules, and the palladium subunit (**33**) commonly used to stitch them together.

The simplest of these systems is created when a tris(pyridylmethyl) ligand (**32**) is combined with Pd-based corner unit **33** in the presence of a suitable organic guest.[83] Two ligands of **32** bind a total of three metal centers (Figure 13a) to produce a C_{3v}-symmetric supramolecular capsule (**38**). The palladium–pyridine bonds are stable in protic solvents and the high overall charge (+6) of the complex imparts water solubility. The hydrophobic interior of the capsule is aptly filled by organic anions such as adamantanecarboxylate. The subunits aggregate into an uncharacterized oligomeric state in the absence of a suitable guest.

Analogous rigid planar threefold-symmetric ligands form higher order geometric structures. Ligand **35**, with three 4-pyridyl subunits around a central triazine core, forms supramolecular capsule **41** in the presence of a *cis*-protected square-planar Pd or Pt subunit (Figure 14a).[84] The metal atoms reside at each corner of an octahedron with the longest metal–metal separation being 1.9 nm and the volume en-

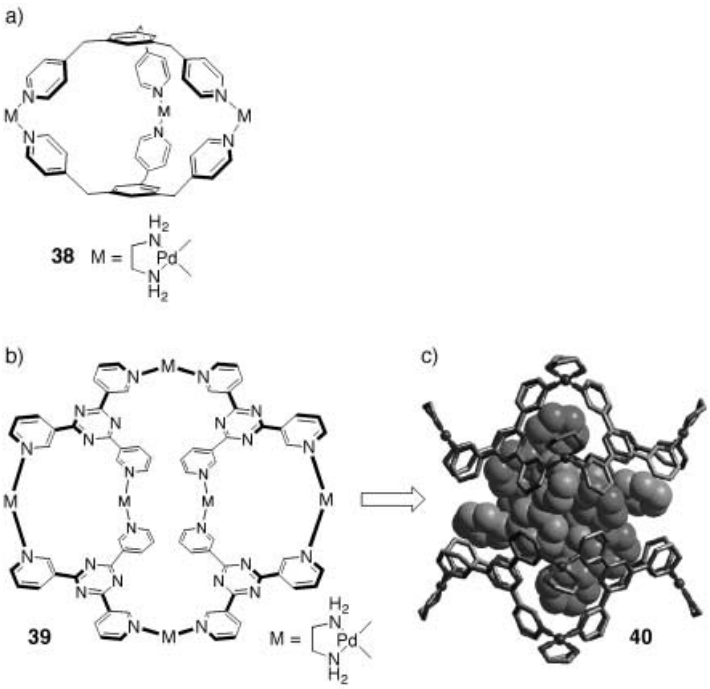

Figure 13. a) A supramolecular capsule built from two flexible ligands and three metal subunits. b, c) Self-assembly of a C_3-symmetric ligand into a bowl-shaped structure which undergoes a hydrophobic dimerization. Four copies of *m*-terphenyl are encapsulated (shown as CPK models). (Reprinted with permission from ref. [89].)

closed by the capsule about 500 Å^3. The platinum-based capsule **41c** is remarkably stable[85] and encapsulates several guests the size of adamantane.[86] The encapsulation of four copies of each guest takes place in a cooperative manner that is independent of the nature of the guest. In contrast, tris(pyrimidine) ligand **36** forms a hexahedral supramolecular capsule when combined with a small excess of Pd^{II} complex **33** (Figure 12).[87] The self-assembly of this hexahedral structure entails recognition and binding among a total of 6 triangular ligands and 18 metal ions. Unlike the previous structure (**41**) in which planar ligands filled alternating faces of a polygon, each face of the hexahedral capsule **42** is completely enclosed by the planar threefold-symmetric ligands (Figure 14b). The volume of the cavity enclosed by this capsule is considerable (about 900 Å^3), but only water or small gas molecules may pass through the meager pores (2×2 Å) in the structure. Ligand **37**, a variant of **36**, also gives rise to a capsule with hexahedral geometry analogous to that of **42** (Figures 12 and 14), but with some vacant metal binding sites that result in formation of hydrophobic clefts.[88] These apertures allow for the encapsulation of small molecules such as CBr_4, a behavior that is not displayed by the parent capsule.

The 3-pyridyl-substituted ligand **34** is unable to form a closed-shell topology with organometallic corner subunits. Instead, four copies of ligand **34** and six copies of Pd-subunit **33** self-assemble into an open bowl-shaped structure **39** (Figure 13b).[89] These hemispherical superstructures assemble in water into discrete dimeric supramolecular capsules (**40**) in the presence of large aromatic guests (Figure 13c). X-ray crystallographic studies reveal that four copies of *m*-terphenyl or six copies of *cis*-stilbene form compact hydro-

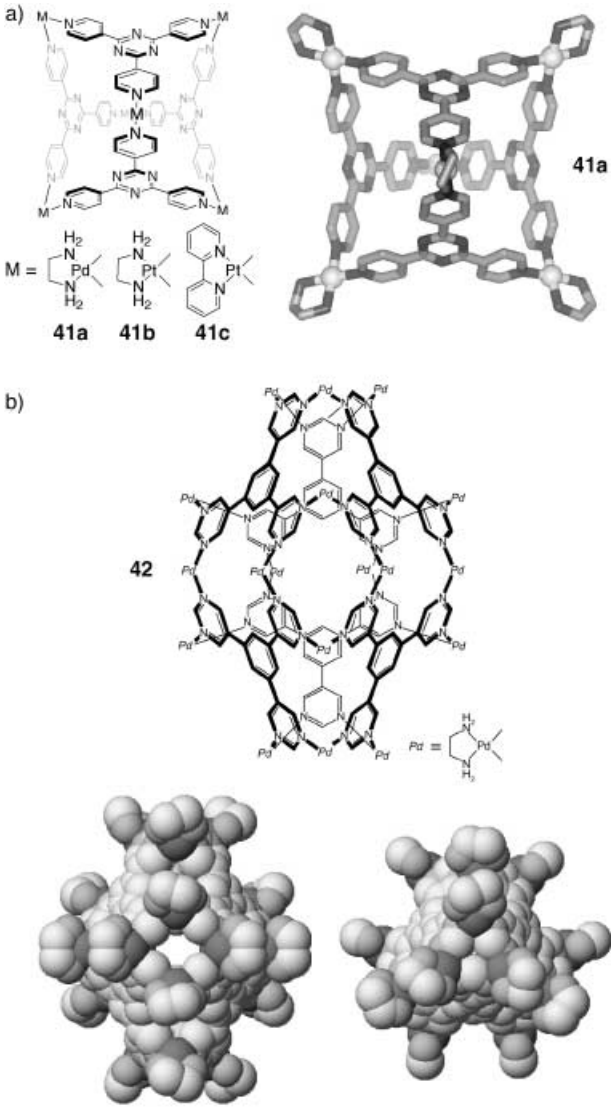

Figure 14. a) A supramolecular capsule constructed from 4 triangular ligands and 6 metal units. The metal atoms define the corners of an octahedron and the ligands occupy alternating faces. b) A hexahedral supramolecular capsule composed of 18 metal ions and 6 triangular ligands. (Reprinted with permission from ref. [87].)

phobic clusters that are encapsulated by the discrete dimeric superstructure. Only dispersive forces and the hydrophobic effect act to hold the capsule together—there is no direct metal–ligand bonding between the supramolecular bowls that comprise the capsule halves. In the absence of direct contacts between the molecules that make up the bowls, it is the guests—bound within both bowls—that provide the bridging interactions that drive dimerization.

The metal-induced self-assembly of non-C_3-symmetric ligand **43** (Figure 15a) is guest-dependent.[90] An open cone structure made up of four ligands and eight metals is formed in the presence of benzil. More remarkable is that the addition of CBr_4 drives the assembly of the four triangular ligands and eight metal centers into a closed-shell tetrahedral capsule **44** (Figure 15a). In this case the ligands are arranged in a head-to-tail manner, and fill each face of the tetrahedron so as to completely surround the encapsulated guest.

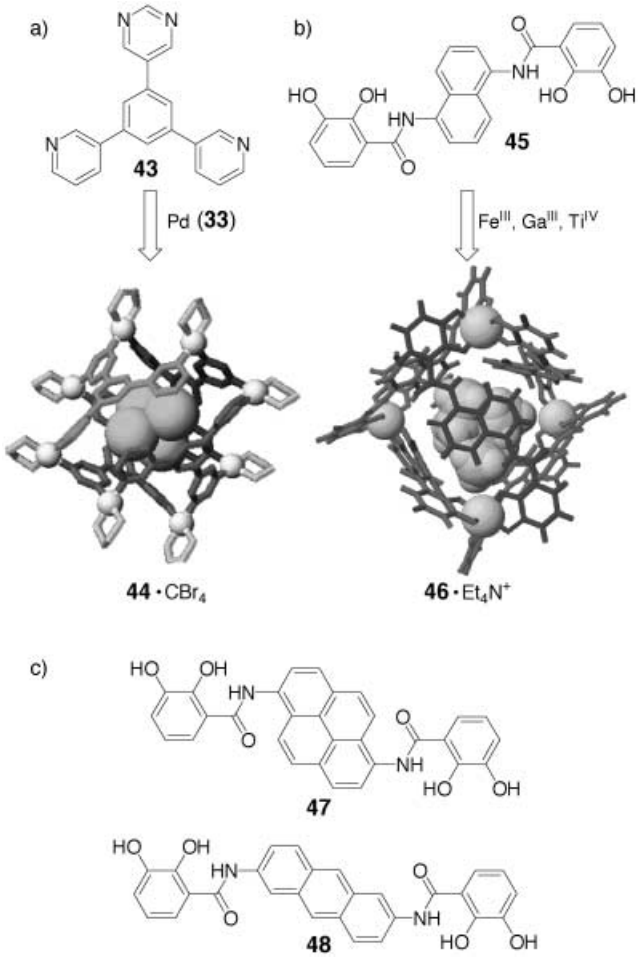

Figure 15. Self-assembly of tetrahedral supramolecular metal–ligand clusters: a) four triangular ligands **43** occupy the faces of the tetrahedron containing eight metal ions (reprinted with permission from ref. [88]), b) four metal ions define the corners of the tetrahedron and six ligands span the edges, c) two other bis(catechol) ligands that form tetrahedral capsules in a manner analogous to ligand **45**.

2.5. Tetrahedral Metal–Ligand Clusters as Supramolecular Capsules

Other motifs have been explored for the creation of tetrahedral ligand–metal clusters. Saalfrank et al. have reported a family of M_4L_6 capsules of tetrahedral symmetry,[91, 92] and have also shown one example that encapsulates its NH_4^+ counterion.[93] Other research groups have achieved similar results with different metal–ligand combinations, the encapsulated species being either a counterion or adventitious solvent molecule.[94–99]

The rich host–guest chemistry of tetrahedral metal–ligand clusters has been beautifully developed by the research group of Raymond. In their system, six bis(catechol) ligands span the edges between four metal atoms that define the corners of a tetrahedron. Most bridged bis(catechols) form M_2L_3 helicates as the thermodynamically most-favored framework, but here the structure of the spacer between the catechol ligands instructs the assembly. Bis(catechol) **45** is linked with a spacer that encourages the adoption of a rigid C_2-symmetric conformation. The beautiful self-assembly of M_4L_6 tetrahedral

clusters **46** is observed when the ligand is combined with Ti^{IV}, Ga^{III}, or Fe^{III} ions (Figure 15b).[100, 101] The capsule bears a net −8 charge, and reveals an aptitude for binding positively charged guests. The tetrahedral clusters select tetraalkylammonium guests on the basis of size, yet are also capable of adjusting their cavity volumes from about 200 to 300 Å^3 in response to guests of different sizes.[102] Like **24**, they form complexes-within-complexes through the encapsulation of small alkali ions held by crown ethers.[103] The pyrene-bridged ligand **47** (Figure 15c) self-assembles into a tetrahedron only in the presence of guests, which are bound in a manner analogous to that with **45**,[104] while the anthracene-bridged ligand **48** displays more intricate behavior.[105] In the absence of guests, the combination of **48** with appropriate Ti^{IV} or Ga^{III} subunits results in the formation of the M_2L_3 helicate as the most stable supramolecular structure. The addition of tetramethylammonium ions to the mixture, however, orchestrates a spontaneous rearrangement to the capacious M_4L_6 tetrahedral cluster. Here, the binding of a relatively small guest molecule provides the thermodynamic bias for a wholesale reorganization of six large organic ligands and four metal centers. More complex metal–ligand systems based on multiple copies of two different metals bridged by ditopic ligands have also been developed, but their guest encapsulation properties have not yet been fully explored.[106]

3. The Ins and Outs of Encapsulation Complexes

3.1. Guest Dynamics and Behavior

Encapsulation places obvious constraints on the translational motion of the guest molecule. Böhmer and co-workers provided some of the earliest understanding of dynamics within the calix[4]arene–tetraurea capsules **14** (Figure 4). The diffusion coefficients of encapsulated and free guest molecules were determined by the pulse gradient spin echo (PGSE) NMR technique.[107] The diffusion coefficients of the encapsulated guests were found to match well with those of the assembled host, while those of the free guest were much higher.

The effects of encapsulation on the guest's rotational freedom is usually apparent from the NMR spectra. Benzene tumbles rapidly and *p*-xylene slowly on the NMR timescale in the cylindrical capsule **18** (Figure 6); toluene shows a broadened signal characteristic of an intermediate tumbling rate. In the softball **3b** (Figure 1) with encapsulated [2.2]paracyclophane, ^{13}C spin-lattice relaxation studies gave evidence of correlated bulk host–guest movement. This large guest is apparently wedged into a limited space.[108]

The research group of Böhmer took advantage of hydrogen-bonded calixarene capsules (**14**) with decreased symmetry to study the rate of capsule dissociation ($0.26\ s^{-1}$) and the rate of guest exchange ($0.47\ s^{-1}$) using ^1H NMR NOESY experiments.[109, 110] The intimate relationship between the host and guest is also reflected in the determination of the geometry and dynamics of an encapsulated guest through NMR spectroscopic analysis of the host alone. The overall symmetry of the host complex is affected by the binding orientation and dynamics of the guest molecule bound within the cavity. In one elegant example by Fujita and co-workers, simple 1D NMR studies on host **41** (Figure 14) yielded detailed information on both the binding orientation and the temperature-dependent dynamics of the included guest.[111]

Effects on the guest's internal molecular dynamics are also directly measurable. The ring inversion of cyclohexane within capsule **6** (Figure 2) was studied through the use of $[D]_{11}$-cyclohexane as a guest molecule.[112] The barrier to ring inversion within the flattened cavity of **6** ($10.55\ kcal\,mol^{-1}$) is increased by $0.3\ kcal\,mol^{-1}$ relative to the value found in free solution ($10.25\ kcal\,mol^{-1}$); ground-state stabilization through CH-π interactions within the cavity is thought to be the cause for this difference. The encapsulation of $[D]_{11}$cyclohexane within a calixarene–tetraurea capsule (**14**, Figure 4) that described a roughly spherical cavity resulted in no observable change in the barrier to ring inversion. Conversely, the internal dynamics of 1,4-dioxane and 1,4-thioxane encapsulated within capsule **19** (Figure 6) are significantly restricted.[113] Despite the pseudo-spherical nature of the cavity surrounding the guests, the barrier to conformer interconversion is increased by a relatively large $1.6–1.8\ kcal\,mol^{-1}$ upon binding. In general, these experiments suggest that the internal dynamics of included guests are controlled specifically by host–guest interactions.

3.2. Control of Guest Release

For the development of encapsulation-based applications it is more urgent to control guest exchange than to understand it. The guests within most hydrogen-bonded capsules are liberated by the addition of solvents that compete effectively for hydrogen bonds. The dissociation is thermodynamically and kinetically facilitated by these competitive solvents. Capsules based on metal–ligand interactions are in general subject to decomposition (and concomitant guest release) by the addition of strong nucleophiles and/or subjection to elevated temperatures. Although these environmental changes do successfully bring about the liberation of guests, there is a need for more specific and reversible methods for the control of guest encapsulation and release.

A convenient stimulus for the reversible control of many metal–ligand based encapsulators involves changes in pH values. Harrison and co-workers have used pH changes to reversibly trigger the self-assembly of resorcinarene–iminodiacetate capsules and accompanying guest encapsulation.[77] The cobalt-based capsule **29** (Figure 10) is assembled at pH 6, but exists in a monomeric state at pH 1. The exchange between these two states is reversible. The uptake of gases in the tennis ball **2c** (Figure 1) has also been controlled by the action of acids and bases on the peripheral amino groups.[39]

Instead of altering the structural components of the capsule, guest release can be accomplished most simply by guest exchange. If the system is under thermodynamic control (as are most self-assembled capsules) then the weakly held guest is displaced by the strongly held one. One example of this type of supramolecular substitution reaction is the exchange of adamantane with paracyclophane in the softball **3b** (Fig-

ure 16).[114] At the millimolar concentrations convenient for study by NMR spectroscopy the exchange takes place with a half-life of about one hour and the process has much in common with conventional substitution reactions. At low concentrations of the incoming guest the slow step is S_N2-like, while at high concentrations of the incoming guest the slow step is S_N1-like. In both cases, complete dissociation of the capsule is not necessary, as this would rupture all 16 hydrogen bonds. Instead, a lower energy process is proposed that involves opening "flaps" on the softball's surface (Figure 16). This exposes the resident guest to the incoming "nucleophile," which is either the solvent or new guest. As a consequence the guest exchange is faster than dissociation (see Section 4.1).

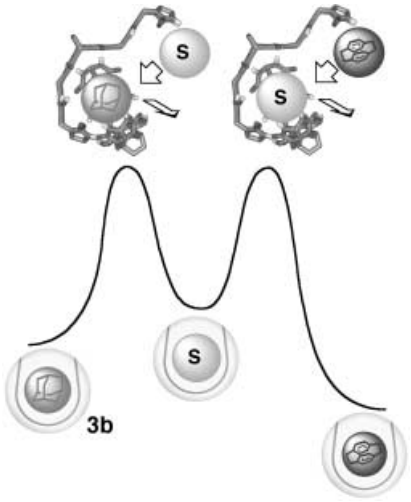

Figure 16. A two-step substitution reaction in a supramolecular capsule. The solvent-filled capsule is intermediate in the replacement of adamantane by the thermodynamically more favored [2.2]paracyclophane. Partially open capsules are proposed as transition states (S = solvent).

4. Form to Function

Supramolecular chemistry has matured to a degree that the design and synthesis of molecules that self-assemble into predictable supramolecular structures is becoming routine. Much of this research is curiosity driven, but the application of self-assembling systems to the development of functional devices should not be ignored, particularly in this, the "nano" decade. The development of functional properties from self-assembly is merely the first step towards this goal.

4.1. Chirality in Encapsulation Complexes

Chiral supramolecular complexes are always popular topics, especially when noncovalent interactions direct the assembly of achiral components into chiral superstructures. In the absence of a chiral bias the structures appear as racemates, but with chiral information present in the system, the spontaneous formation of an excess of the appropriate supramolecular structure can be the outcome.[115, 116] Several studies have taken advantage of the intimate relationship between encapsulated molecules and the supramolecular capsules that bridle them, thus granting a unique perspective on the transfer of information within complexes that is governed by noncovalent interactions. At the outset, the larger distances (compared to covalent bonds) and the flexibility of the weak, often nondirectional forces, did not guarantee success.

The tendency for calixarene–tetraurea monomer **13b** functionalized with aryl sulfonamides to exclusively (>98%) form heteromeric capsules with monomer **13a**, functionalized with a simple aryl group, has previously been discussed in Section 2.2.[52] When heteromeric dimers such as **13a**·**13b** form, the cyclic directionality of the urea hydrogen bonding seam results in the generation of racemic chiral species (Figure 17b).[54] The head-to-tail arrangement of the

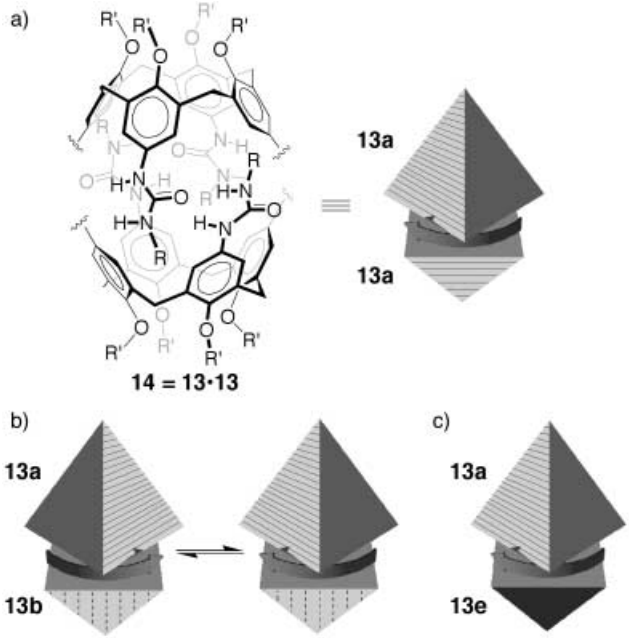

Figure 17. Chirality in calix[4]arene–tetraurea capsules: a) cyclic directionality of the urea hydrogen-bonding seam, b) capsules constructed from two different achiral components (for example, **13a**·**13b**) are formed as equilibrating cycloenantiomers, c) the presence of chiral groups on one of the two subunits can induce complete selectivity in urea directionality to produce an optically pure capsule (for example, **13a**·**13e**).

urea units at the equator can be clockwise or counterclockwise, given a reference point of the poles. Interconversion of these enantiomers occurs through the rotation of functional groups that make up the hydrogen-bonding seam, or through complete dissociation and recombination of monomers. Either mechanism would require the eventual breaking of all 16 hydrogen bonds, and as such the reversal of hydrogen-bonding directionality (and thus interconversion of enantiomers) is slow on the NMR timescale.[109] Chiral guests, however, were not capable of significant differentiation of the two resulting enantiomeric capsules **13a**·**13b**.[54]

A bias was introduced with chiral auxiliaries attached to the distal urea nitrogen atom. A screening of amino acid derivatives led to the observation that calixarenes appended in this manner with β-branched amino acids have a predi-

lection for association with calixarenes bearing aryl-substituted urea groups.[55] Mixing the valine-derived monomer **13e** and aryl monomer **13a** favors the assembly of the heterodimeric capsule **13a**·**13e** almost exclusively (>98%). This capsule is analogous to the capsule **13a**·**13b** formed from achiral components. Here, the presence of chiral groups on one subunit results in complete asymmetric induction of the capsule's cycloenantiomerism (Figure 17c). The resulting enantio- and diastereopure capsule **13a**·**13e** shows an approximately 13% excess of one diastereomeric complex for the binding of the chiral guest norcamphor from a racemic mixture. The chiral auxiliary groups are not in direct contact with the encapsulated guest molecule. Instead, their influence is transmitted to the guest through the directionality imparted to the hydrogen-bonding seam that lines the cavity.

Glycoluril-based monomers (Figure 1) have also been employed in the construction of chiral self-assembled capsules. The simple monomers (**1**, **3**) contain two mirror planes, which are both preserved in the dimeric assembled state. Analogous monomers lacking one of the two mirror elements have been synthesized.[117] These monomers are achiral, but self-assemble into dimeric supramolecular capsules that retain no mirror planes in the assembled state (Figure 18a).

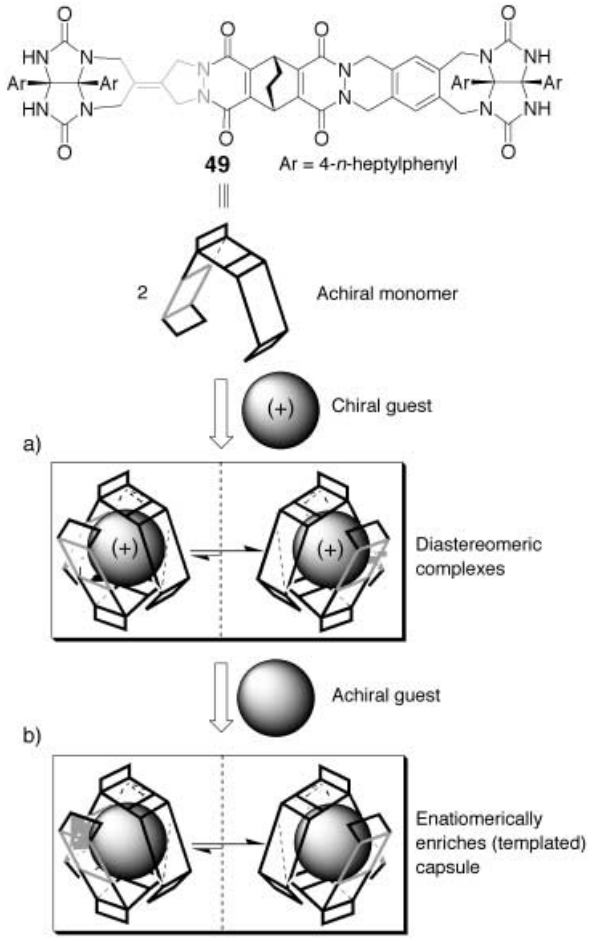

Figure 18. "Softball" monomers possessing only one mirror element spawn dimeric structures lacking any mirror symmetry: a) the host is templated with a chiral excess by the binding of a chiral guest, b) host racemization is slow following removal of the chiral guest and the enantiomeric excess of the capsule persists for several hours.

Again, the chiral capsules formed from these achiral components are formed as an equilibrating racemic mixture. The use of monomer **49**, which incorporates symmetry-breaking elements adjacent to the encapsulated guest, results in a host–guest pair capable of significant transfer of chiral information.[118, 119] The binding of an enantiomerically pure guest can bias the self-assembly process (a form of imprinting) such that one enantiomeric capsule is favored over the other by as much as a factor of four. In a reversal of the flow of chiral information, this diastereomeric host–guest complex can then be used for noncovalent chiral templating (Figure 18).[120] In this procedure, an optically pure guest is used to imprint the formation of a single chiral softball enantiomer and is then rinsed out rapidly by an excess of an achiral guest or solvent molecule. Since the exchange of guests in glycoluril-based capsules is much faster than the dissociation of the capsule, the exchange occurs without racemization of the capsule itself. The ghost of the chiral guest allows the chiral capsule to discriminate between guest enantiomers for several hours before it returns to its thermodynamically determined state.

A recent study by Shinkai and co-workers has revealed a capsule that possesses helical chirality.[121] Monomer **50** (Figure 19) undergoes metal-directed self-assembly to form a dimeric capsule analogous in structure to **27** (Figure 9). The decreased angle of the ligating atoms in **50** (120°) relative to **27** (180°) results in a *trans*-substituted metal subunit being utilized for the formation of a closed-shell dimeric assembly (**51**). The binding of alkali metal ions at the oxygen-rich lower rim of homooxocalix[3]arenes is known to affect the geometry and binding properties of the capsules constructed from such building blocks.[76] In the case of **51**, the binding of Na^+ ions

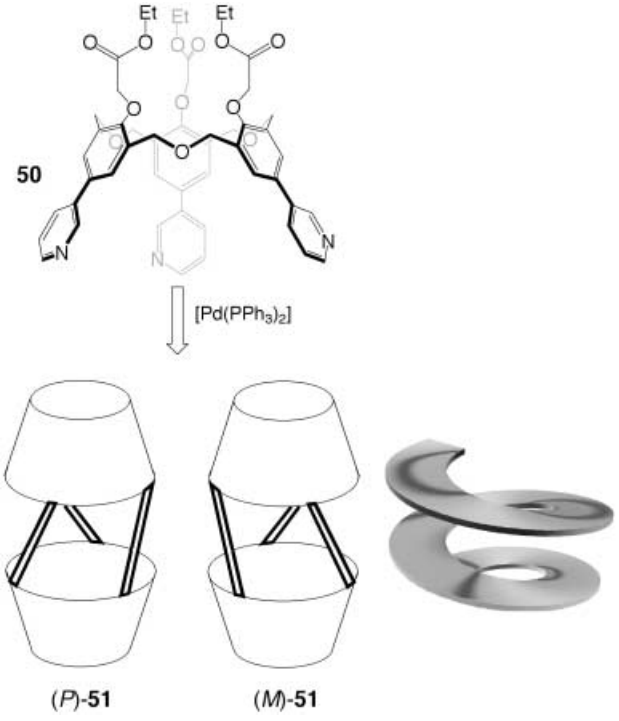

Figure 19. A homooxocalix[3]arene monomer forms helically chiral dimeric capsules in the presence of suitable metal subunits.

induces a dramatic conformational shift that yields a helical arrangement of the capsule walls down the long axis of the capsule (Figure 19). Both *M* and *P* enantiomers are formed, as revealed by experiments with chiral shift reagents. As in the softball, chiral guests are able to induce a bias (up to 55 % for the encapsulated (*S*)-2-methylbutylammonium ion) in favor of one helical enantiomer over another.

In another example, the direction of chiral information flow is reversed. Derivatization of compound **9** (Figure 3) with a single hydroxy group provides a new monomer (**52**) that is chiral and resolvable into single enantiomers (Figure 20).[122] Self-assembly occurs spontaneously in the presence of an appropriate guest, and the enantiopure capsule (**53**) exhibits enantioselective (d.e. 60%) binding of chiral guests from a racemic mixture. The interaction of a single copy of monomer **52** with a single chiral guest molecule is presumed to offer a small energetic differentiation, but significant chiral recognition emerges when multiple copies of monomer **52** form a closed chiral space.

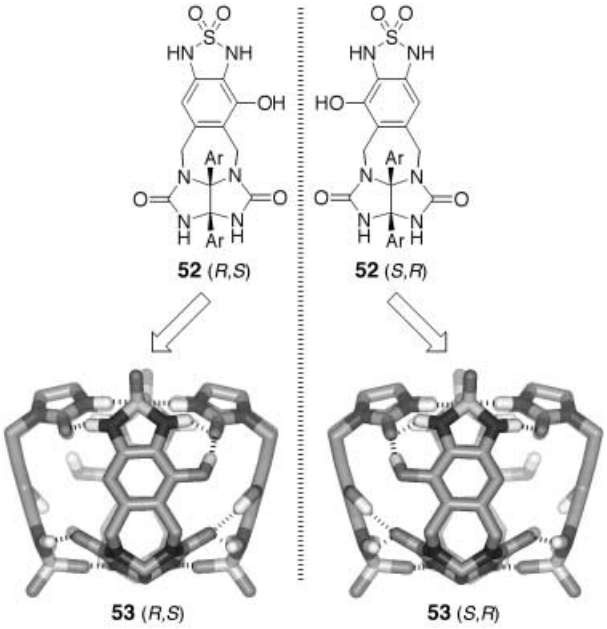

Figure 20. The self-assembly of an enantiopure monomer yields a chiral tetrameric capsule capable of discriminating between guests on the basis of chirality.

A common origin of chirality in metal-based supramolecular complexes is the Δ/Λ helical chirality associated with the octahedral arrangement of three bidentate ligands around a metal center. The tetrahedral clusters of Raymond and coworkers[101] demonstrate the spontaneous generation of supramolecular chirality within self-assembled capsules based on metal ligation. The chirality of the four metal centers present in each tetrahedral cluster is strongly coupled by the bis(catechol) ligand **45** (Figure 15); the $\Delta\Delta\Delta\Delta$ and $\Lambda\Lambda\Lambda\Lambda$ clusters are formed to the exclusion of clusters of mixed configurations. The two resulting diastereomeric complexes formed when the (−)-*N*-methylnicotinium cation is encapsulated by Ga^{III} complex **46** (Figure 21) can be easily separated.[123] Removal of the chiral guest by replacement with the

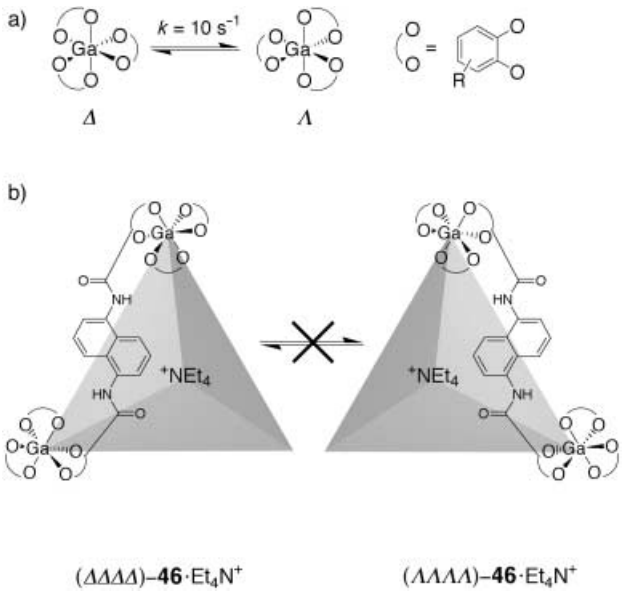

Figure 21. a) Facile racemization between the Δ and Λ configuration of chiral octahedral gallium(III) catecholates. b) An optically pure self-assembled tetrahedron containing four such metal centers in a mechanically linked framework is isolated through encapsulation of a chiral guest, and is stable to racemization even after extended heating.

achiral Et_4N^+ ion yields the enantiopure tetrahedral clusters **46** · Et_4N^+. The mechanical coupling of metal centers within the tetrahedral framework not only favors the presence of four homoconfigurational metal centers in a cluster, but also confers to each metal center a remarkable resistance to racemization. The racemization rate for isolated tris(catecholate)–Ga^{III} centers is fast ($10\ s^{-1}$) at room temperature. In contrast, an aqueous solution of ($\Delta\Delta\Delta\Delta$)-**46** · Et_4N^+ remains enantiopure after eight months at room temperature, and even extended heating does not induce racemization.

4.2. Dynamic Libraries of Molecular Receptors

Great diversity can be generated through the combination of relatively few components and a large library of multicomponent species can be developed. Lehn has pioneered the field of dynamic combinatorial chemistry, in which the composition of equilibrating libraries of molecular receptors is trained by the presence of the desired target.[124–127] Molecular capsules are suitable candidates for this treatment. As such, the selection of molecular receptors from a library under thermodynamic control has been achieved by both hydrogen-bonded and metal–ligand based supramolecular capsules.

Our efforts involved the monomer **9** that self-assembles to form hydrogen-bonded tetrameric capsule **10** (Figure 3). The variation of the substitution patterns at the central aromatic carbon atom gave a total of five complementary (and self-complementary) subunits (**9, 52, 54–56**, Figure 22). The added functionality doesn't disrupt the forces responsible for the assembly but does modify the size, shape, and chemical lining of the cavity. The five monomers represent a library of 613 possible tetrameric capsules with 70 different compositions.[128] The mixture was monitored by using electrospray

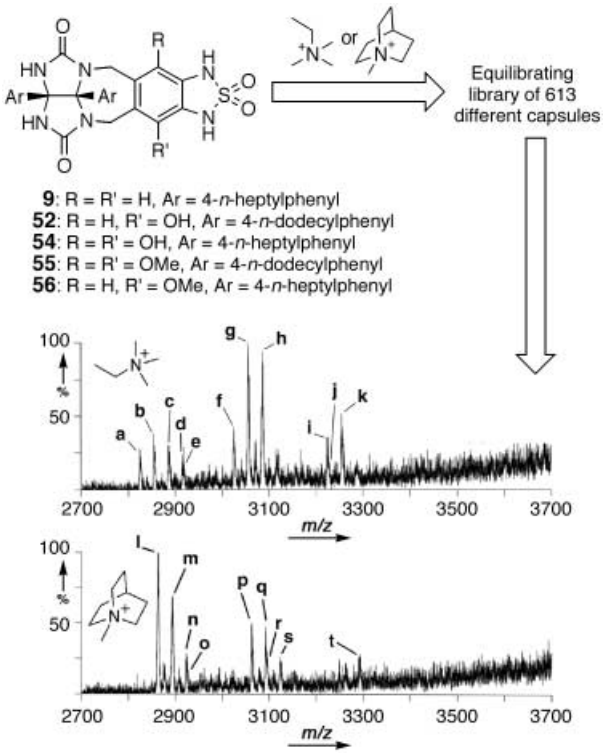

Figure 22. A dynamic library of self-assembled tetramers arises from the combination of five complementary monomers. Each letter indicates a mass spectral peak corresponding to a unique molecular host that forms in varying quantities in response to the presence of different guest molecules. The composition of the library is biased towards the hosts that interact most favorably with the added guest.

mass spectrometry, a method that has recently come of age in the characterization of supramolecular complexes.[129, 130] The distribution of tetrameric capsules was measured by taking advantage of mass-labeled monomers. The composition of the mixture depends strongly on the nature of the guest: the receptors that best fit the structure of the added guest molecule spontaneously emerge as the predominant species in solution.

In another example, a variant on the tris(pyridine) triangular ligands (Figure 12) developed by Fujita and co-workers, is the set of supramolecular capsules arising from mixing one 4-pyridyl and two 4-pyridylmethyl subunits as ligands with a single metal unit as an adhesive. The C_3 symmetry of the ligand (**57**) is broken, and metal-mediated self-assembly gives two isomeric capsules (Figure 23). The formation of the two receptors is strongly guest-dependent: one is favored by aromatic guests, while the other is favored by more spherical guests such as CBr_4.[131] The diversity of receptors present in the library was increased by the addition of another ligand, **32**. Equilibration within the resulting library of four receptors was efficiently controlled by the presence of suitable guest species (Figure 23).[132]

4.3. Capsules as Sensors

One function of supramolecular capsules is in small-molecule sensing, and we use an example of calixarenes to show how a binding event gives a detectable signal: a common transduction path is used for the detection of analytes at low concentration. Calixarene–tetraureas **58** and **59** were substituted[52] at the lower rim with fluorescent dyes (Figure 24).[133] The self-assembly and encapsulation processes of these monomers proceed in the usual manner with heteromeric capsule **60** preferred to the formation of each homodimer (as in **13a**·**13b**). The dyes were selected such that the emission spectrum of one dye (the donor, **58**) overlaps the excitation spectrum of the other (the acceptor, **59**). When the two dyes are in proximity to one another, excitation of the donor results in significant fluorescence resonance energy transfer (FRET) to the acceptor, and emission at the acceptor's emission wavelengths is observed. The result is a FRET signal that is dependent on the assembly of **58** and **59**. Nonspecific aggregation is negligible at the nanomolar concentrations of the experiment, and no FRET is observed in the absence of a suitable guest species. In the presence of a

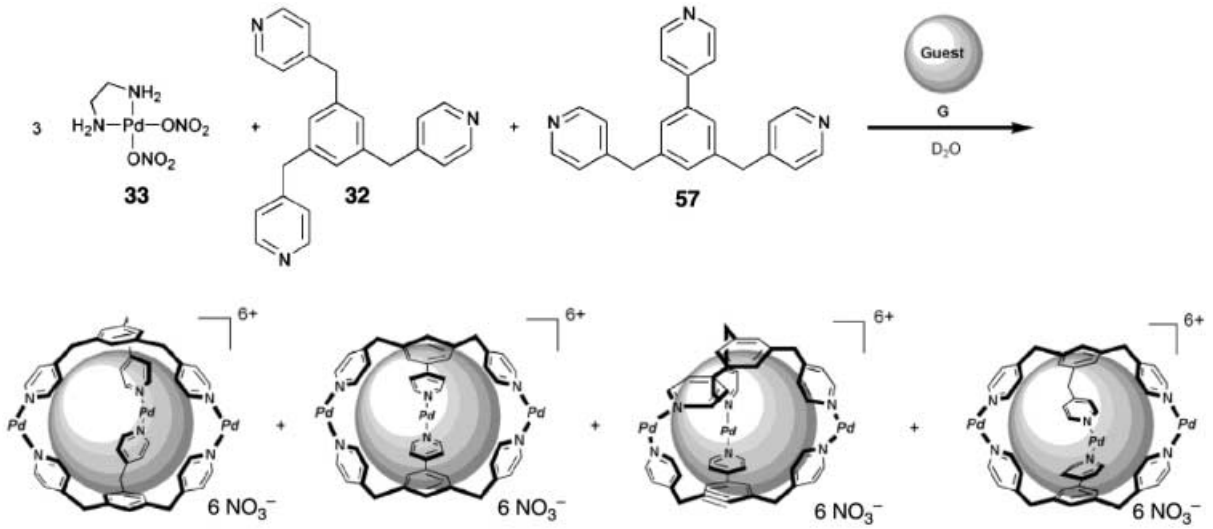

Figure 23. A dynamic library of four receptors arising from the combination of two ligands in the presence of a suitable metal subunit. Spherical guests such as CBr_4 or $CBrCl_3$ give rise to different hosts than include aromatic guests such as benzene or *p*-xylene. (Reprinted with permission from ref. [132].)

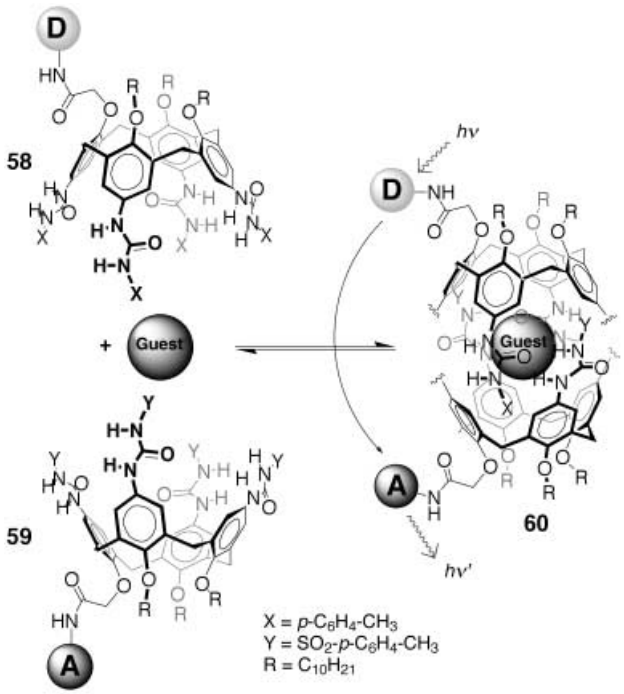

Figure 24. Encapsulation-dependent sensing of a guest. The presence of a guest encourages capsule dimerization, which in turn produces an optical signal through fluorescence resonance energy transfer between dyes covalently attached to each monomer.

suitable guest, encapsulation occurs and a FRET signal arises. In this way the encapsulation-dependent detection of 3-methylcyclopentanone was achieved by the combination of **58** and **59** in *p*-xylene.

4.4. Self-Assembled Capsular Polymers

New structural and physical properties emerge from the polymeric assembly of compound **61**, produced by covalently coupling a calixarene–tetraurea monomer at the lower rim to another calixarene–tetraurea monomer (Figure 25a).[52, 134] The use of a rigid linker creates divergent tetraurea recognition elements that are unable to bond in an intramolecular sense. Instead, the encapsulation-driven self-assembly results in a polymeric chain of capsules (Figure 25b). Like other polymers, "polycaps" display new properties on the macroscopic scale. Unlike traditional polymers, the chains use reversible interactions and are formed under equilibrium conditions. Polarized light microscopy studies on concentrated solutions of **61** reveal that the polymer displays a nematic liquid crystalline state, that is, the polymer chains self-organize in a linear array.[135] Chiral nematic (cholesteric) liquid crystalline phases emerge from analogous chiral monomers. Fibers that are pulled from the liquid crystalline melt also display order under a polarized light microscope, a behavior that is, perhaps, responsible for their surprising strength (crude measurements show that these fibers have a yield stress within an order of magnitude of that of covalent polymer fibers such as nylon-6). These samples also display bulk viscoelastic properties related to their polymeric nature.[136]

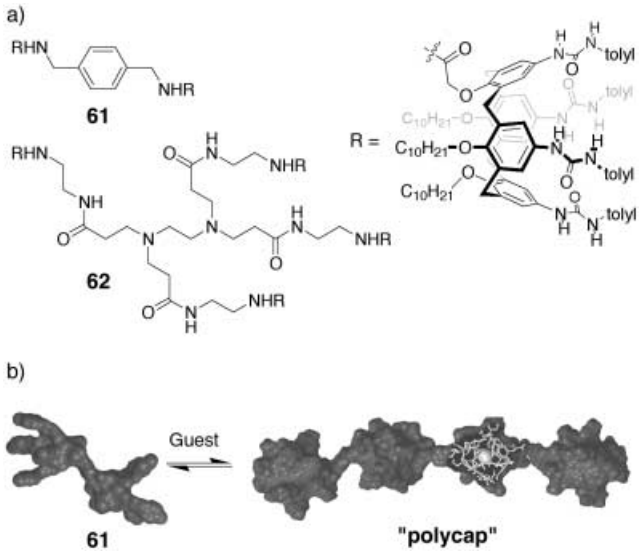

Figure 25. Encapsulation-dependent polymerization and gel formation. Monomer **61** forms polymeric chains of capsules (polycaps) in the presence of a suitable guest. Addition of noncovalent cross-linker **61** results in the formation of physical gels.

The doping of monomer **61** with a compatible cross-linking species (**62**) has dramatic effects on the bulk properties of the mixture.[136] Compound **62** relies on encapsulation to form self-assembled cross-links between polymer chains. Cross-linker **62**, when present in concentrations as low as 5% relative to **61**, causes the formation of a gel phase. These gels are reminiscent of conventional physical gels, in which covalent linear polymers are cross-linked by weak noncovalent interactions. Here, the structural components are reversed, but the viscoelastic behavior of the gels is quite similar. For example, the gels are dilatant: their viscosity increases with the application of shear. This result points to increased ordering under anisotropic flow, and ordered structures have been observed in surface transmission electron microscopy images obtained from frozen chloroform.

In every case, the bulk properties of the polycaps are dependent on the presence of a suitable guest species and a solvent that does not compete for hydrogen bonds. The formation of polymeric chains, liquid crystalline phases, viscous polymeric solutions, and gels are properties fundamentally derived from, and dependent on, molecular encapsulation.

5. Control of Reactivity through Encapsulation

The most direct illustration of the effects of encapsulation on small molecules is the mediation of chemical reactions. Encapsulated molecules are removed from a sphere of solvation and placed in enforced proximity to the host and, if space permits, to other guests. This constrained environment governs the guest's encounters with potential reactive partners, as well as fundamentally altering the concentration (molecules per volume) of reactive species. This influence is exerted for the duration of the lifetime of the encapsulation complex, which may be from microseconds to hours.

5.1. Acceleration and Catalysis

Two different approaches to supramolecular catalysis through encapsulation have been reported in the literature: 1) bimolecular catalysis can occur when two reactive partners are bound within a single capsule and 2) phase-transfer catalysis can occur when the capsule transports guests from one solvent phase to another. Both rely on turnover, the release of product (or passenger) and the re-uptake of reactants. Reversibility is the key to this behavior.

Initial reports of the self-assembled softball (**3**, Figure 1)[40] and its propensity for the simultaneous encapsulation of two guest molecules[41] raised the possibility of catalyzing a bimolecular reaction by encapsulation. Rate acceleration through encapsulation was observed in the Diels–Alder reaction of benzoquinone (**63**) and cyclohexadiene (**64**) mediated by **3b** (Figure 26a).[137] In the resting state of the system two molecules of benzoquinone are encapsulated

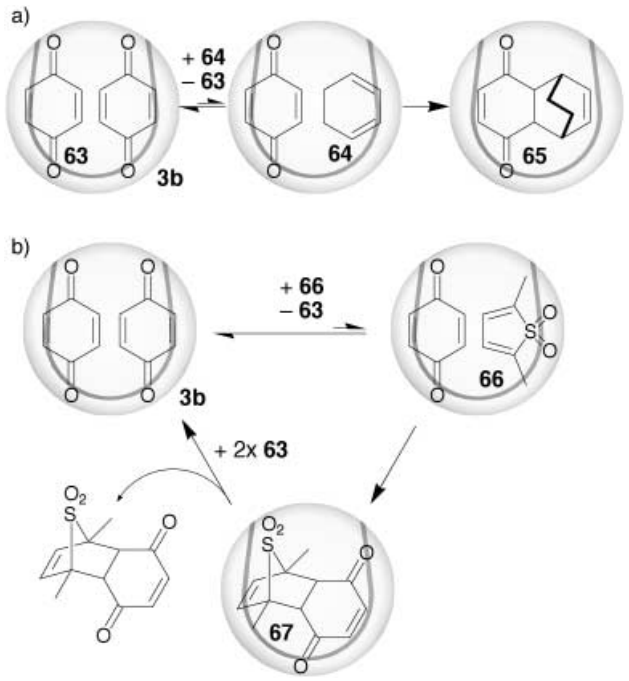

Figure 26. Diels–Alder reactions mediated by a self-assembled capsule: a) the reaction of benzoquinone and cyclohexadiene is accelerated through encapsulation, but product inhibition prevents catalytic turnover, b) the reaction of benzquinone and **66** is accelerated by the capsule, and subsequent dissociation of product results in catalytic turnover.

strongly by **3b**: neither the capsule containing only cyclohexadiene nor the mixed encapsulation complex can be observed by NMR spectroscopy. Nevertheless, an encapsulation-dependent rate acceleration of nearly 200-fold occurs in the Diels–Alder reaction between the two substrates. The rate acceleration likely arises from a mixed encapsulation complex, the counterpart of the Michaelis complex.[138] Derivatives of **63** and **64** that are not of appropriate size for encapsulation show no rate acceleration. Addition of a nonreacting guest that competes effectively for the catalytic site (an inhibitor) also prevented rate acceleration. Unfortunately, the product (**65**) of the reaction of **63** and **64** is a good guest for the capsule, and strong product inhibition prevents turnover, that is, catalysis (Figure 26a). The reaction of **66** with **63** was examined in the expectation that the loss of SO_2 from the Diels–Alder adduct would result in product (**67**) release and catalyst turnover (Figure 26b). Instead, it was found that loss of SO_2 does not occur under the reaction conditions. Nevertheless, the product (**67**) is fortuitously ejected from the softball by the quinone and catalytic turnover is the outcome.[139]

A different approach to encapsulation-dependent catalysis uses capsules constructed through metal–ligand interactions operating in aqueous environments. Capsule **41a** is highly charged (+12), yet shows a propensity for encapsulating a variety of neutral hydrophobic molecules. This combination of properties make **41a** a unique candidate for the encapsulation-dependent phase-transfer catalysis of reactions in water. The effect of **41a** on the Wacker oxidation of styrene catalyzed by $[Pd(NO_3)_2(en)]$ (en = ethylenediamine) was examined to test this hypothesis (Figure 27).[140] In the absence of capsule **41a**, the transformation of styrene to acetophenone catalyzed by $[Pd(NO_3)_2(en)]$ proceeds only to a small extent in water (4%) as a result of the substrate's low solubility in aqueous media. Under the same conditions, the

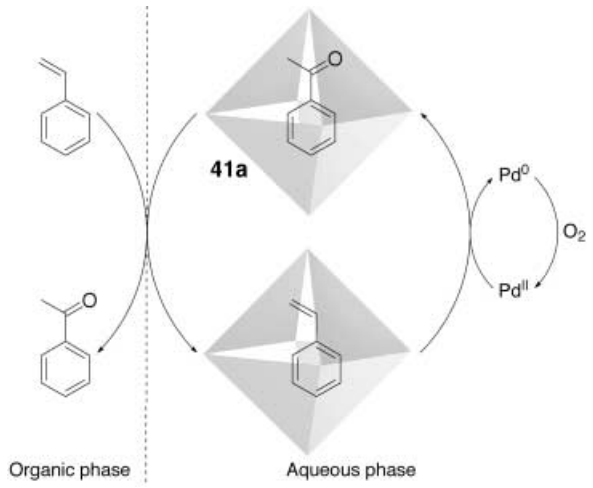

Figure 27. Reverse phase-transfer catalysis of the Wacker oxidation of styrene by a supramolecular capsule.

presence of a catalytic amount of **41a** results in a dramatic increase in the yield of acetophenone (82%). Experiments carried out in the presence of styrene and a competing guest (1,3,5-trimethoxybenzene) decreased product formation dramatically (3%). The structural Pd^{II} components of capsule **41a** alone are not sufficient for catalysis of the reaction; in all cases the addition of catalytic $[Pd(NO_3)_2(en)]$ is necessary. The result is a unique "double catalyst" system wherein **41a** acts as a phase-transfer catalyst and a separate Pd^{II} species acts as the oxidation catalyst (with reoxidation by air). This reverse phase-transfer methodology can be extended to other substituted styrenes that are encapsulated by **41a**.

In another example, complex kinetic behavior reminiscent of autocatalysis is observed when reagents are compartmentalized within a supramolecular capsule.[141] Dicyclohexylcar-

bodiimide (DCC) is encapsulated by cylindrical capsule **18** (Figure 28). Addition of benzoic acid **68** and aniline **69** to the mixture gives rise to complex kinetic behavior. Trace amounts of DCC free in solution promotes the formation of an amide bond between the acid and amine reactants. The products of this reaction are anilide **70** and dicyclohexylurea (DCU), both of which are better guests for capsule **18** than DCC. Accordingly, increasing amounts of DCC are displaced from the capsule by **70** and DCU, and the rate of the reaction increases as the reaction proceeds. The kinetics possess a sigmoidal character that depends on product formation, yet this is not classical autocatalysis, as there is no single catalyst in the system. The nonlinear kinetics can be viewed as an emergent property of the system as a whole, with the partnership of compartmentalization and molecular recognition giving rise to chemical amplification. This result, while not easily classified, highlights the role that compartmentalization may play in the creation and maintenance of complex systems.

5.2. Stabilization of Reactive Species

Reversibly formed capsules have successfully stabilized species that are not otherwise stable in free solution. The processes that are responsible for self-assembly and encapsulation can provide enough free energy for an encapsulated guest to alter its own internal equilibria. In the simplest of these cases, encapsulated guests display altered conformational preferences. Supramolecular capsules can also stabilize encounter complexes formed between multiple guests that are not otherwise observed. In the most dramatic examples, encapsulation can be used for the stabilization and isolation of reactive intermediates.[142]

As described in Section 2.2, self-assembled capsule **18** is capable of encapsulating long cylindrical molecules that are complementary in both shape and size to the dimensions of its elongated cavity.[66] A preference for the binding of *trans*-stilbene over *cis*-stilbene underscores this selectivity.[143] The binding of *N*-methylbenzanilide (**71**) demonstrates a more subtle set of characteristics imparted by the host capsule. Although **71** is known to prefer the *E* conformation in free solution, the physical constraints provided by capsule **18** force **71** to adopt the unfavored *Z* conformation (Figure 29).[143] Like all properties governed by encapsulation, the preferences imparted upon **71** arise from a combination of equilibrium processes. The self-assembly of the capsule, the encapsulation of the guest, and the conformational state of the guest molecule are all dynamic processes that conspire to yield the end result—in this case a simple conformational shift.

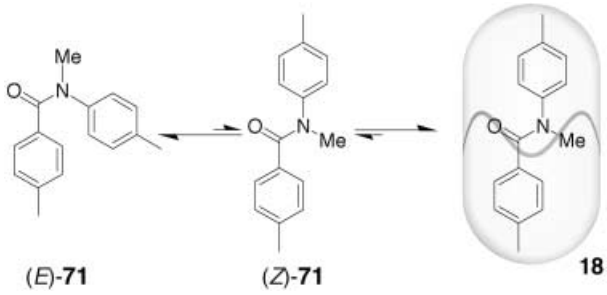

Figure 29. A shift in conformational equilibrium (*E*)-**71** ⇄ (*Z*)-**71** brought about by shape-selective encapsulation within an elongated capsule.

Kusukawa and Fujita used capsules constructed with metal–ligand interactions for the stabilization of unfavored conformations. The treatment of an aqueous solution of capsule **41a** with a solution of 4,4′-dimethylazobenzene (**72**, *cis*:*trans* 1:6) in hexane results in the formation of an unusual complex within the capsule walls (Figure 30a). The capsule selectively binds two equivalents of *cis*-**72**.[144] 2D NMR studies using the analogous *cis*-stilbene **73** shows NOE contacts between the vinyl protons and methyl protons of the guest, which provides additional evidence for the proposed dimeric guest cluster. The *cis*-azobenzene molecules are considerably stabilized within this encapsulation complex: exposing the solution to visible light for several weeks did not result in the production of any of the thermodynamically favored *trans*-azobenzene. Molecular modeling studies reveal that the dimeric hydrophobic guest complex is too large to have formed outside the capsule and entered as a single species. Since the structural elements of the capsule are not equilibrating under the conditions of these experiments, the hydrophobic dimer must form within the capsule walls.

This "ship-in-a-bottle" encapsulation process is not unique to azobenzene and stilbene guests. The exposure of Pt-based cage **41c** to phenyltrimethoxysilane results in the formation of a cyclic silanol trimer **74a** within the cavity of the supramolecular capsule (Figure 30b).[145] Cyclic trisilanol oligomers of this type are considered to be intermediates in the sol–gel condensation. Although the cyclic tetramer has been prepared by other methods, the highly reactive cy-

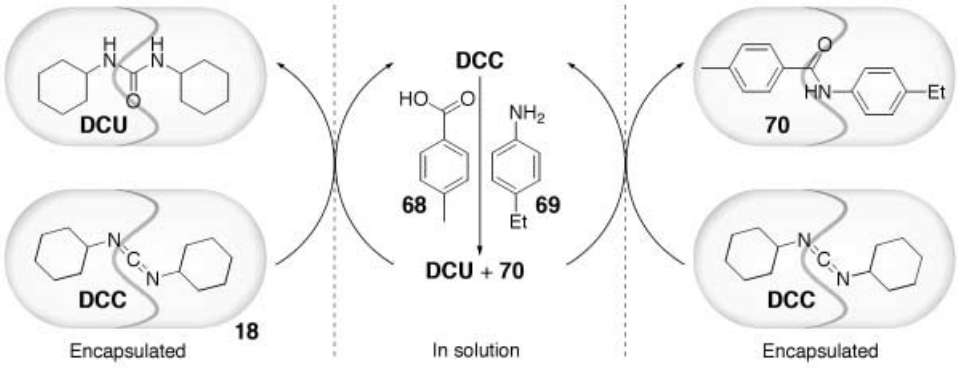

Figure 28. Compartmentalization of reactants and products gives rise to emergent nonlinear behavior. DCC is initially sequestered from the reaction medium through encapsulation within cylindrical capsule **18**. As the reaction between acid **68** and amine **69** proceeds, the coupled product **70** and DCU are generated and both displace DCC from the reversibly self-assembled capsule.

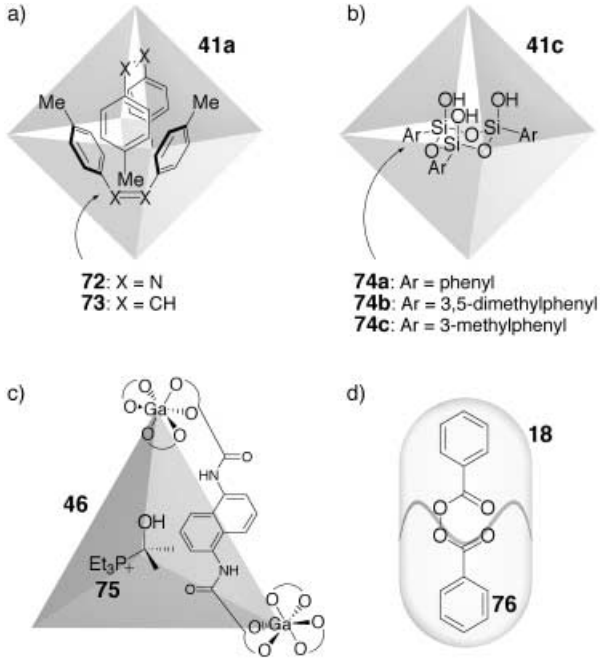

Figure 30. Stabilization of reactive species through encapsulation: a) formation of unique tennis ball shaped hydrophobic dimers **72** and **73** within a metal-based supramolecular capsule **41a**; b) encapsulation and stabilization of highly reactive cyclic trisilanols **74a–c**, proposed to be intermediates in the sol–gel polycondensation process; c) formation of a water-sensitive phosphane–acetone adduct **75** within a tetrahedral metal–ligand cluster **46** in the aqueous phase; d) the cylindrical capsule **18** is able to prevent reactions of the shape-complementary guest benzoyl peroxide (**76**) even at elevated temperatures for prolonged periods of time, even though the capsule structure is maintained entirely through hydrogen bonds.

clic trimer had not been observed. Evidence for encapsulated cyclic trimer **74** is provided by NMR spectroscopy, mass spectrometry, and, for **74c**, X-ray crystallography.[111] In all cases, the trimer is formed as the C_3-symmetric all-*cis* isomer. The reactivity of **74** is greatly attenuated by encapsulation. No change in the complex is observed for over one month in neutral aqueous solution; the guest also survives the acidic conditions ($pH < 1$) required for the isolation of the complexes. Again, the guest is too large for formation outside the capsule; instead, the polycondensation process that traps this reactive intermediate must take place within the confines of the capsule walls.

The tetrahedral metal clusters of Raymond and co-workers[101] offer a radical approach for the stabilization of reactive intermediates. The treatment of a solution of Ga–catecholate based capsule **46** (Figure 15) in D_2O with PEt_3 resulted in the observation of new signals for encapsulated guest in the ^1H and ^{31}P NMR spectra. These signals did not correlate with the expected encapsulation of PEt_3, but instead can be attributed to the encapsulation of the cationic phosphane–acetone adduct $[Me_2C(OH)PEt_3]^+$ (**75**) that arises as a consequence of the presence of adventitious acetone remaining from the synthesis of capsule **46** (Figure 30c).[146] This adduct has been previously synthesized under anhydrous conditions, but decomposes rapidly in aqueous solution as a result of the low concentration of acetone. It is likely that **75** forms upon entry of protonated phosphane into a cavity already containing residual acetone. To confirm the structure of the encapsulated species, $[Me_2C(OH)PEt_3]Br$ was prepared under anhydrous conditions and added to the capsule in CD_3OD. The resulting ^1H and ^{31}P NMR spectra agreed with those obtained previously in D_2O. Mass spectrometric studies of the methanolic solution provided further evidence for the composition of the encapsulated species.

Even capsules constructed through relatively weak hydrogen bonds can act to stabilize reactive species through encapsulation. Benzoyl peroxide (**76**) readily undergoes homolytic bond cleavage at room temperature to give reactive radical species that are commonly used for the initiation of radical chain reactions or the oxidation of various substrates. The size and shape of **76** make it an excellent guest for capsule **18** (Figure 30d).[147] A variety of agents normally reactive to **76** at room temperature undergo no detectable reaction in the presence of the preformed encapsulation complex of **76** and **18** during prolonged heating at 70 °C. The addition of a small amount of DMF disrupts the hydrogen bonds responsible for encapsulation and results in immediate reaction of the reporter molecules with **76**. Likewise, the addition of a competing guest molecule that displaces **76** from the capsule also results in the release of the reactive species and the onset of oxidation or chain reactions. Studies on complexes of other guests with **18** indicate that the partial opening of the capsule walls is probably responsible for the rapid exchange of small guests, but little is known about the exchange of large rod-shaped guests. Perhaps the complete dissociation of the complex—a rare event—is required. The surprising stability of this complex highlights the subtle effect of shape-selective host–guest interactions on guest-binding and -exchange processes.

6. Summary and Outlook

The final paragraph of a review asks the writer to predict the future—or worse, to tip his hand about the direction his own research will take. Naturally, we are hesitant to do either, but we confess an interest in the construction of synthetic systems that possess nonlinear properties such as autocatalysis and chemical amplification. These characteristics are integral properties of living systems, and they give rise to desirable behaviors such as increased sensitivity, responsiveness, and self-replication. Other questions that remain to be answered lie in the realm of supramolecular mechanisms. In simple encapsulation complexes, an understanding of paired receptor and guest movement during binding and release events is attainable, whereas in the biological realm of complex receptor–ligand systems the flexibility and intricate movement of a receptor and guest during a binding event are difficult to study, and are often overlooked.[148] The study of simple systems does not limit the details of questions that may be asked, instead, exploring well-defined systems can allow for the understanding of intricacies that otherwise may not even be considered.

We emphasize that reversible encapsulation is not intended as a model of anything; it provides the current outlet for our curiosity about the nature of intimate molecular relationships

and their manipulation. Yet we cannot deny that the compelling nature of encapsulation has its roots in biology. There, compartmentalization provides ways to separate incompatible reagents and environments (endosomes and mitochondria isolate media of widely differing pH values). We believe that reversible encapsulation can provide a probe operating at the boundary of chemistry with biology, the most intriguing of which is how the former gave rise to the latter—the "West Coast" approach to chemical biology. Given the activity at The Skaggs Institute,[15, 149, 150] the Scripps Oceanographic Institute,[151] the University of California at San Diego,[152] and the Salk Institute,[9] what better location is there to explore this question than La Jolla?

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[1] This is alleged by no less of an authority than Woody Harrelson in the movie *Indecent Proposal* (USA, 1993). For the original Khan quote, see *The Encyclopedia of Twentieth-Century Architecture* (Ed.: R. Stephen Sennott), Fitzroy Dearborn, Chicago, **2002**.
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