Self-assembled Architectures from Glycoluril

Johannes A. A. W. Elemans, Alan E. Rowan, and Roeland J. M. Nolte*

Department of Organic Chemistry, NSR Center, University of Nijmegen, Toernooiveld, 6525 ED Nijmegen, The Netherlands

The controlled self-assembly of derivatives of the concave building block glycoluril into three-dimensional architectures of well-defined shape and dimension is discussed. It is shown that the hexameric glycoluril macrocycle cucurbituril can be applied to construct a variety of oligo- and polyrotaxane assemblies. In a different approach, bis(glycoluril) compounds have been used to form "tennis ball"- and "softball"-like assemblies which can complex small guest molecules in their inner compartment and carry out reactions between them. Finally, the self-assembling properties of molecular clip receptors based on glycoluril are discussed. These clips can be modified in such a way that assemblies of well-defined shape and nanosized dimension, such as "golf balls", "razorblades", and "cigars", are formed in water.

Introduction

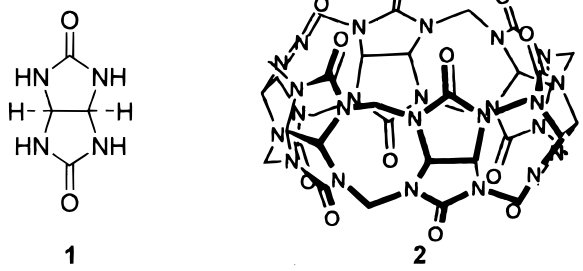
The controlled self-assembly of simple low molecular weight compounds into predictable and functional architectures is an exciting challenge facing today's chemists.[1−3] Self-assembly usually involves the design and synthesis of building blocks that contain specific information needed for intermolecular recognition processes, viz., hydrogen-bonding, π-stacking, van der Waals, and electrostatic interactions. By means of complementarity and directed attractive forces, in combination with entropically driven processes involving solvent molecules, the assembly of these building blocks can lead to organized structures of nanosized dimensions. Numerous predesigned supramolecular assemblies are known which are based on two-dimensional hydrogen-bonding arrays, e.g., tapes and sheets.[4] To assemble molecules into a three-dimensional architecture, additional structural information, e.g., curvature, is needed. Excellent examples of this are the self-assembling calixarenes of Reinhoudt[5] and the peptide nanotubes of Ghadiri.[6]

It is the aim of this paper to give an account of controlled self-assembly phenomena which involve one particular building block, viz., glycoluril (**1**, Chart 1), a molecule with an intrinsically rigid and curved structure. Over the past years glycoluril has been utilized in the synthesis of oligo- and polyrotaxanes, the formation of molecular capsules, and the self-assembly of water-soluble molecular clip receptors into well-defined nanostructures. It has been demonstrated that by incorporation of specific groups in the building blocks control can be obtained over the size and shape of the assemblies and to some extent over their function.

Cucurbituril Rotaxanes

The story of the glycoluril building block **1** goes back to research carried out in 1905, when Behrend et al. published the results of an acid-induced condensation reaction of urea, glyoxal, and formaldehyde.[7] A product characterized as $C_{10}H_{11}N_7O_4 \cdot 2H_2O$ was obtained; a structure for it was, however, not offered. The compound proved to be very stable toward strong acids and bases, and it was found to form crystalline complexes with a variety of metal salts. It was only in 1981, when

Chart 1



Freeman et al. solved the crystal structure of the calcium bisulfate complex of **2**, that it became clear that the compound was a cyclic hexamer of glycoluril units linked by methylene bridges (Chart 1).[8] It was named "cucurbituril" because of its resemblance to a pumpkin (Latin name: *cucurbita*).

A remarkable feature of cucurbituril is its internal cavity with a diameter of approximately 5.5 Å, which is accessible via two portals of 4 Å width. As a consequence of this architecture, the macrocycle has been used as a receptor for a variety of (di)ammonium ions,[9,10] and more recently the groups of Buschmann and Kim have carried out some very elegant studies on the self-assembly of cucurbituril molecules into (poly)rotaxane structures. Buschmann has described the construction of bipyridinium−cucurbituril pseudorotaxanes[11] and also the synthesis of polyrotaxanes with cucurbituril as the circular component and polyamides as the linear chain.[12] The recurring theme in Kim's work is the very efficient threading of the dication *N*,*N*′-bis(4-pyridylmethyl)-1,4-diaminobutane dihydronitrate or -chloride **3** in the cucurbituril macrocycle. The pseudorotaxane **4**, which is obtained in 83% yield by just simply stirring the two components in an aqueous solution, is the exclusive and stable product (Scheme 1).[13] The pyridine functions on both termini of the linear component allow coordination to transition metals, resulting in the formation of oligo- and polyrotaxanes of which the morphology is strongly dependent on the metal coordination geometry. Reaction of pseudorotaxane **4** with $Cu(NO_3)_2$ gave a coordination polymer, the chain of which is composed of alternating copper ions and **4**.[14] Its crystal structure showed that the polymer had a "zigzag"

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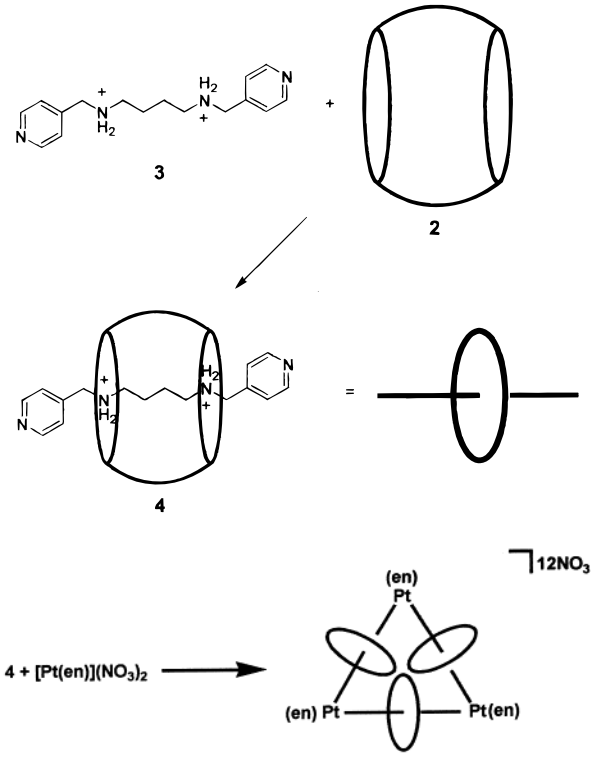
Scheme 1



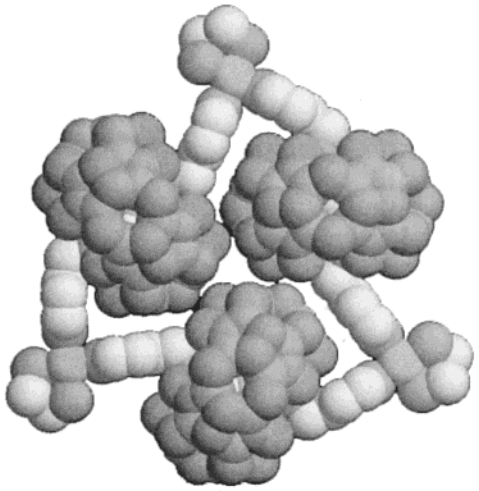
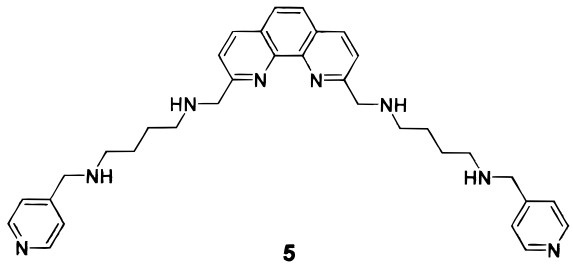


Figure 1. Crystal structure of the [4]rotaxane molecular necklace formed by the reaction of **4** and $[Pt(en)](NO_3)_2$. Reprinted with permission from *J. Am. Chem. Soc.* **1998**, *120*, 4899−4900. Copyright 2000 American Chemical Society.

shape due to the cis coordination of the pyridine ligands at the copper centers.

Similar to the strategy of the synthesis of circular metalloassemblies by Fujita and Ogura[15] and Stang and Olenyuk,[16] reaction of **4** with $[Pt(en)](NO_3)_2$ (en = ethylenediamine) resulted in the nearly quantitative one-pot synthesis of a so-called "molecular necklace", consisting of a cyclic trimer of **4**, cis-connected at the corners by platinum centers.[17] Its crystal structure determination (Figure 1) confirmed this four-component structure and suggested, furthermore, that van der Waals interactions between the outsides of the cucurbituril rings strongly favor the efficient formation of the "necklace". A five-component necklace was also prepared, however using a different approach. A new,



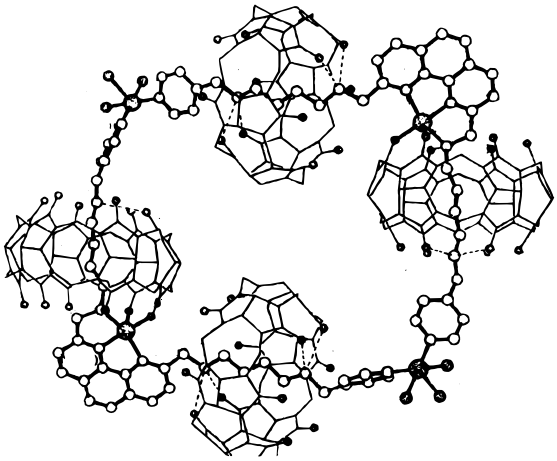
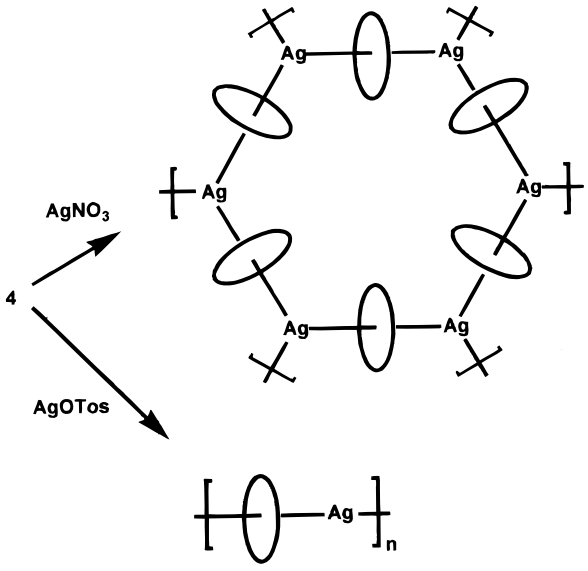


Figure 2. Crystal structure of the [5]rotaxane molecular necklace based on **5**, cucurbituril and $Cu(NO_3)_2$. Reprinted with permission from *Angew. Chem., Int. Ed.* **1999**, *38*, 638−641. Copyright 2000 Wiley−VCH.

Scheme 2



L-shaped linear component **5** was designed, based on 1,10-phenanthroline, to which 2 equiv of cucurbituril was added (Figure 2). The resulting [3]pseudorotaxane was reacted with $Cu(NO_3)_2$ to give the five-membered molecular necklace, confirmed by its X-ray structure.[18]

The reaction of **4** with $AgNO_3$ as the coordinating metal salt resulted in an entirely different architecture, viz., a network consisting of large edge-sharing hexagons, which are chair-shaped having a silver ion at each corner and a molecule of **3** at each edge connecting two silver ions (Scheme 2).[19] Every edge is tightly holding a cucurbituril macrocycle. The polyrotaxane network

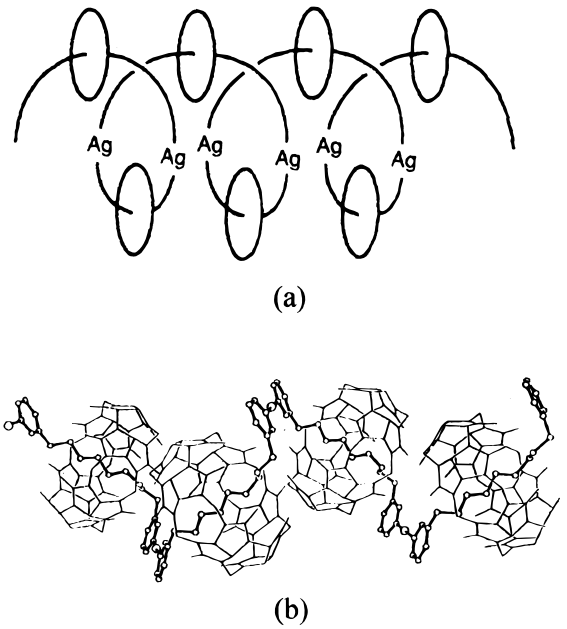


Figure 3. (a) Schematic representation of a helical polyrotaxane based on cucurbituril and the 3-pyridylmethyl derivative of **4** and (b) part of its crystal structure. Reprinted with permission from *Chem. Commun.* **1997**, *120*, 2361−2362. Copyright 2000 The Royal Society of Chemistry.

forms layers stacked on top of each other with an interplane separation of 9.87 Å. In the formation of these silver-based assemblies, it is easy to illustrate the consequences of small changes in the components which can be quite dramatic. For example, when, instead of nitrate anions, tosylate anions are used, only a one-dimensional (1D) coordination polymer is formed (Scheme 2). When the pyridyl groups in the linear unit **3** are connected to the chain at the 3-position instead of the 4-position, a 1D coordination polymer arranged in a helical fashion is generated (Figure 3).[20]

The main key to the successful assembly of these cucurbituril rotaxanes is the high affinity between the macrocycle and the diamino linear component. In addition, the highly symmetrical structure of cucurbituril, which sets this molecule apart from, e.g., cyclodextrins, helps to form polyrotaxanes and networks with a high structural fidelity.

Molecular Capsules

The insolubility of the cucurbituril macrocycle in most common organic solvents restricts its use as a receptor molecule to strongly acidic solutions. Attempts to solubilize the molecule by derivatizing it at its periphery with lipophilic groups, such as methyl or phenyl, were unsuccessful primarily for steric reasons. The monomeric glycoluril unit, however, turned out to be a very versatile building block for the construction of 3D receptors. During the past 5 years, the literature concerning the self-assembly of glycoluril-based host molecules has been dominated by the work of Rebek[21−23] and Nolte.[24,25] The former group investigated the self-assembly of a bis(glycoluril) building block into a "molecular tennis ball".[26] This well-defined, pseudo-spherical capsule consists of two identical building blocks **6** (Figure 4), which were prepared by reacting tetrabromodurene with a large excess of diphenylglycoluril. Although the yield of this reaction is relatively low because of the formation of large amounts of polymeric material, the desired product can be obtained in nearly pure form by simple extraction of the crude product with chloroform.

Compound **6** has several hydrogen bond donor and acceptor functionalities and has an intrinsic rigid curvature. The capsule **6**−**6** is stabilized by a seam of eight hydrogen bonds. It has the shape of a tennis ball and is formed both in solution and in the solid state (Figure 4).[27] In solution, small guests, such as methane[28] and xenon,[29] can be included in its cavity. The occluded guests exhibit properties different from those outside the capsule.

In the development of larger capsules, it is important to rationally design molecules which, despite their larger dimensions, can still form self-complementary hydrogen-bonding networks. This was accomplished by Rebek's group when three instead of two glycoluril units were coupled to a central aromatic framework to give molecule **7** (Figure 5).[30,31] Two molecules of **7** self-assemble to give a capsule **7**−**7**, which has an aromatic ceiling and floor and is held together by a seam of 12 hydrogen bonds. This capsule, because of its flattened shape, was given the name "jelly doughnut". It appeared to be an ideal host for cyclohexane, which according to molecular modeling fitted perfectly in the cavity. The binding of this guest is enthalpically driven by favorable CH−π interactions between the axial hydrogen atoms of the guest and the aromatic surfaces of the capsule. Because of these interactions, the ring-inversion barrier of an encapsulated cyclohexane guest was found to be 1.25 kJ/mol higher than that of a free cyclohexane molecule.

In another case, two glycoluril units were connected across as many as nine ring systems, of which the central one contained an ethylene bridge function that supplied the required curvature for hydrogen bonding. Structures **8a** and **8b** were found to dimerize, forming a capsule resembling a "softball", held together by eight hydrogen bonds (Figure 6a,b). For these molecules, the information encoded within the monomer allows, however, higher aggregates to be formed as well.[32,33] Be-

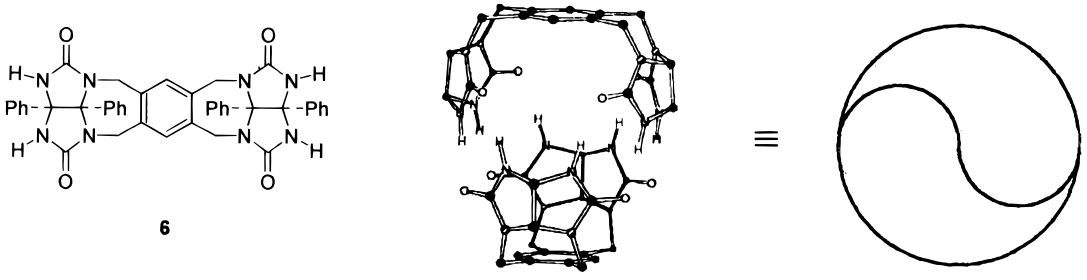


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Figure 4. Assembly of two molecules of **6** into a self-assembled capsule resembling a tennis ball. Reprinted with permission from *J. Am. Chem. Soc.* **1995**, *117*, 85−88. Copyright 2000 American Chemical Society.

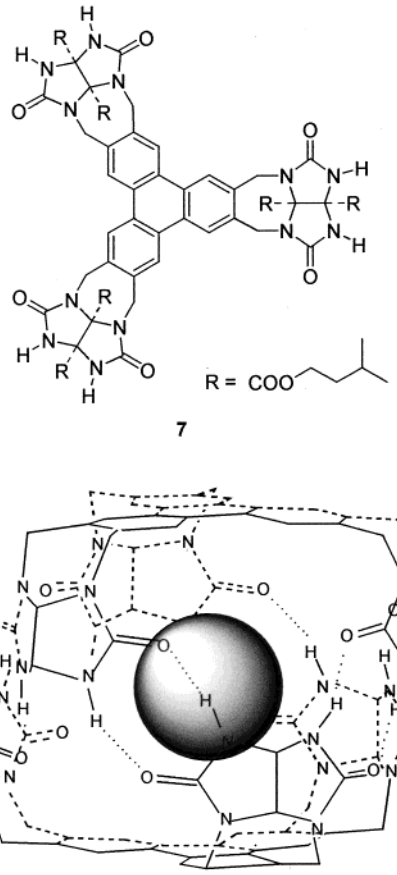
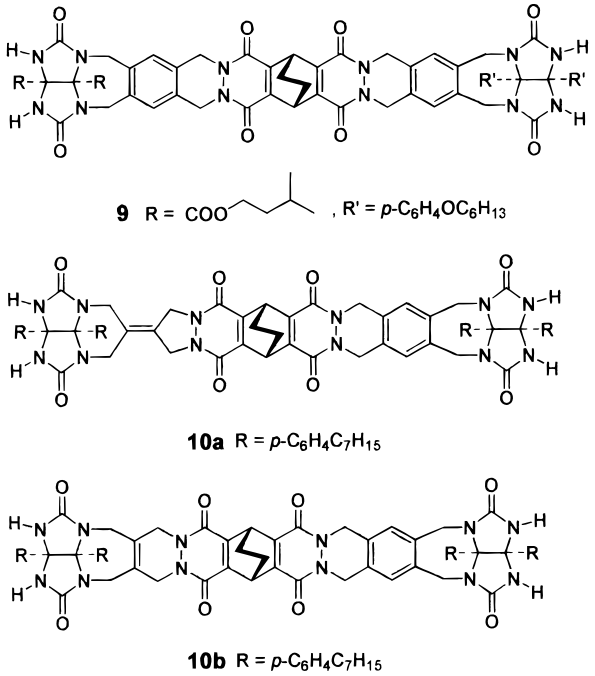


Figure 5. Assembly of two molecules of **7** into a dimer resembling a jelly doughnut. The gray sphere represents an encapsulated cyclohexane molecule.

cause of this, glycoluril derivative **8c** was designed and synthesized. It has four additional hydrogen-bonding donor groups, as a result of which the capsule dimer is favored over other assemblies.[34] Interestingly, guest encapsulation by **8c**−**8c** appears to be entropy-driven; i.e., the association constant increases with temperature. This is an unexpected result, because most host−guest complexation processes in organic solvents are

Chart 2



entropically unfavorable and enthalpy-driven. It is proposed that upon binding one guest, such as adamantane or ferrocene in **8c**−**8c**, two molecules of solvent which are present in the cavity are released, resulting in a favorable increase in entropy. Additional evidence for this binding mechanism comes from studies on **8c** in a mixture of fluorobenzene and hexadeuteriobenzene. NMR spectroscopy revealed that in this solvent mixture three different capsule species are present, confirming that two solvent molecules are encapsulated within one dimer.

A very interesting consequence of two solvent molecules occupying the cavity of **8c**−**8c** is the opportunity to use the capsule as a microreactor for bimolecular reactions. An example is depicted in Figure 6c, viz., the Diels−Alder reaction between *p*-benzoquinone and cyclohexadiene.[35,36] In a *p*-xylene-d_{10} solution, the rate of

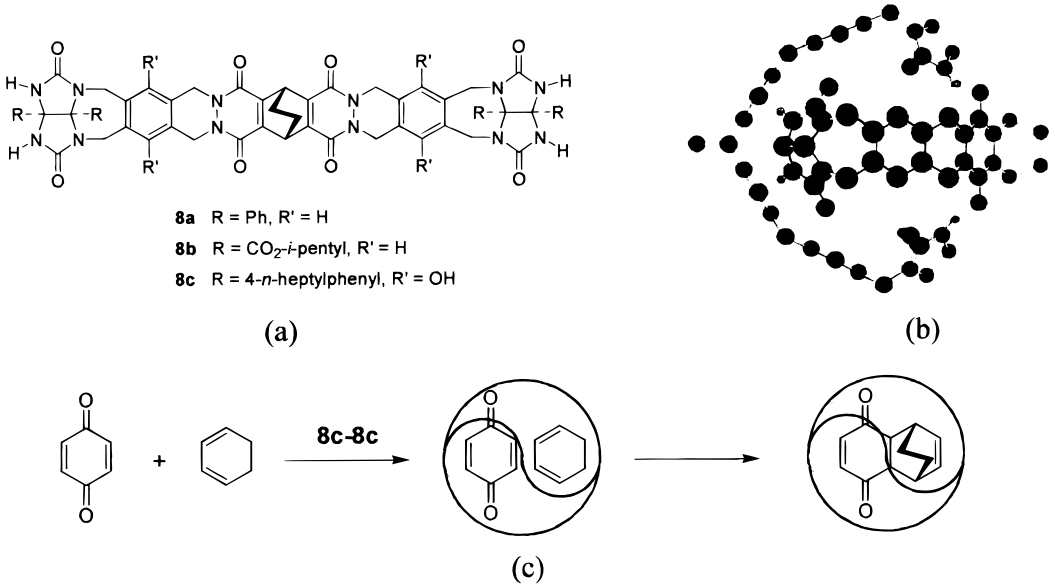


Figure 6. (a) Bis(glycoluril) compounds that form softball-like dimers. (b) Computer-modeled structure of the softball formed by two molecules of **8a**. (c) Schematic representation of the Diels−Alder reaction between cyclohexadiene and *p*-benzoquinone in the microreactor **8c**−**8c**. Reprinted with permission from *J. Am. Chem. Soc.* **1997**, *119*, 77−85. Copyright 2000 American Chemical Society.

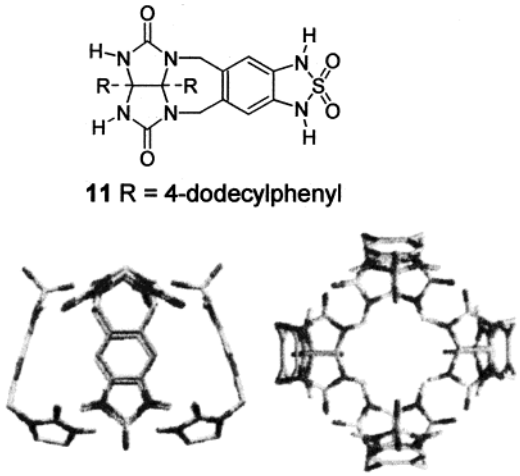


Figure 7. Assembly of four molecules of **11** into a tetramer resembling a football (left, side view; right, top view). Reprinted with permission from *Science* **1998**, *281*, 1842−1845. Copyright 2000 American Association for the Advancement of Science.

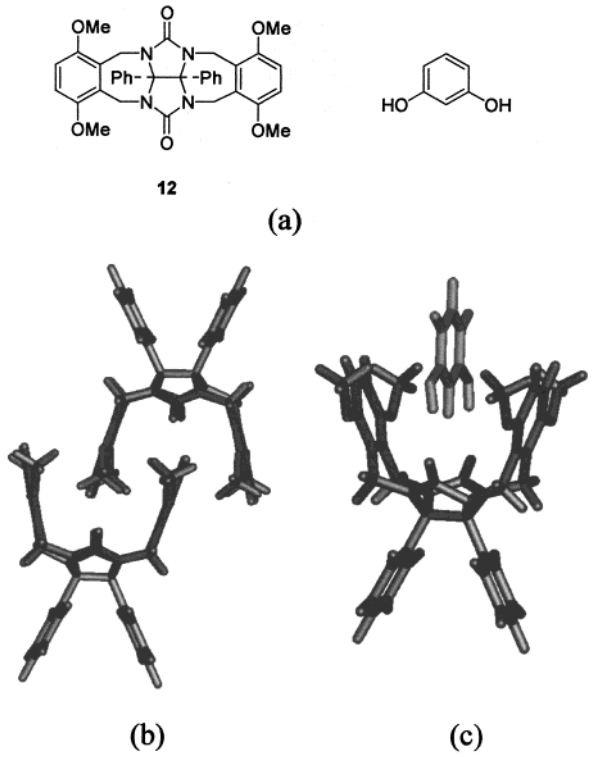
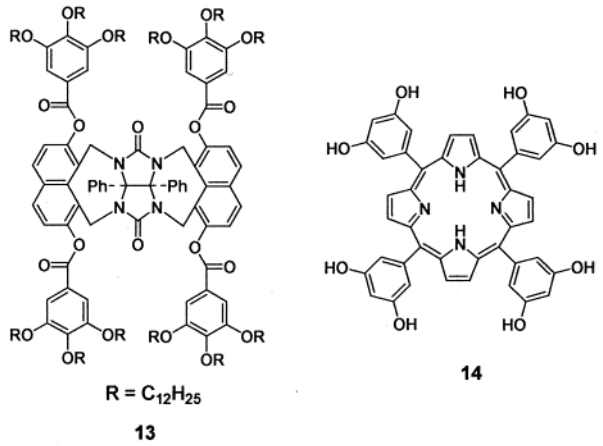


Figure 8. (a) Structures of clip **12** and a dihydroxybenzene guest. (b) X-ray structure showing the dimeric packing of two molecules of **12**. (c) Computer-modeled representation of the host−guest complex between **12** and a dihydroxybenzene guest.

this reaction is 200 times higher in the presence of the **8c**−**8c** capsule. This can only be explained if it is assumed that both starting compounds are complexed within the capsule and that, because of their close proximity, the rate of reaction is enhanced. Because of the restricted space inside the capsule, the endo isomer is the exclusive product of the Diels−Alder reaction. Control experiments prove that the acceleration of the reaction is solely the result of the encapsulation of the reaction components in the capsule. In contrast, when 1,4-naphthoquinone, a molecule that does not fit in the capsule, is used as the dienophile, the reaction is not accelerated. Not unexpectedly, turnover in the catalytic reaction is a problem because of product inhibition, because the resulting product fits perfectly in the



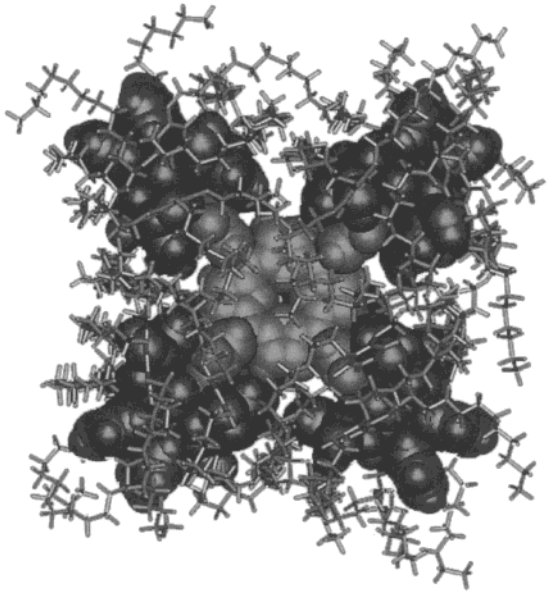


Figure 9. Computer-modeled structure of the 4:1 complex between host **13** and porphyrin guest **14**.

capsule ($K_a > 10^5$ M^{-1}). To make the capsule a true catalyst, product release is necessary, and this was accomplished by using 2,5-dimethylthiophene dioxide as the diene in the cycloaddition reaction with *p*-benzoquinone. The Diels−Alder product does not perfectly fit within the capsule and is thus immediately replaced by new reactants.[37]

The most recent achievements in capsule chemistry concern the introduction of chirality. The two glycoluril moieties forming the softball were modified with different groups on their convex side (**9**, Chart 2).[38] Upon dimerization, a racemate of two enantiomeric capsules is formed. The chirality introduced at the outside of the capsule has, however, no influence on the stereoselective binding of chiral guests. For enantiomeric discrimination, chirality inside the capsule is needed, and this was accomplished by the synthesis of softball derivatives **10a** and **10b**, which have their glycoluril moieties linked by unsymmetrical spacers.[39] The monomers themselves are achiral, but upon dimerization a racemate of two enantiomeric capsules with a chiral inner space results. When the dimerization is induced by the addition of an enantiomerically pure guest, e.g., camphor, one of the enantiomers of the capsule is preferentially formed over

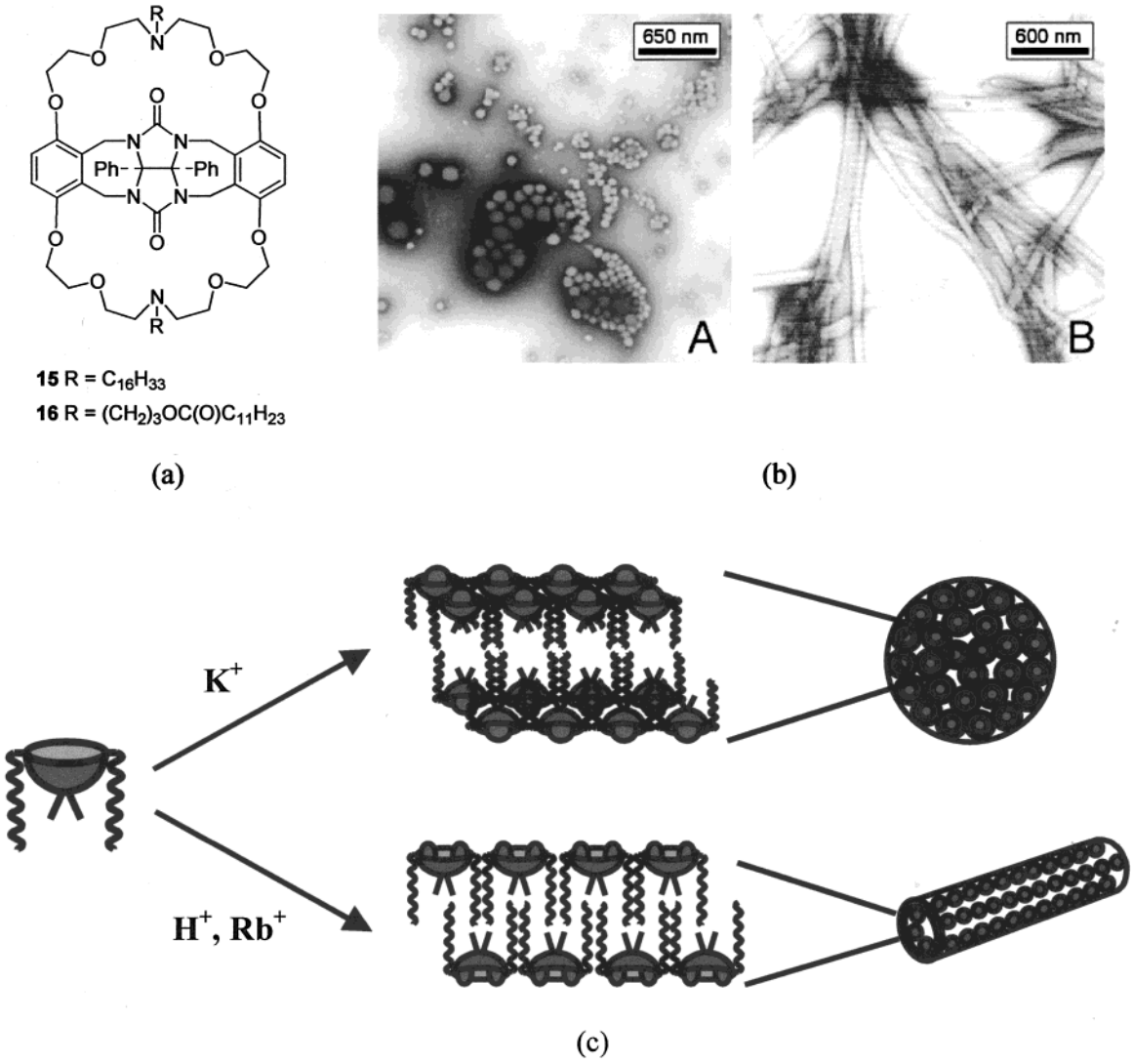


Figure 10. (a) Amphiphilic baskets **15** and **16**. (b) TEM micrographs of aggregates formed by **15** in water (A) and of aggregates formed by **16** in an aqueous H^+ or Rb^+ solution (B). (c) Proposed structures of the aggregates of **16** in the presence of K^+, H^+, or Rb^+. Reprinted with permission from *Acc. Chem. Res.* **1999**, *32*, 995−1006. Copyright 2000 American Chemical Society.

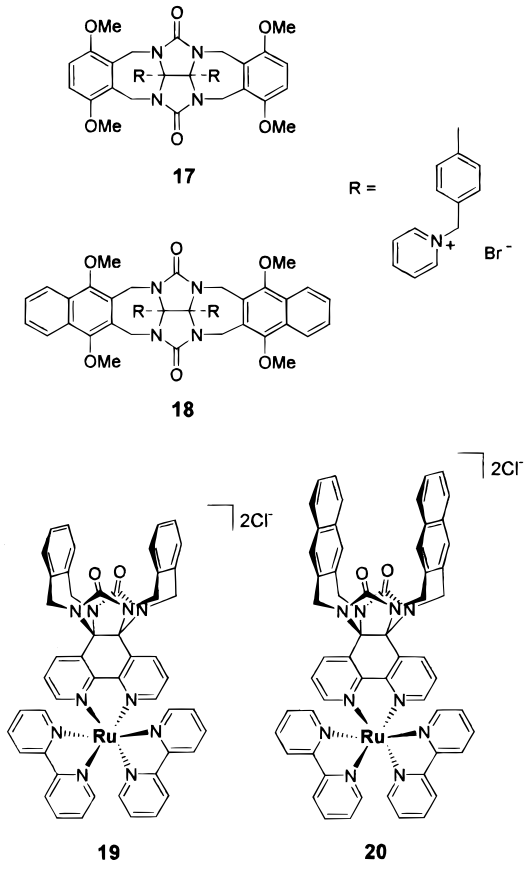
the other one. Depending on the guest, host−guest complexes with a diastereomeric excess up to 35% can be formed.

Finally, capsules which are composed of more than two self-complementary building blocks could be constructed by the self-assembly of four molecules of **11** into a cyclic tetramer $\mathbf{11}_4$, which is stabilized by a pattern of 16 hydrogen bonds[40] (Figure 7). In the assembly, the four molecular units are arranged in a "head-to-tail" fashion, which enables ideal geometries and distances between the various hydrogen bond donors and acceptors. In addition, the most acidic hydrogen bond donors (the sulfamide N−H protons) are paired in this way with the most basic hydrogen bond acceptors (the glycoluril carbonyl oxygen atoms). Unlike in the case of the softball, the "football", as the assembly of $\mathbf{11}_4$ was named, was not formed in benzene or a *p*-xylene solution. Only when an appropriate guest, such as adamantane, was added to a suspension of **11** in dichloromethane was a capsule generated which contained an encapsulated adamantane molecule. Because the exchange of free and encapsulated guest was slow on the NMR time scale, an apparent association constant could be calculated from the integration of the NMR signals; this association constant amounted to K_a(app) = 19 M^{-1}. When a guest containing hydrogen-bonding acceptors, e.g., adamantane-2,6-dione, was added, higher binding constants were measured (K_a(app) = 3200 M^{-1}), which suggests that the guest is also forming hydrogen bonds with the hydrogen bond donors in the capsule.

Molecular Clips

Over a period of 15 years, our group has also been exploring a wide variety of receptors (molecular clips) based on glycoluril.[24,25] Molecules of type **12** (Figure 8) possess a well-defined and rigid U-shaped cavity, which is formed by the glycoluril framework and two aromatic side walls. With their preorganized cleft, molecular clips are ideal receptors for 1,3-dihydroxybenzene guest molecules in a chloroform solution.[41] Binding of the guest is the result of three factors: (i) hydrogen bonding between the guest's phenolic OH groups and the carbonyl groups of the clip, (ii) $\pi-\pi$ stacking interactions between the aromatic ring of the guest and the two side walls of the clip, and (iii) a so-called "cavity effect", which is the entropically favorable filling of the empty cavity of the clip by the guest (Figure 8c).[42] Many variations in the clip structure have been studied, such

Chart 3



as changes in the urea carbonyl groups,[43] changes in the cavity side walls,[44] and more recently also changes in the glycoluril framework.[45] As a result, the precise factors which determine guest binding and the relative contribution of hydrogen bonding, $\pi-\pi$ interactions, and cavity effects have been quantified.[42] Depending on the nature of the clip and the 5-substituent on the guest, association constants larger than $K_a = 10^6$ M^{-1} in $CDCl_3$ have been measured.

Initially, we used this host−guest binding property to develop biomimetic catalysts which display substrate selectivity in oxidation[46] and hydrogenation[47] reactions. More recently this property was applied to create well-defined nanosized materials. A clip (**13**) with twelve long hydrocarbon tails was designed and synthesized, with the aim to introduce liquid crystalline (L. C.) properties in the host (Figure 9).[48−50]

Despite the fact that **13** itself was not liquid crystalline, its complexes with a variety of guests turned out to be mesogenic over wide temperature ranges. One of the host−guest complexes studied was the 4:1 complex of **13** with porphyrin **14**. It displayed liquid crystalline behavior from 17 to 149 °C, and when instead a nonbinding porphyrin was used, no mesophases were observed, confirming that the host−guest complex is the mesogenic species. Not only were the material properties of the porphyrin changed but also its redox properties. Electrochemical studies revealed that the porphyrin core is encapsulated in the 48 hydrocarbon tails of the four clips, forming a well-defined nanostructure with a dimension of approximately 7 × 7 nm. The reduction potentials of the porphyrin appeared to have altered in a way reminiscent of certain porphyrin-containing enzymes, such as cytochrome P450 and cytochrome C.

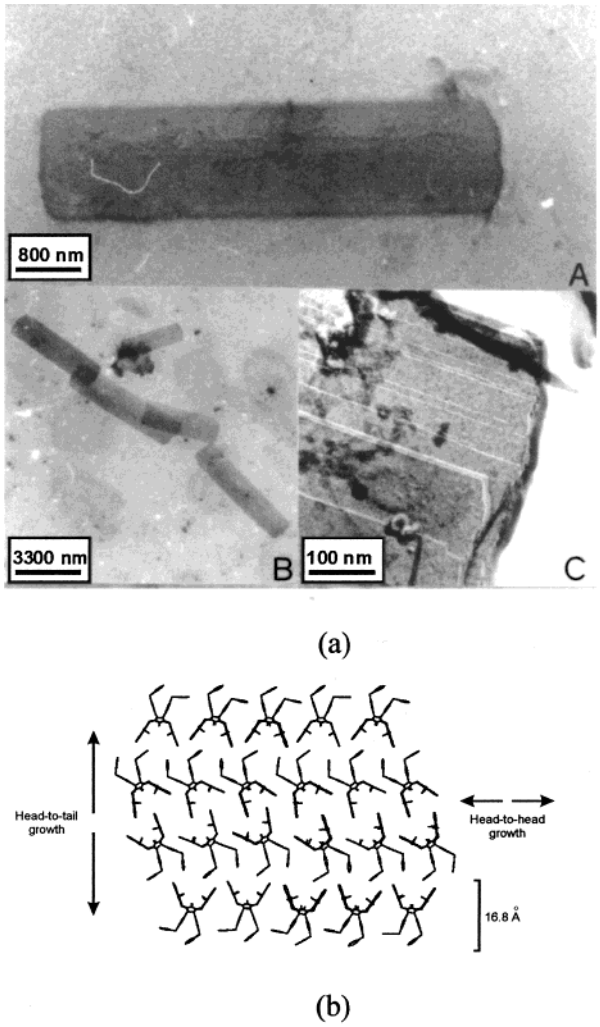


Figure 11. (a) Razorblade-like aggregates formed by **18**: TEM micrographs obtained by the platinum shadowing technique (A and B) and a freeze fracture TEM micrograph (C). (b) Proposed structure of the aggregate.

Around the same time as the groups of Rebek and De Mendoza began their investigations on self-assembling capsules, our group was investigating the assembly behavior of water-soluble clip receptors. Initially, long hydrocarbon tails were attached to the nitrogen atoms of azacrown ether functionalized clips, to give "molecular baskets" **15** and **16** (Figure 10). Upon dispersion of **15** in water, well-defined vesicles with diameters between 500 and 4000 Å were formed.[51] It is assumed that in these vesicles the charged receptor cavities are pointing toward the water layer. These "supramolecular golf balls", as they became known, were able to bind guests, such as magneson [4-[(4-nitrophenyl)azo]resorcinol], in their dimples. UV titrations indicated that below the critical aggregation constant (cac) of the compound 1:1 host−guest complexes ($K_a = 10^6$ M^{-1}) were formed. Above the cac, the titration data could only be fitted by assuming a 2:1 host−guest complex ratio. It was therefore concluded that above the cac only the receptors on the outside of the vesicle were able to bind magneson and that the internal receptors could not be accessed by the guests.

Host **16** was found to give tubelike assemblies with a diameter of 100 nm in aqueous HCl and vesicles in an aqueous KCl or NaCl solution.[50] The morphology of these superstructures could be manipulated by the

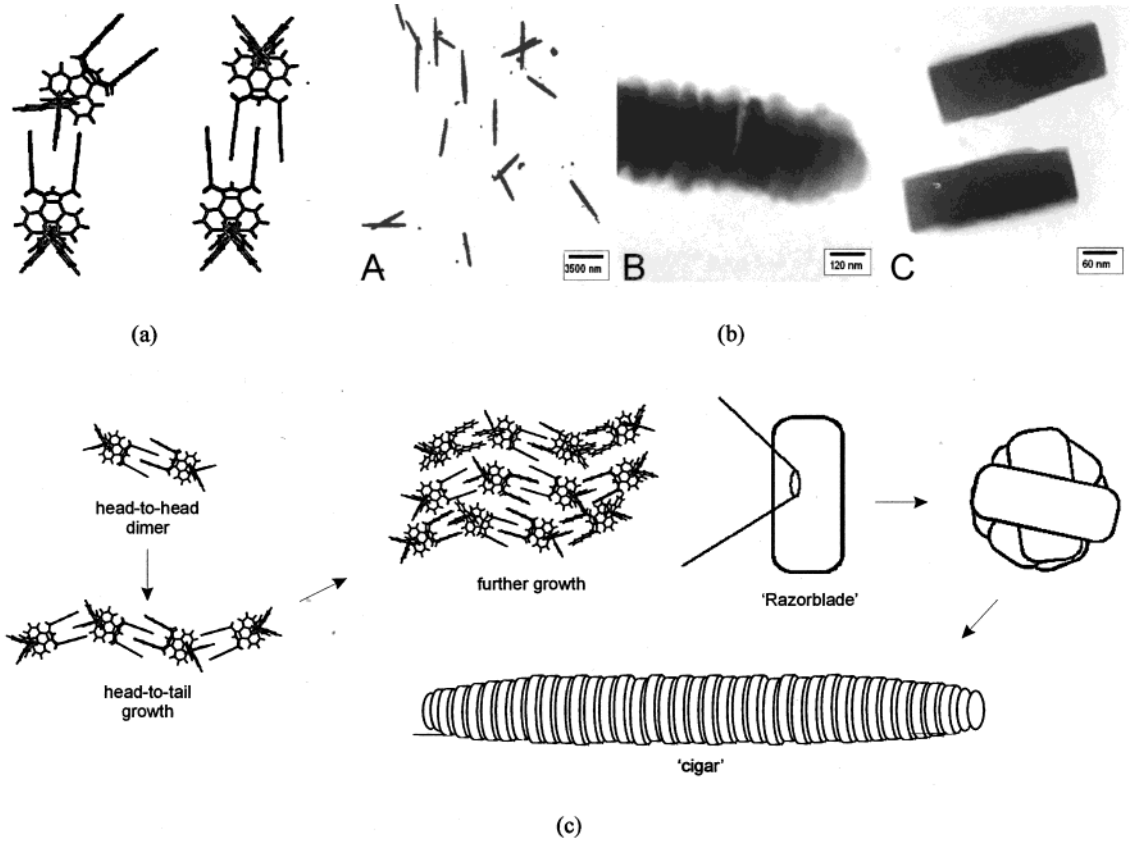


Figure 12. (a) Computer-modeled representations of the head-to-tail and head-to-head self-association geometries observed for **20**. (b) TEM micrographs of aggregates formed by **20**: (A) cigar-like aggregates; (B) magnification of a cigar showing its segmented structure; (C) razorblade-like subaggregates. (c) Proposed growth mechanism of the aggregates.

addition of different cations, such as Rb^+, which resulted in the formation of a mixture of tubes and vesicles, or Cs^+, which gave nanotubes.

More recently, it was discovered that also molecular clips without long tails can display self-association and ultimately self-assembly. In the absence of guest molecules, clip **12** was found to dimerize in chloroform as a result of cavity-filling effects and favorable intermolecular electrostatic interactions.[52] In the dimer, the side wall of one clip molecule is bound in the cavity of its dimeric partner and vice versa (Figure 8b). This dimerization, although relatively weak in a chloroform solution ($K_{dimer} = 16\ M^{-1}$), is also observed in the crystal structure of a wide range of clip molecules.

To utilize the property of the clips to dimerize, new water-soluble derivatives were designed and synthesized.[53] It was thought that the dimerization might be favored by utilizing the hydrophobic effect as a driving force for the self-assembly.[54] Pyridinium-functionalized clip **17** (Chart 3) was found to dimerize in water with a dimerization constant $K_{dimer} = 300\ M^{-1}$, a value which indeed is much higher than that observed for **12**. In the case of the naphthalene-walled clip **18**, an even higher dimerization constant ($K_{dimer} > 5000\ M^{-1}$) was measured. Remarkably, the NMR shifts observed upon dilution of **18** indicated that two modes of self-association occurred, a "head-to-head" dimerization and a "head-to-tail" one in which the pyridinium groups are docked in the cavities of their neighbors. Interestingly, when the solution of **18** in water was left to stand at room temperature, a pearly-like dispersion was gradually formed. Electron microscopy studies revealed the presence of well-defined "razorblade-like" aggregates (Figure 11a), all of which had approximately the same shape and dimensions ($1.2 \times 8\ \mu m$).

Closer inspection of the aggregates showed that they were built up from a limited number of thin layers (approximately 50). Electron diffraction experiments proved that the structures were not crystals, and powder diffraction studies on dried samples of **18** showed a clear repeating distance of 16.8 Å, which corresponds approximately to the length of one clip molecule. Based on the NMR and powder diffraction studies, the following aggregate structure was proposed (Figure 11b): initially, a head-to-head dimeric "seed" is formed, which can further grow in one dimension because of strong $\pi-\pi$ interactions between the clip dimers (these interdimer interactions are also present in the crystal structures of many clip molecules). In an additional, competing process, monomeric clip molecules are attached to the pyridinium moieties at the back of these dimeric seeds. The repeating 16.8 Å distance observed in the powder diffraction experiment corresponds to this head-to-tail growth. Eventually, 2D lamella are formed, of which the outside edges are always hydrophilic. Sheets of these lamella on top of each other finally give rise to the overall aggregate structure. The most intriguing aspects of these aggregates are their precise finite size and the fact that they stop growing after a certain moment. We believe that the balance between the molecular recognition processes determining aggregate growth and the loss in entropy upon self-assembly is responsible for the defined shape and monodisperse nature of the nanostructures.

A further step toward the construction of functional nanostructures is the incorporation of metal centers into

the aggregates. A series of molecular clips were designed, possessing a bipyridine ligand at their convex side.[55] Complexation of these clips to $[Ru(bipy)_2]Cl_2$ gave metalloclips **19** and **20** (Chart 3), which were found to be water-soluble. Fluorescence experiments showed that upon concentration of the solutions of **19** and **20** in water the fluorescence of the complexes was quenched, indicative of the formation of assemblies. This quenching was more pronounced for **20** than for **19**, and for both clips, quenching was much more pronounced than the self-quenching of the reference compound $[Ru(bipy)_3]Cl_2 \cdot 2H_2O$. Detailed ^1H NMR studies revealed that benzene-walled clip **19** self-associated in water in an exclusive head-to-tail geometry, in which one of the bipyridine ligands of a clip is docked in the cavity of its neighbor. A K_{dimer} of 50 M^{-1} was calculated from an NMR dilution titration in D_2O. Under the electron microscope, only undefined aggregates were observed for this compound. In the case of the naphthalene-walled derivative **20**, these aggregates were much more well-defined. NMR studies on very dilute solutions of **20** in D_2O indicated that, in contrast to **19**, this clip self-associated in two different geometries: head-to-head and head-to-tail (Figure 12a), which are in competition with each other, with the head-to-head assembly being approximately 10 times stronger than the head-to-tail one. At concentrations above 1 mM, the solution became turbid, because of the formation of larger aggregates. Electron microscopy studies on samples of **20** (Figure 12b) showed the presence of well-defined cigar-like aggregates (typical dimensions 3500 × 400 nm, with a high monodispersity in shape and size; ratio length/width = 11 ± 2). Close inspection of the cigars suggested that these are built up from smaller subaggregates (typical dimensions 400 × 75 nm), resembling the razorblades described above. The mechanism of self-assembly of the clips into the cigar-like assemblies is as yet unclear. The razorblade-like subaggregates are undoubtedly formed in a manner similar to that seen for the pyridinium-functionalized clips (Figure 12c).

Conclusion and Outlook

The self-assembling properties of the glycoluril compounds described in this paper are governed by electrostatic interactions, directed hydrogen-bonding interactions, and hydrophobic effects. The information for this is built into the constituting glycoluril building blocks.

Future work in the development of these structures is focused on further fine-tuning of the properties of the assemblies by specific design and synthesis and by control of the structural parameters which determine the interactions between the molecules. This will be easier to achieve for the rotaxanes and capsules described above, which are constructed from only a few components, than for the aggregates of the molecular clips, in which thousands of molecules define the assembly and hierarchical growth starts to play a significant but rather elusive role.

For the self-assembled architectures, interesting physical and material properties can be foreseen. To achieve this, the building blocks have to be supplied with specific functional groups or, even more excitingly, with groups that express their function only when the final assembly is completed. This will be the ultimate challenge for the supramolecular chemist, i.e., to have control not only over the growth and final morphology of the assembly but also over its specifically designed function.

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