Cage Compounds

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Shape-Persistent Organic Cage Compounds by Dynamic Covalent Bond Formation

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boronic acids · cage compounds · dynamic covalent chemistry · Schiff bases · self-assembly

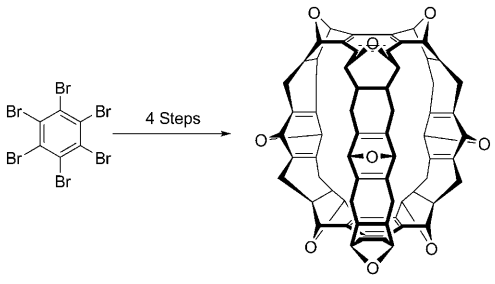
One area of supramolecular chemistry involves the synthesis of discrete three-dimensional molecules or supramolecular aggregates through the coordination of metals. This field also concerns the chemistry of supramolecular cage compounds constructed through the use of such coordination bonds. To date, there exists a broad variety of supramolecular cage compounds; however, analogous organic cage compounds formed with only covalent bonds are relatively rare. Recent progress in this field can be attributed to important advances, not least the application of dynamic covalent chemistry. This concept makes it possible to start from readily available precursors, and in general allows the synthesis of cage compounds in fewer steps and usually higher yields.

1. Introduction

Interest in compounds with defined pores has increased over the last few decades. In principle, two classes of porous compounds can be identified: extended porous frameworks and discrete hollow cage molecules. The most prominent representative class of extended, highly ordered porous compounds today is probably that of metal–organic frameworks (MOFs).[1] These MOFs are built up from metal ions or clusters and rigid organic ligands, with the metal ions or clusters forming the nodes and the organic ditopic or oligotopic ligands forming the spacers or rods. A similar approach could be used to synthesize supramolecular cage compounds with defined structures in high yield: The defined coordination behavior (coordination number and predetermined geometries) of certain metal ions and well-chosen rigid ligands form a construction set which allows the synthesis of various cage compounds with designed space, geometry, and functionality.[2,3] Although the highest number of publications on supramolecular cage compounds has been with such coordination compounds, other typical supramolecular interactions such as hydrogen bonding can also be used for the construction of cage compounds.[4,5] Some of the supramolecular cage compounds exhibit extraordinary properties: for example, they can stabilize reactive molecules such as white phosphorus[6] or enable "uncommon reactions" such as Diels–Alder reactions with unusual regioselectivities to be carried out.[7]

In contrast to supramolecular cage compounds that usually self-assemble from simple precursors, organic cage compounds[8] based only on covalent bonds are rarer. This is probably due to the fact that most covalent bonds are built "irreversibly" and, therefore, a "self-healing" process is excluded. Most cage compounds synthesized this way require multiple steps and often have low overall yields. One example is a structure-directed, multistep synthesis of trinacrene (Scheme 1).[9] Starting from hexabromobenzene and furan, trinacrene was synthesized in four steps, but in a low overall yield of $< 0.01\,\%$.

Fullerene C_{60} is also an organic cage compound that continues to fascinate physical researchers as well as chem-



Scheme 1. Synthesis of trinacrene.[9]

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ists.[10] Despite the great interest in fullerene derivatives, a rational, high-yielding synthetic procedure is still lacking.[11] Initial steps towards a rational synthesis were made in 2002: The first total synthesis of C_{60} was presented, which demonstrated that it is possible to prepare the compound from a defined molecular precursor.[12] The precursor was converted into C_{60} in less than 1% yield by flash-vacuum pyrolysis. Very recently it was confirmed that these precursors could be converted into the corresponding fullerenes and diazafullerenes by placing them onto a platinum(111) surface and heating them up to 750 K under a ultrahigh vacuum.[13] This is perhaps the first step towards a new method for the synthesis of fullerene derivatives.

As already mentioned, most organic cage compounds are not simply synthesized—they are often synthesized with the aim of using them for a particular function. For example, organic cage compounds are often constructed as host molecules that will act as receptors or sensors for organic guest molecules such as hydrocarbons,[14] carbohydrates,[15] or steroids.[16] The recognition of anions such as nitrate[17] or fluoride[18] by such organic cage compounds as well as artificial siderophores[19] has also been described. One example of a water-soluble carbohydrate receptor is depicted in Figure 1. Besides the application of cage compounds as receptor molecules for certain analytes, shape-persistent organic molecules have also been made for other purposes. For example, a very labile and reactive expanded cubane was made after great synthetic effort.[20] The cubane derivative loses MeO fragments under high-resolution Fourier-transform ion-cyclotron-resonance (HR-FT-ICR) mass spectrometry conditions, thereby forming various fullerene derivative ions.

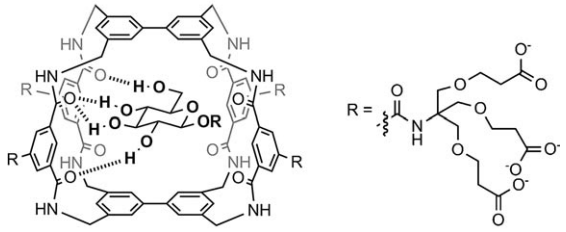


Figure 1. Proposed binding model for a water-soluble synthetic lectin.[15]

After vocational training as a chemical technician (Thyssen Stahl AG), in 2002 Michael Mastalerz completed his Diploma in chemistry at the University of Duisburg, and completed his PhD in the group of Prof. Gerald Dyker at the Ruhr-University Bochum. In 2005 he worked with Taros Chemicals GmbH (Dortmund), before moving to Cambridge (USA) in 2006 to work in the group of Prof. Gregory C. Fu at MIT. Since 2007 he has been working towards his habilitation at Ulm University, associated to the group of Prof. Peter Bäuerle. His current research interests include the synthesis of organic cage compounds and functional porous materials.

Almost all of the above-mentioned organic cage compounds were synthesized either in multiple steps and/or in very low yield, mainly because of irreversible bond formations. A possible approach to synthesize cage compounds from simpler precursors in fewer steps is dynamic covalent chemistry (DCC). The concept of DCC, introduced by Jean-Marie Lehn, offers the opportunity to exploit reversible covalent bond formations to achieve the most thermodynamically stable product out of a virtual combinatorial library (VCL).[21] This approach allows product formation to be directed to one member of the VCL by changing the parameters, for example, by switching solvents, pH value, or template. It has already been demonstrated in the field of shape-persistent macrocycles that applying dynamic covalent bond formation to relatively simple precursors can enhance the formation of macrocycles to give high yields in a one-pot reaction.[22] In addition, sophisticated three-dimensional molecular topologies,[23] such as Borromean rings[24] or Solomon knots are accessible through a combination of metallasupramolecular interactions and DCC. These structures are interconvertible.[25] Those borromeates have not so far been synthesized by "conventional" methods.

In recent years chemists have increasingly exploited the use of DCC for the synthesis of organic cage compounds with covalent bonds. The starting materials are typically simpler, and the formation of the cage occurs in one step with good to excellent yields.

This Minireview gives an overview of recent developments in the application of dynamic covalent processes for the formation of organic cage compounds. The term "cage compound" is used here for molecules that are a priori not very flexible (shape persistent) and contain a cavity that is able to take up smaller molecules or ions. Smaller cage compounds the size of dodecahedrane, adamantane,[26] urotropine (hexamethylenetetraamine),[27] and natural products such as tetrodotoxine derivatives are not within the scope of this Minireview. This is also true for all sorts of "classical" cryptands,[28] even if the formation of an imine bond was used for their synthesis.

2. Cage Compounds through Formation of Imine Bonds

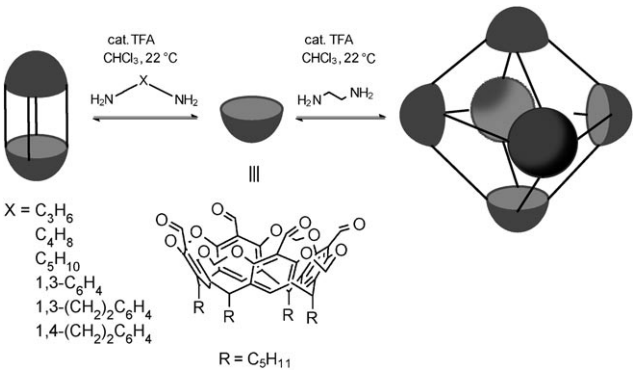
In 1991 Cram and Quan introduced a large hemicarcerand based on an eightfold imine condensation of two resorcinarenes and four 1,3-diaminobenzene molecules as bridging units (in the following text this reaction is described as a [2+4] condensation).[29] After heating the reactants at 65 °C in dry pyridine for four days they obtained the hemicarcerand in 45% yield. Kaifer and co-workers showed that the same compound is also accessible at room temperature by the addition of $MgSO_4$; the $MgSO_4$ probably acts not only to bind the water but also as a Lewis acid that promotes the imine condensation.[30] Later, Stoddart and co-workers demonstrated that the conversion can be achieved quantitatively at room

temperature after just one hour by the addition of a catalytic amount of trifluoroacetic acid (TFA).[31]

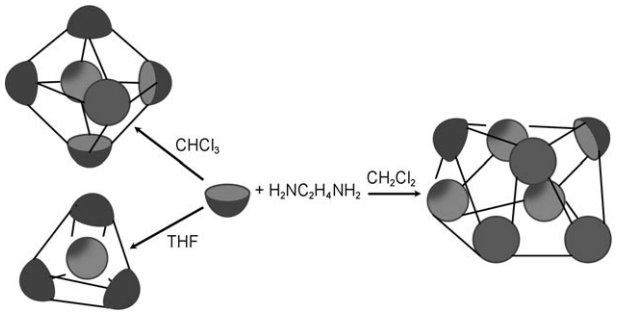
Various guests can be encapsulated in the hemicarcerand to give hemicarceplexes.[29,30] The tightest bound guest was ferrocene, with a reported half-life $t_{1/2} = 19.6$ h for its release at 112 °C in $C_2D_2Cl_4$[29] or > 300 h at 25 °C in CD_2Cl_2. The catalytically driven dynamic exchange of the imine spacers by traces of TFA was confirmed by adding a different imine source to the hemicarcerand.[31] The exchange was monitored by ^{1}H NMR spectroscopy and verified by fast-atom bombardment mass spectrometry (FAB-MS). Analysis of the dynamic mixture by the latter technique showed signals with m/z values for all the possible products. The half-life of the ferrocene release was monitored in the presence of a) the other diamine, b) TFA, and c) mixtures thereof by NMR spectroscopy. The authors concluded on the basis of the large decrease in half-lives that the reaction occurred through a "bar-opening mechanism" rather than through a direct exchange by imine metathesis (Scheme 2).[31]

Warmuth and co-workers found that a similar cavitand—with pentyl moieties instead of phenethyl moieties at the lower rim—in the presence of 1,2-diaminoethane forms an octahedral nanocage when stirred in chloroform with a catalytic amount of TFA (Scheme 3).[32a] This octahedral cage compound consists of 6 cavitand molecules and 12 linking units. Most interestingly, this octahedron is formed exclusively with 1,2-diaminoethane; other diamines with longer tethers ($H_2N(CH_2)_nNH_2$, with $n = 3$–5) or with rigid aromatic cores (H_2NXNH_2, X = 1,3-C_6H_4, 1,3-$(CH_2)_2C_6H_4$, 1,4-$(CH_2)_2C_6H_4$ form [2+4] hemicarcerands.[32a,b] The dynamic nature of the cage-forming process was later excellently proved by using different conditions for the condensation reactions. The use of various solvents as reaction media led to octahedral ($CHCl_3$), tetrahedral (THF), or square-antiprismatic (CH_2Cl_2) nanocages (Scheme 4).[32b]

By using a rigid D_{3h}-symmetric triamine in combination with the tetraformylcavitand Warmuth and co-workers were able to synthesize a giant rhombicuboctahedron in a [6+8] condensation (Scheme 5).[33] The solvodynamic diameter of this compound was estimated by DOSY NMR spectroscopy to be 3.9 nm, which is in good agreement with a MM3-optimized space-filling model. This model gives an inner diameter of approximately 3 nm and a cavity volume of 4700 Å^3, which is the highest value for a covalent cage compound reported so far.

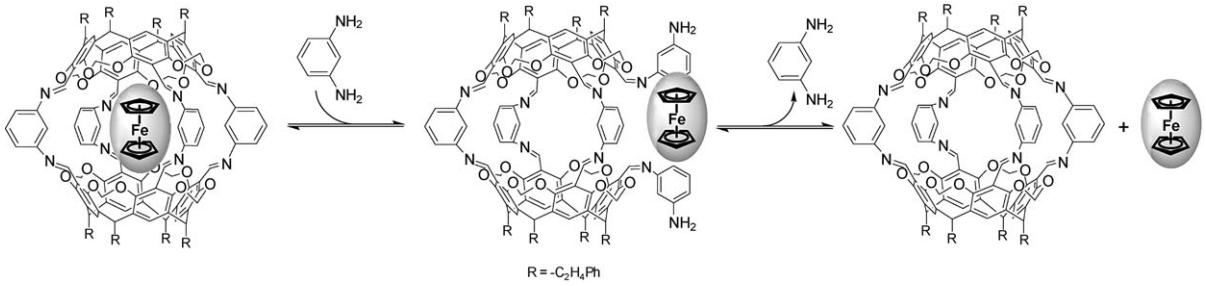


Scheme 3. Synthesis of an octahedral nanocage and hemicarcerands from a resorcinarene tetraaldehyde precursor.[32a]

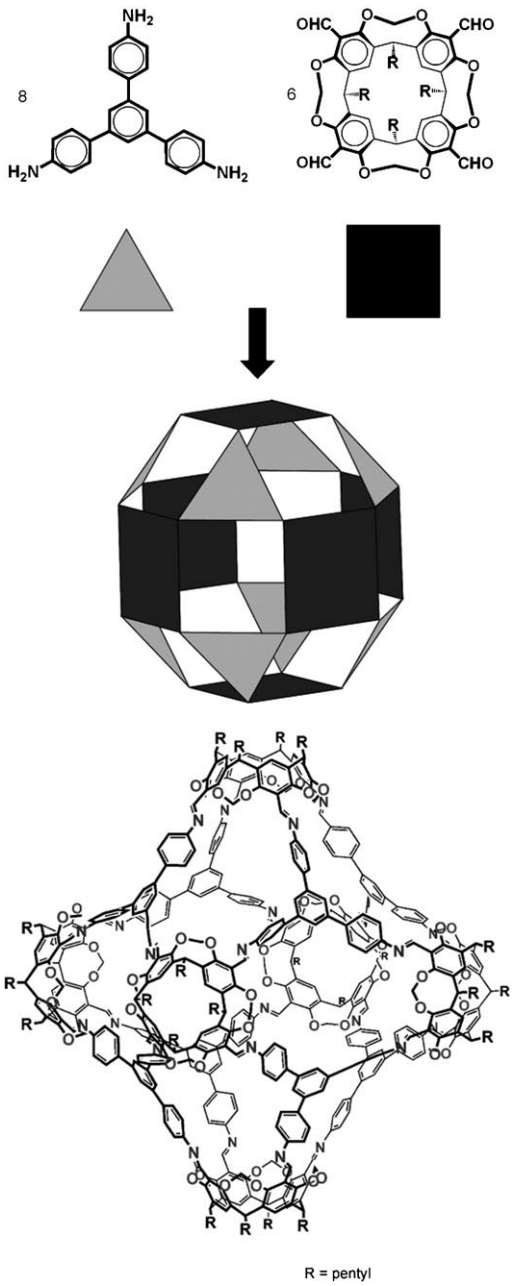


Scheme 4. Three different cage compounds as products in three different solvents to show that the dynamic nature of the cage formation depends on the solvent system.[32b]

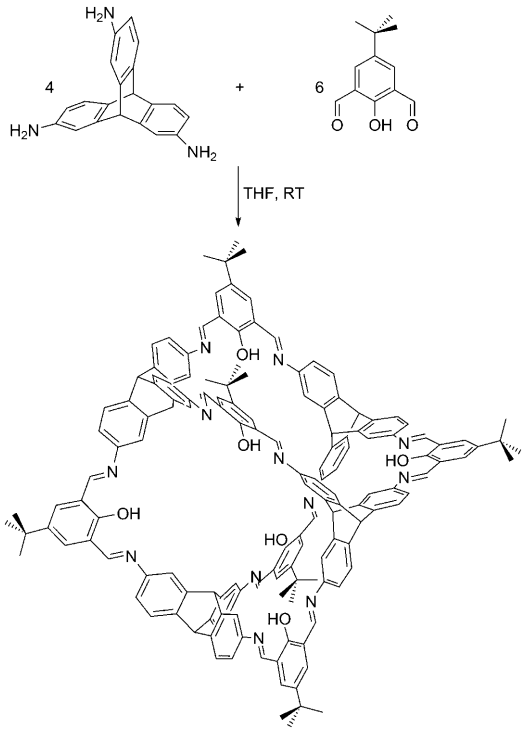
An adamantoid nanocage was formed in 58% yield by condensation of four trisaminotriptycenes and six salicyl dialdehydes (Scheme 6).[34] It was suggested that the salicylic hydroxy group promotes the formation of the cage by activating the aldehyde moieties through the formation of intramolecular hydrogen bonds. A directing effect of the reactants was also assumed. The difference between this cage compound and the other aforementioned compounds generated by DCC is that the functional groups point synergistically into the center of the cavity, thus making these compounds potential hosts for the recognition of smaller guest molecules.



Scheme 2. The cage releases and enclathrates the guest molecule by a "bar-opening mechanism".[31] This process demonstrates the reversible character of the imine bonds.

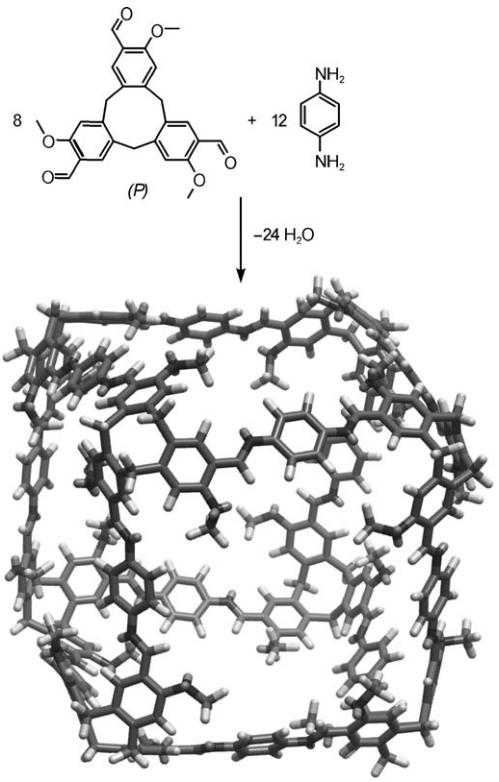


Scheme 5. Formation of a giant rhombicuboctahedron in a [6+8] condensation. Reproduced from Ref. [33].



Scheme 6. Synthesis of an *endo*-functionalized adamantoid cage based on a triptycene triamine.[34]

More recently, Xu and Warmuth reported a chiral nanocube based on chiral cyclotriveratrylenes (CTVs) with three salicylaldehyde functional groups (Scheme 7).[35] The CTVs form the corners of the cube in a condensation reaction with linear 1,4-diaminobenzene molecules, which form the edges of the cube. Dynamic imine condensation with a chiral diamine was performed to resolve the racemic CTVs used as the starting material. The reaction with (*R*,*R*)-diaminocyclohexane led to the formation of C_3-symmetric cages in which the (*M*)-CTV was completely inverted through the process to give enantiopure (*P*)-CTV. Subsequent condensation with the achiral aromatic diamine gave the nanocube in 90% yield. An



Scheme 7. Synthesis of a chiral cube based on inherently chiral CVTs.[35]

approximate diameter of 3.7 nm was estimated for the cage compound by solvodynamic measurements.

David and co-workers demonstrated that it is possible to combine the copper-catalyzed 1,3-dipolar addition of azides and alkynes (Huisgen reaction) with the reversible formation of an imine from cyclohexyldiamine and formyl groups to generate a chiral cage compound in 70% yield in just one step from simple precursors.[36] This compound shows a high selectivity for nickel(II) ions and opens up the possibility to use these structures as enzyme mimics or as chiral catalysts.

Skowronek and Gawronski reported the synthesis of a chiral tetrahedral cage compound by a [6+4] condensation of 1,3,5-triformylbenzene and (*R*,*R*)-1,2-diaminocyclohexane.[37a] Two possible structures were suggested for the formed cage compound: one with *T* symmetry and one with D_2 symmetry. The theoretically calculated UV/Vis and CD spectra of a tetrahedral cage match those of the experimentally obtained compound; the tetrahedral symmetry was verified by Cooper and co-workers through a single-crystal X-ray structure.[37b] This compound was also one of a series of three which where characterized by single-crystal X-ray diffraction.[37b] More important than the structural information of the molecules themselves, is the observation that slight variations of the cage peripheries (H, Me, or cyclohexene substituents) have a major impact on the porosities of the crystalline materials (Figure 2). The unsubstituted cages pack tightly and the voids are dictated by the cage cavities (orange balls), whereas the crystal of the methyl-substituted cage compound has additional channels (yellow) along one crystallographic axis, and the crystals of the cyclohexene-substituted cages have pores interconnected in a diamondoid fashion (yellow). These differences in crystal packing are also reflected in the different measured surface areas (SA_{BET}) of 24 $m^2 g^{-1}$ for the H-substituted, 600 $m^2 g^{-1}$ for the methyl-substituted, and 624 $m^2 g^{-1}$ for the cyclohexylene-substituted cage compounds as well as by the uptake of gases.[37b]

Several smaller cage compounds based on 1,3,5-trisaminomethylbenzenes were formed by [3+2] imine condensation reactions with various dialdehydes and subsequent reduction of the imine bonds with sodium borohydride to give amine bonds (Scheme 8).[38–40] The pyrrolic cage compound selectively recognizes β-glucopyranosides,[38] whereas the other cage compounds were studied for their ability to recognize anions. Although a 1:1 complex of the pyrrolic cage compound with the β-glucopyranosides was assumed by NMR spectroscopic titration, the authors suggested that the guest molecule is only partly included in the cavity. The cage compound selectively discriminates the β-saccharides from the α-saccharides in the gluco, galacto, and manno series. The selectivity for different anions can be tuned by controlled protonation of the pyridylic and xylylic cage compounds.[39,40] The binding of the anions occurs predominately within the cavities of the cage compounds, which was proved in several cases by X-ray crystal structure analysis (see, for example, Figure 3).

In all the examples discussed above, the precursors were readily accessible in a few steps from commercially available compounds. Although the syntheses of precursors in the next example required more steps, it clearly demonstrates that the formation of imine bonds is a versatile tool to construct functional cage compounds in high yield. A blue-emitting truxene moiety can be incorporated in the plane between two cavities. This cage compound was synthesized in good yields by a [1+2] imine condensation, although the synthesis of the hexaaldehyde precursor required multiple steps.[41] Both the hexaimine and the hexaamine cage compounds show bright greenish-blue emissions. The double cavity of these compounds makes these attractive molecules for sensing double binding events of one or two analyte molecules through changes in the emission.

Another sophisticated approach uses the formation of a hydrogen bond between amide hydrogen atoms and adjacent oxygen atoms to preorganize the precursor before formation of the reversible imine bond leads to [3+3] condensations and

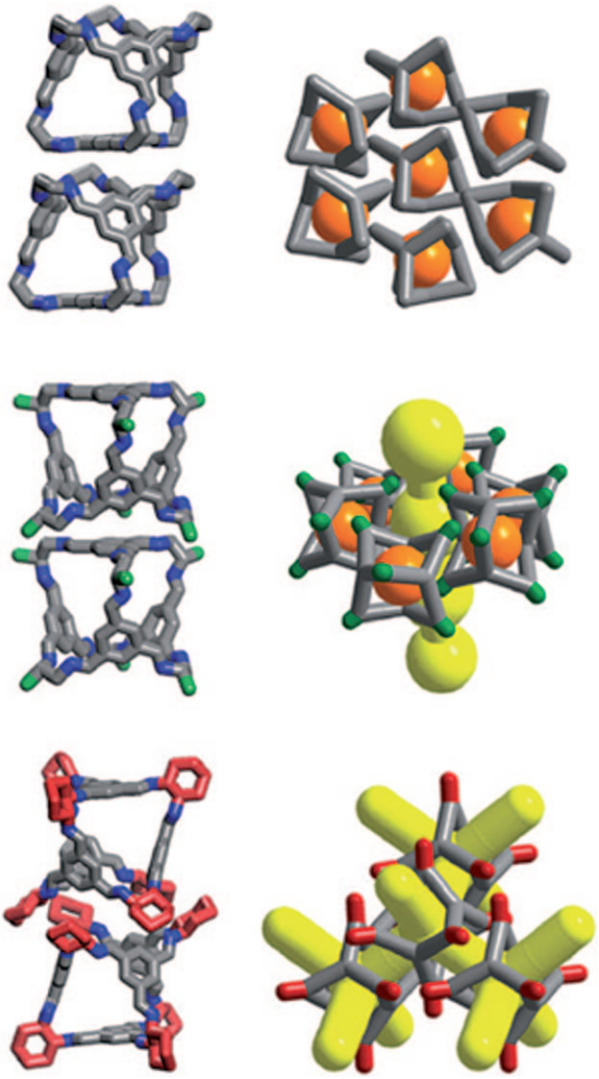
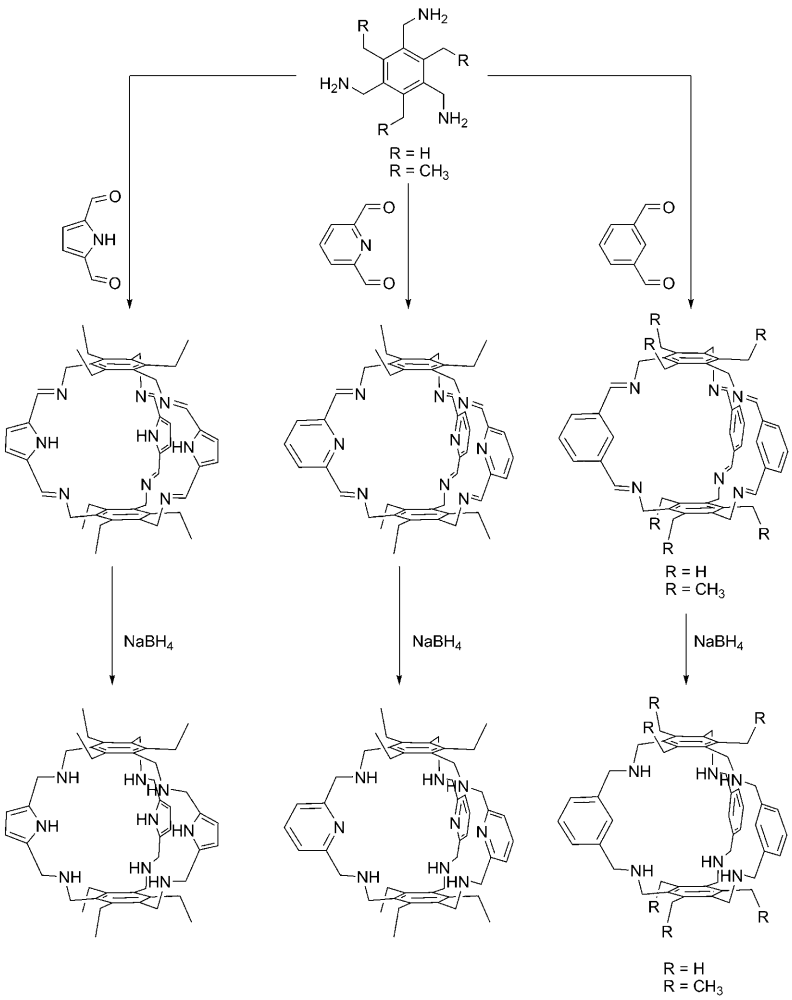


Figure 2. Pore structures (right) and single-crystal structures (left) of the tetrahedral cage compounds.[37b] From top to bottom: cage compounds based on ethylene, 1-methylethylene (methyl group in green), and cyclohexylene spacers (red). The cavities are highlighted in orange, and the channel structures in yellow. Reproduced from Ref. [37b] with permission from the Nature Publishing Group.



Scheme 8. Synthesis of various cage compounds based on 1,3,5-tris(aminomethylene)benzene and dialdehydes.[38–40]

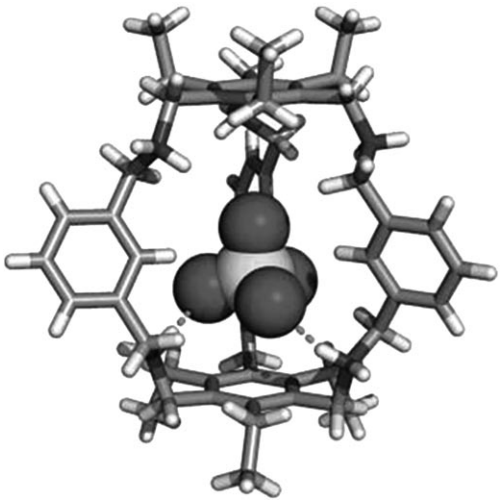


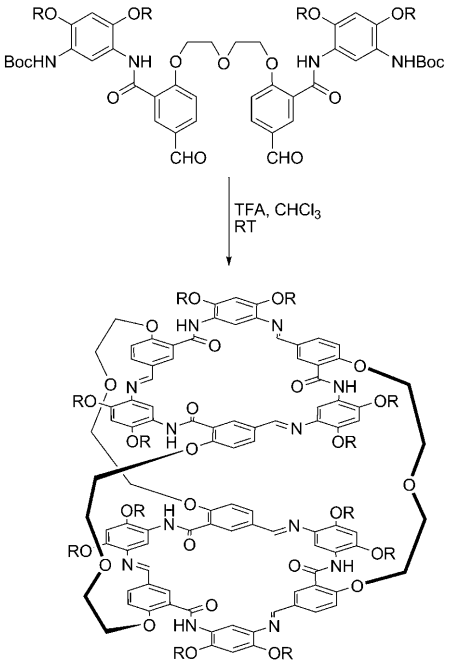
Figure 3. X-ray crystal structure of a xylilic cage compound with a sulfate anion bound inside the cavity. Reproduced from Ref. [40] with permission from the Royal Society of Chemistry.

cage compounds in excellent yields (Scheme 9).[42] The cage compounds consist of two macrocycle planes in a coplanar arrangement with polar inner rims linked through $C_2H_4OC_2H_4$ units. These polar macrocyclic units could be further used for the construction of pseudo[3]rotaxanes with various diammonium salts.[42] After reduction of the imine bonds, the compound was subsequently transformed to the corresponding hexaammonium macrobicycles, which were shown to form vesicles with a mean diameter of 1.5 μm in chloroform.[43] However, the formation of those vesicles seems to be unique only for the macrobicycles with the more flexible $C_2H_4OC_2H_4$ spacers, not those with 1,4-benzylidene bridging units.

The formation of an imine bond is still the most frequently used bond formation for the construction of cage compounds. The second most common route is the formation of boronic esters, which will be discussed in Section 3.

3. Cage Compounds through Formation of Boronic Esters

Similar to the reversible formation of imines from aldehydes and amines, the reaction of boronic acids with diols result in the reversible formation of the corresponding esters.[44] This binding motif can be used for the recognition of carbohydrates[45] as well as for the construction of new

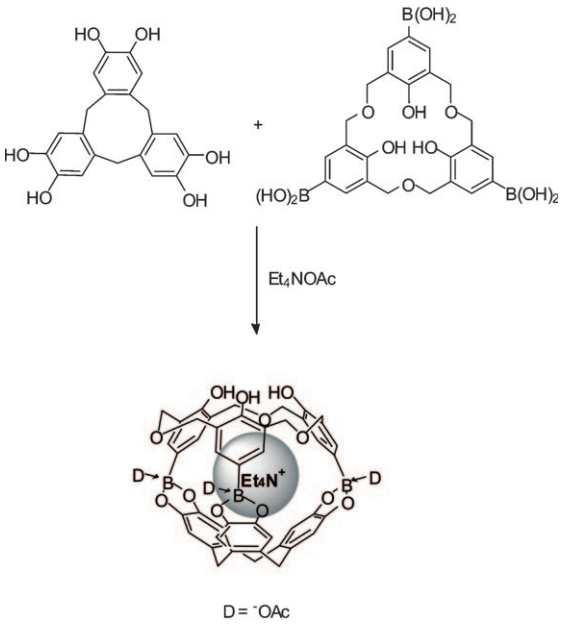


Scheme 9. [3+3] Condensation of precursors preorganized through hydrogen bonds.[42]

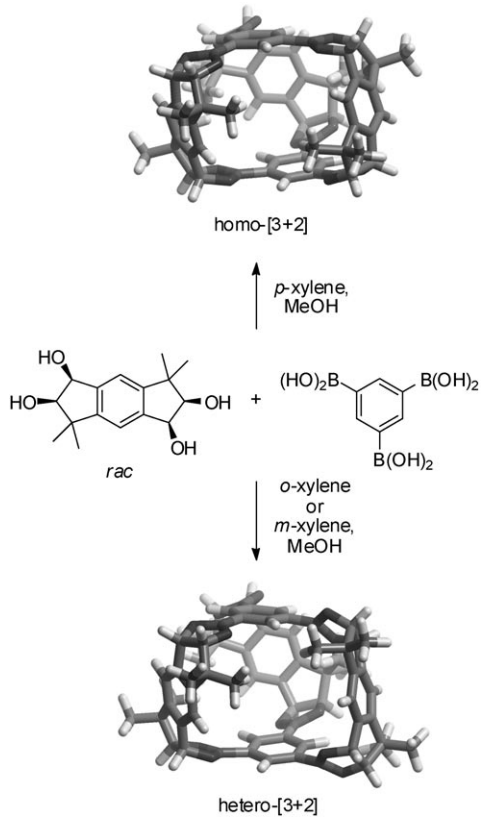
materials such as covalent organic frameworks (COFs),[46] functional polymers,[47] as well as discrete molecules, such as dendrimers.[48,49] Some examples of organic cage compounds recently synthesized by this condensation method are given below.

A [1+1] condensation of a rigid cyclotricatechylene (CTC) and a flexible hexahomotrioxacalix[3]arene trisboronic acid was reported by Kubo and co-workers (Scheme 10).[50] They found that the condensation does not occur at room temperature in a protic solution; the addition of $Et_4N^+OAc^-$ triggers the formation of a trisboronated capsule, where the cation probably functions as a template through cation–π interactions. At the same time, the counterion also plays an important role in the formation of the capsule. For example, the association constant for the formation of the capsule with $Et_4N^+OAc^-$ is one order of magnitude higher than with $Et_4N^+F^-$. Interestingly, the use of larger cations, such as nBu_4N^+, did not result in capsule formation at all; this fact was later exploited to form "empty" capsules:[51] the addition of nBu_3N to the precursors resulted in the formation of an unoccupied anionic trisboronate capsule that could complex cationic guests.

A racemic mixture of an asymmetric tetraol with 1,3,5-benzenetriboronic acids affords [3+2] cage compounds (Scheme 11).[52] Depending on the solvent, either a highly symmetric [3+2] homoproduct (all three molecules of one enantiomer) or a diasteromeric [3+2] heteroproduct (from two molecules of one enantiomer and one molecule of the other enantiomer) was formed. This diastereoselectivity was used for the separation of regioisomers of *o*, *m*-, and *p*-xylenes by precipitation.

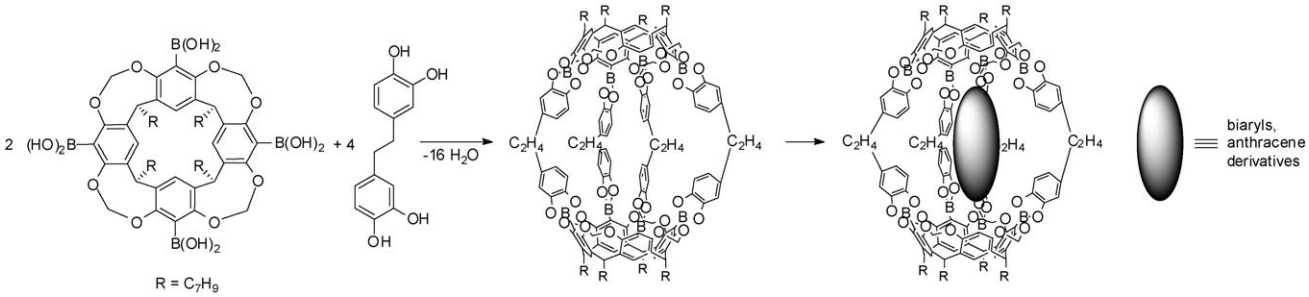


Scheme 10. [1+1] Condensation of a CTC and a homooxacalix[3]arene trisboronic acid templated by tetraethylammonium ions.[50]



Scheme 11. Solvent effect of different regioisomers of xylene on the formation of cage compounds from a racemic tetraol precursor and 1,3,5-benzenetrisboronic acid.[52]

Kobayashi and Nishimura formed large capsules by the reaction of a tetraboronic acid—a tetramethylene-bridged resorcinarene cavitand—with a flexible tetraol (Scheme 12). Various biaryls or anthracene derivatives were encapsulated as guest molecules.[53]

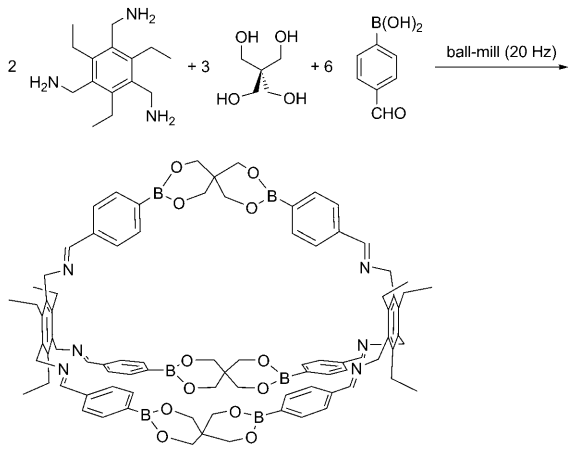


Scheme 12. [4+2] Condensation of a resorcinarene tetraboronic acid and a tetraol.[53a]

These few examples show that the formation of boronic acid esters is a versatile method for the construction of cage compounds. Until now, only a few host–guest interactions with guest molecules have been studied; this leaves room for futher investigations, especially with respect to the development of new applications.

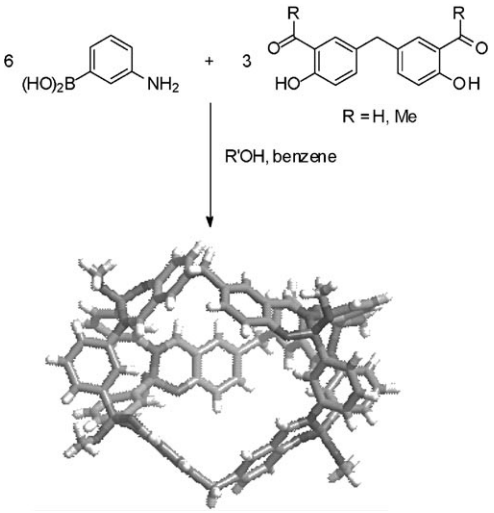
4. Cage Compounds through the Combination of Boronic Ester and Imine Bond Formation

There are a few examples that either combine both imine and boronic ester condensation[54] or involve the formation of iminoboronates.[55,56] Starting from the flexible triamine (tris-2-aminoethyl)amine (tren), pentaerythritol, and a 4-formylphenylboronic acid, Severin and co-workers were able to isolate the corresponding cage compound in 82% yield.[54a] This is quite remarkable, since 18 covalent bonds are formed in one step. Preliminary studies on the complexation of transition-metal ions showed that two copper ions are bound within the cage compound, probably at the tren subunits. The condensation reaction was generally carried out using a Dean–Stark trap. Severin and co-workers later demonstrated that the use of a ball mill in the absence of solvent resulted in the yields of the formed cage compounds increasing from 24% to 94% (Scheme 13).[54b]



Scheme 13. [2+3+6] Condensation of simple precursors to form a cage compound based on boronic acid ester and Schiff base condensations.[54b]

A [6+3] condensation of a bis(salicylaldehyde) and 3-aminophenylboronic acid or the corresponding methyl ketone in the presence of various alcohols as solvents led to 12 iminoboronate bond condensations and the formation of various cage compounds (Scheme 14).[55] Determination of

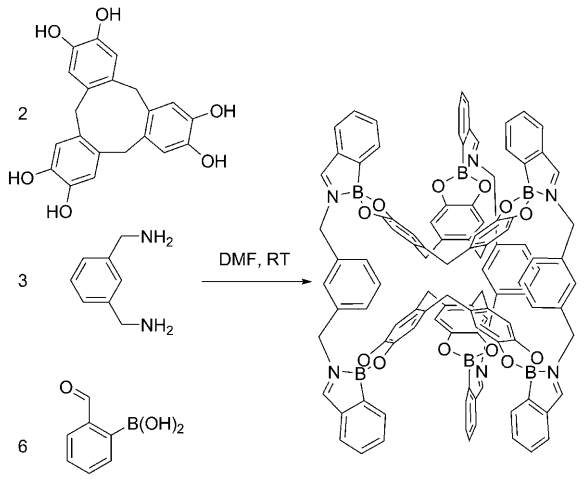


Scheme 14. [6+3] Condensation of a bis(salicylaldehyde) or the corresponding methyl ketone with a 3-aminobenzeneboronic ester. R′ = Me, Et, Pr.[55]

the X-ray crystal structure show two enclathrated benzene molecules inside the cavity of the cage compound. By mixing a tricatechylene with a 1,3-di(aminomethyl)benzene and *ortho*-formylphenylboronic acid in an NMR tube, the research group of Nitschke was able to observe the formation of an iminoboronate cage in situ (Scheme 15).[56] In a similar manner, Höpf and co-workers showed that 3-pyridylboronic acid self-assembles first to boroxine rings and then to cagelike structures, where the pyridine nitrogen atoms coordinate to the boron atoms of the previously formed boroxin rings.[57]

5. Cage Compounds through Formation of Disulfide Bridges

Although disulfide bonds are frequently used in the field of dynamic covalent chemistry,[58] only one example of the formation of a rigid, macrobicyclic cage with disulfide bonds



Scheme 15. Three-component condensation to give a cage compound with iminoboronate bonds.[56]

is known to date.[59] It was shown that the formation of the cage is reversible and it is possible to switch between the cage structure and the tripodal trissulfide precursors. Horng et al. grew suitable single crystals for X-ray diffraction (Figure 4); when the formation of the disulfide bond was carried out in DMF, one solvent molecule was enclathrated inside the cavity.

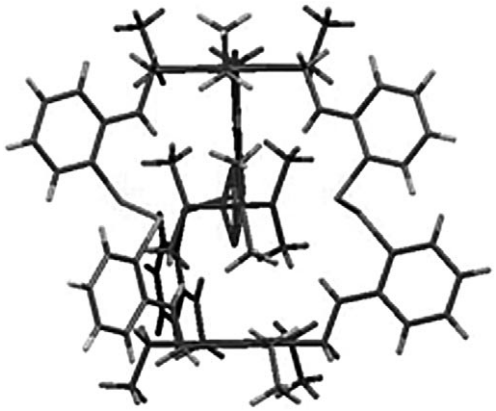
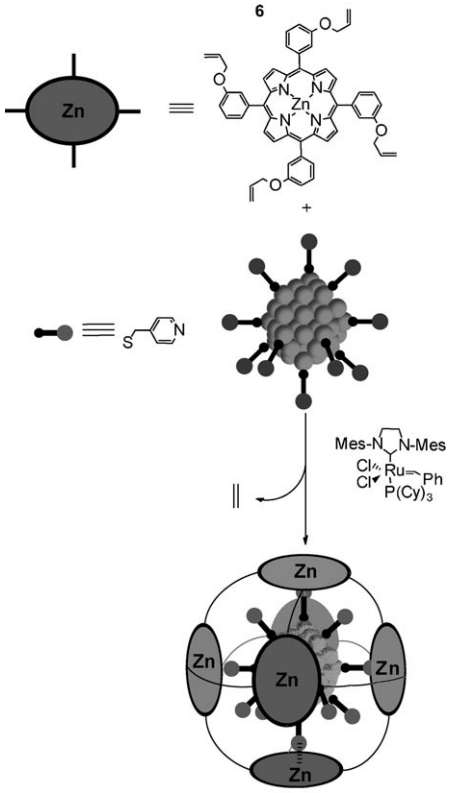


Figure 4. X-ray crystal structure of the disulfide cage compound. The complexed DMF molecule (disordered) can be clearly seen inside the cavity.[59]

6. Cage Compounds through Alkene Metathesis

Alkyne and alkene metathesis is a powerful synthetic tool for the synthesis of shape-persistent macrocycles from rather simple precursors.[60] This construction principle has not been used extensively for the formation of three-dimensional structures. One example from Inomata and Konishi shows that Au_{55} clusters were incorporated into a cage compound built up from six zinc porphyrin units (Scheme 16).[60] The porphyrin rings were attached to the Au_{55} surface via 4-methylthiolpyridine, which ligates the zinc metal through the pyridine nitrogen atom and the gold surface through the



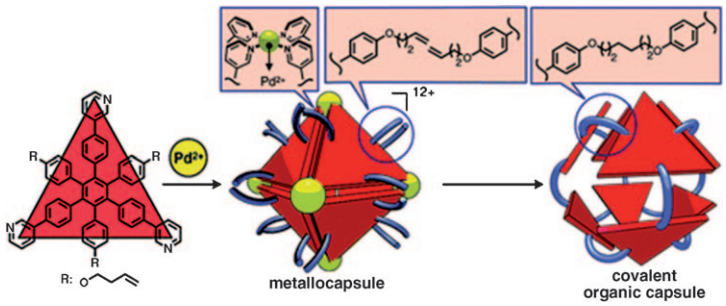
Scheme 16. Synthesis of Au_{55} clusters stabilized by a zinc porphyrin cage.[60] Cy = cyclohexyl, Mes = 2,4,6-trimethylphenyl.

thiolate sulfur atom. A subsequent ruthenium-catalyzed alkene metathesis of the terminal flexible alkene moieties at the periphery of the porphyrin rings closed the shell covalently. It was later shown that the analogous complex formed between the gold cluster and a manganese porphyrin could be used for the polymerization of styrene.[61]

Another approach was used by Shionoya and co-workers to synthesize cage compounds by alkene metathesis,[62] wherein eight tripodal pyridine ligands first generated a supramolecular octahedron through coordination with palladium(II) ions. The triangular sides of the octahedron were then "joined" to one another through olefin metathesis and the palladium ions were removed with DMF. The pyridine nitrogen atoms were subsequently "blocked" by methylation (Scheme 17).

7. Cage Compounds through Resorcinol/Aldehyde Condensation

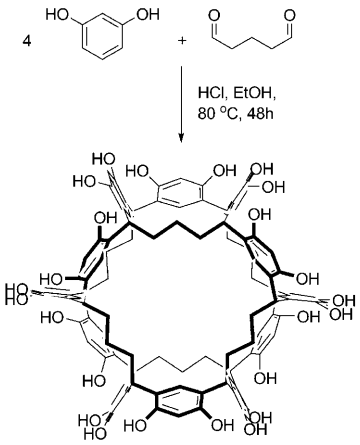
Gutsche et al. found by deuteration experiments that the transformation of calix[8]arenes into calix[4]arenes at high temperatures occur by the dynamic covalent-bond formation of small units rather than by molecular mitosis.[63] Possibly, the calix[8]arene macrocycle breaks down at the high temperatures into eight molecules of *ortho*-quinomethane, which then recombine to form calix[4]arene. This is probably true for any kind of hydroxybenzene/aldehyde condensation that



Scheme 17. Synthesis of an organic covalent cage compound in three steps. 1) Formation of an octahedral coordination cage through square-planar complexation of palladium(II) ions (yellow); 2) alkene metathesis; and 3) removal of the palladium(II) ions. Reproduced from Ref. [62] with permission from the American Chemical Society.

results in the formation of well-defined larger molecules as products, as is the case in the following example.

A molecular waterwheel (so called "noria") was synthesized in one step and in high yield by the condensation of resorcinol and 1,5-pentanedial in the presence of hydrochloric acid as catalyst (Scheme 18).[64] The reaction was monitored



Scheme 18. One-pot synthesis of the "molecular waterwheel" by condensation of resorcinol and 1,5-pentanedial.[64]

by size-exclusion chromatography (SEC), which clearly showed that some polymer and higher molecular weight oligomers were generated at the beginning of the reaction. Only small amounts of polymer and oligomer were present after 48 h, thus proving that the noria is the thermodynamically favored product of a VCL. The Boc-protected noria is used as a molecular glass resist in supercritical carbon dioxide.[65] Recently it was shown that particles of noria selectively take up CO_2 over H_2 and N_2.[66]

Conclusions and Future Perspectives

The concept of dynamic covalent bond formation was succesfully adopted for the synthesis of (functional) organic cage compounds. Since Cram and co-workers introduced reversible imine condensation for the construction of cage compounds at the beginning of the 1990s, the number of publications has increased significantly. The main building unit for the construction of the cage compounds is the imine bond, although the condensation of boronic acid esters is also used. To date, other binding motifs, such as disulfides, alkenes, and alkynes, which have been investigated thoroughly in other research areas of dynamic combinatorial chemistry, have been used only seldomly. There is still a lot of room for further developments.

Although most of the contributions discussed above show that the cage compounds have interesting features (for example, the recognition of guest molecules, porosity for gas uptake), new applications could be addressed in the future, for example, for catalysis, as containers for uncommon reactions, or as drug shuttles for pharmaceutically active molecules, where the cage compounds are cleaved at the desired spot into "harmless" metabolites and the active compound is released.

Other questions still need to be addressed. How much information is necessary within the precursor molecules to form such assemblies (rigidity, bonding motifs etc.)? A major goal will certainly be predicting the resulting structure of complex cage compounds just from the information obtained from the precursors. What is the limitation in terms of size and complexity?[67] Until now, the maximum number of components that have been used for the building of one molecular cage is three. The number of different bond types is two (if additional supramolecular interactions are not taken into account). Orthogonal binding motifs (supramolecular and covalent dynamic) are already used in combination to construct sophisticated arrangements such as Borromean rings.[24] However, the question remains: Will a combination of more orthogonal reversible bond formations lead to the construction of more complex targets? Since this research area is quite young and an enormous number of precursors are readily accessible synthetically, we can expect interesting and striking contributions from this field of research.

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