Molecular and Supramolecular Objects from Glycoluril

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Received June 30, 1999

Introduction

In 1905, a publication appeared in *Liebigs Annalen der Chemie* describing a product which was obtained from the acid-induced condensation reaction of urea, glyoxal, and formaldehyde.[1] This product (**1**) was analyzed as $C_{10}H_{11}N_7O_4 \cdot 2H_2O$ and was found to be exceeding stable toward strongly acidic and basic reagents. Surprisingly, it formed crystalline complexes with a variety of metal salts. Some 75 years later, Freeman et al. solved the X-ray structure of the calcium bisulfate complex of **1**, which precipitated from a sulfuric acid solution.[2] Compound **1** turned out to be a cyclic hexamer of glycoluril units linked by methylene bridges. This hexamer was given the name cucurbituril, from the latin *cucurbita*, because of its resemblance to a pumpkin (Figure 1). Apart from its enigmatic synthesis, a remarkable feature of cucurbituril is the presence of an internal cavity which is accessible via two portals.[3] Mock et al. subsequently showed that this host molecule can strongly bind ammonium salts and can induce cycloaddition reactions between ammonium guests bound in its cavity.[3] More recently, Whang and Kim have shown that this host can be arranged into a variety of polyrotaxane architectures.[4]

When Freeman's paper appeared, one of us was working as a visiting scientist in the group of D. J. Cram, at the University of California, Los Angeles. At that time, Cram's interests were in the synthesis and the study of the host−guest properties of spherands, including compounds containing cyclic urea units. Many of the host molecules were difficult to prepare, which contrasted sharply with the facile, one-pot synthesis of the bis-cyclic urea compound **1**. In February 1982, in Holland, it was decided to initiate a program of research on the preparation and study of glycoluril (**2a**) derivatives with the hope that these molecules might be versatile building blocks for the construction of cage molecules. Initially, we sought a route to modify cucurbituril in such a way that it would become soluble in organic solvents, which would allow us to provide it with transition metal centers for catalytic applications, e.g., as models of metal-containing enzymes (synzymes). Unfortunately, these modifications could not be realized because of the extreme insolubility of **1** (it only dissolves in sulfuric acid and other strongly acid media). During one of these attempts, it was discovered that the reaction of diphenylglycoluril (**2b**) with formaldehyde in benzene as a solvent gave the clip-shaped molecule **3a** in good yield (Figure 1).[5] This serendipitous event subsequently formed the basis of a large number of studies in which molecules of type **2** and **3** were used as building blocks to construct a variety of molecular and supramolecular objects, e.g., in the shapes of clips, baskets, golf balls, cigars, and razor blades. This Account summarizes this work.[6,7]

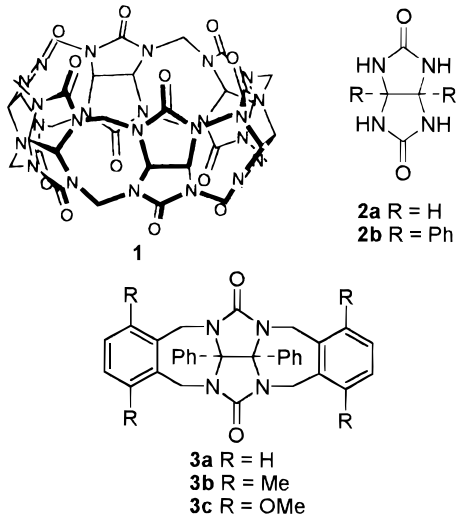

FIGURE 1. Structures of the cyclic urea cucurbituril (**1**), the building block (diphenyl) glycoluril **2**, and the clip **3**.

Synthesis and Binding Mechanism

In the late 1980s, a new class of synthetic receptors was emerging in the literature. These receptors, "molecular tweezers", as they became known,[8] could bind aromatic guests by sandwiching them between two more-or-less parallel aromatic surfaces. Since then, the rapid development of supramolecular chemistry has led to a vast multitude of synthetic host systems which utilize a wide variety of molecular recognition motifs.[8] At the same time as the molecular tweezers were synthesized, the "molec-

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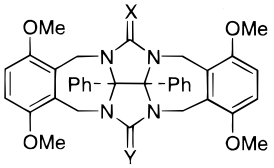
Hans Elemans was born in Nijmegen in 1970. Since 1995, he has been a Ph.D student in the group of Prof. Nolte, working on some of the areas described in this Account. His main areas of research are supramolecular catalysis and the construction of nanosized self-assembled architectures. Currently he is writing his thesis, which is planned to appear in early 2000.

Roeland Nolte was born in Bergh, The Netherlands, in 1944. He received his Ph.D. in physical organic chemistry from the University of Utrecht (1973), where he stayed and became Assistant Professor and then Associate Professor. In 1981, he was a visiting scientist at UCLA in the group of Donald J. Cram. In 1987, he moved to Nijmegen and became Professor of Organic Chemistry, and since 1994 he has also been a Professor of Supramolecular Chemistry at the Eindhoven University of Technology. His principal research interest is supramolecular chemistry, focusing on the design of catalysts and molecular materials.

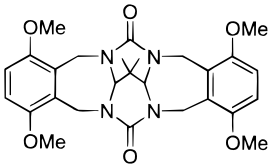
10.1021/ar9702684 CCC: $18.00
Published on Web 11/20/1999

Table 1. Association Constants (M^{-1}) of Complexes between Various Clips and Guests ($CDCl_3$, 298 K)

	Host			
Guest	**3c**	**8a**	**8b**	**9**
G1	1900	450	56	5500
G2	2600	750	51	14000
G3	4400	1300	82	53000
G4	16500	2500	177	2.7×10^5
G5	16000	3500	225	4.2×10^5
G6	1×10^5	—	772	3.4×10^6
G7	7100	—	—	2300
G8	60	—	—	130



3c X=O, Y=O
8a X=S, Y=O
8b X=S, Y=S



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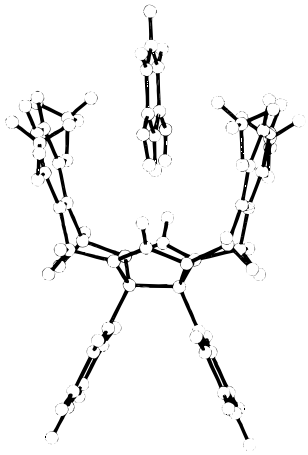
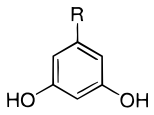
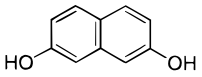
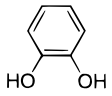




G1 R=CH_3
G2 R=H
G3 R=OCH_3
G4 R=$C(O)OCH_3$
G5 R=Cl
G6 R=CN



G7



G8

ular clip" hosts were being developed in our laboratory. Our molecules are readily synthesized by the condensation reaction of urea with a diketone, followed by reaction with paraformaldehyde and base. This leads to tetrakis(hydroxymethyl)diphenylglycoluril, which cyclizes to give a six-membered cyclic ether (**4**). The final step in the synthesis of the cavity molecules is the addition of the aromatic side walls, and several approaches have been developed which have resulted in a wide variety of clip molecules with identical and differing side walls. A selection is presented in Chart 1.

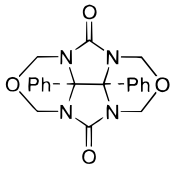
The origin of the term "molecular clip" for these molecules is clearly visible from the X-ray structure of the tetramethoxy derivative **3c** (Table 1).[9] The *o*-xylylene walls define a tapered cavity, the walls at an angle of 40°, with the centers of the benzene rings 6.67 Å apart. The two fused five-membered rings of the glycoluril form a shallow floor which is electron rich, with two hydrogen bond acceptor sites separated by 5.52 Å.

^{1}H NMR studies were the first to reveal that these clip molecules, with their preorganized clefts, are excellent receptors for neutral aromatic guests, particularly phenols and dihydroxybenzenes.[10−14] The binding strength of these types of guests within the host can span a wide range of values ($K_a = 0-10^5$ M^{-1}), which vary with simple modifications in either the host or the guest molecule. The binding is a result of three cooperative effects: hydrogen bonding, $\pi-\pi$ stacking, and a "cavity effect".

Upon binding of resorcinol, the guest simultaneously forms two hydrogen bonds to the π-orbitals of the carbonyl groups of the clip. The strength of this hydrogen bonding can be readily modified by altering the type of donor or acceptor group. Changing the acidity of the OH groups of the guest has a dramatic effect upon binding. The logarithm of the association constants (Table 1) of a series of substituted 1,3-dihydroxybenzene guests with host **3c** increases linearly as a function of the Hammett substituent constant σ.

To quantify the actual contribution the hydrogen bonding makes to the overall binding, the carbonyl moieties were systematically swapped for thiocarbonyl moieties and guanidine functions. Three hosts, **3a**, **8a**, and

Chart 1



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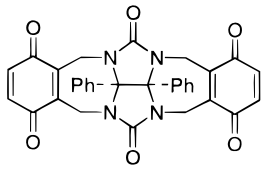

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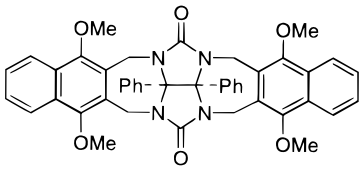

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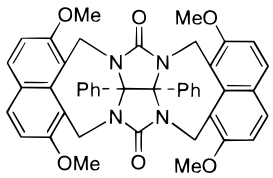

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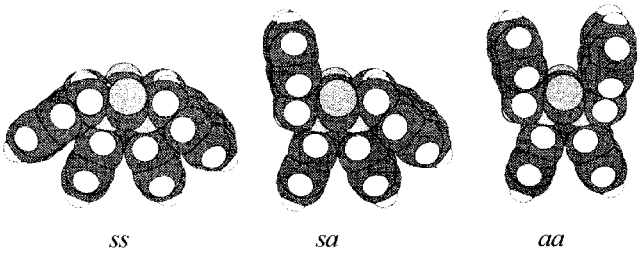


FIGURE 2. The three conformations *ss*, *sa*, and *aa* adopted by naphthalene host **7**.

8b, were synthesized, and their binding behavior was studied. In the case of **8b**, which has two thiocarbonyl functions, the clip still binds guest molecules but only on the basis of $\pi-\pi$ stacking (Table 1).

The substantial amount of data accumulated for the above binding studies has enabled us to quantify precisely what contribution each of the different interactions has on the binding of the 1,3-dihydroxybenzene guests in the clip molecules. Complexes formed with **8b** allow us to obtain the contribution of the two walls to binding (eq 1). Binding to cyclic ether **4** (eq 2) gives the contribution of hydrogen bonding to binding. Combining eqs 1 and 2 should give us the binding to clip **3c**. It can be seen that a good agreement is obtained (compare eqs 3 and 4).

clip **8b** ($2 \times \pi-\pi$ interaction + cavity effect)
$$-\Delta G = 10.4 + 9.1\sigma \text{ kJ/mol} \quad (1)$$

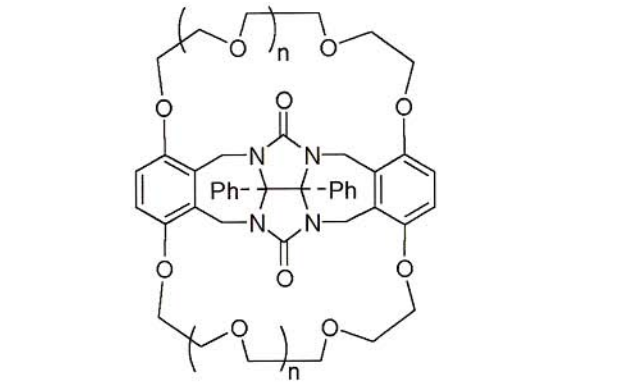
clip **4** (hydrogen bonding)
$$-\Delta G = 7.8 + 6.3\sigma \text{ kJ/mol} \quad (2)$$

eq 1 + eq 2
$$-\Delta G = 18.2 + 15.4\sigma \text{ kJ/mol} \quad (3)$$

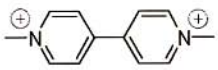
clip **3c**
$$-\Delta G = 19.3 + 14.7\sigma \text{ kJ/mol} \quad (4)$$

The influence of the cavity effect can be also extracted from the above analysis and was calculated to be approximately 6 kJ/mol.[13]

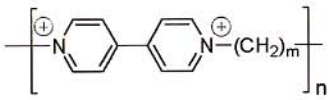
As shown above, the electron density of the guest influences the $\pi-\pi$ interaction between the host and the guest. In a similar manner, the size and electron density of the side walls of the clip can influence the guest binding. Upon going from 1,4 methoxy substituents (**3c**) to methyl substituents (**3b**) to benzene (**3a**), the binding strength decreases due to weaker $\pi-\pi$ interactions. Not all modifications made to the cavity side walls gave predicted results. Cavities possessing quinone side walls



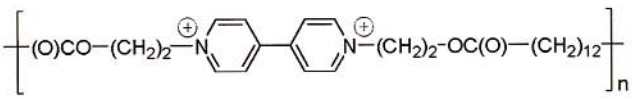
10a n=1
10b n=2
10c n=3



11a



11b m = 5
11c m = 8



11d

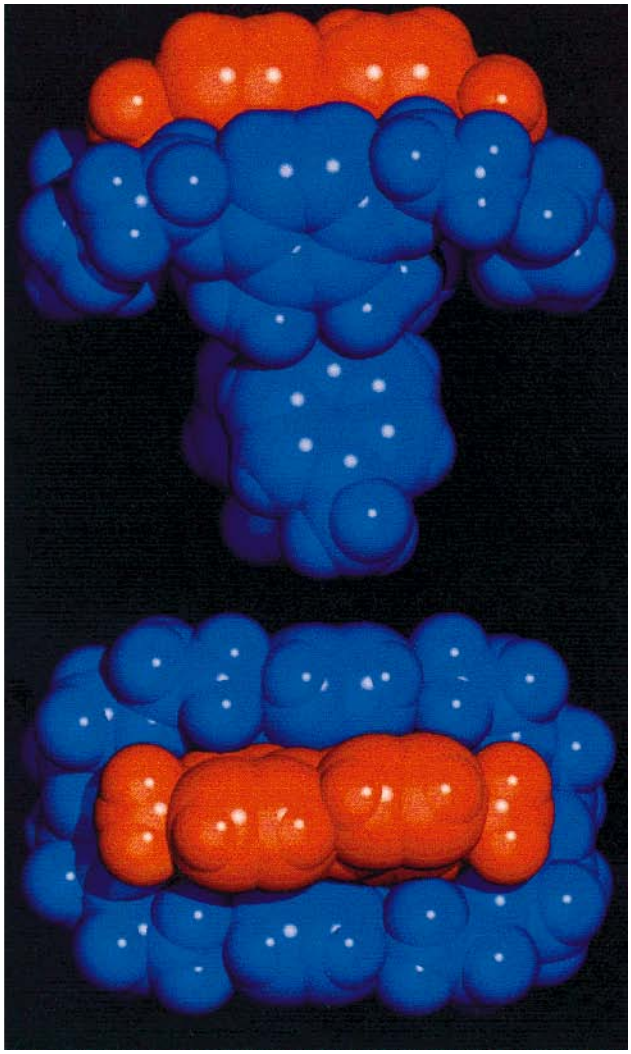


FIGURE 3. (Left) Crown ether hosts **10** and bipyridine guests **11**. (Right) Side and top views of the crystal structure of the complex formed between **10b** and **11a**.

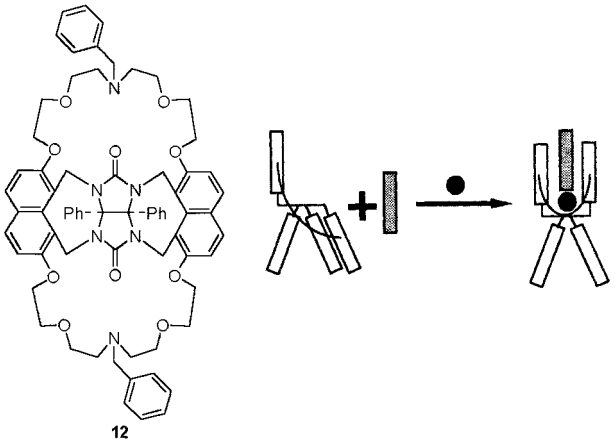


FIGURE 4. Schematic representation of the allosteric binding of nitrobenzene in host **12** in the presence of K^+ ions.

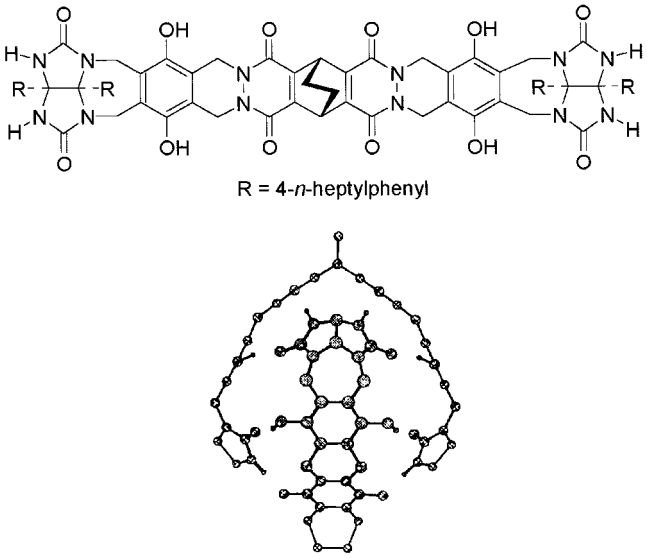


FIGURE 5. Rebek's glycoluril building block which dimerizes to form a tennis ball-shaped assembly.

(**5**) or 1,4 methoxy naphthalene side walls (**6**) were both expected to display enhanced binding affinities for resorcinol, the former due to a reduced electron density on the walls and the latter because of a larger π-surface. Somewhat to our surprise, it was found that both clips are very poor receptors ($K_a = 85$ and <1 M^{-1}, respectively) due to a conflict between the binding geometry favored by the hydrogen bonding and that favored by the $\pi-\pi$ stacking.[13]

For the naphthalene clip, this poor match can be overcome by connecting the naphthalene walls at their 1,8 positions instead of the 2,3 positions (**7**).[15−17] This host (**7**) exists in solution as a mixture of three conformers which interconvert slowly on the NMR time scale (Figure 2). Upon the addition of an aromatic guest, binding occurs only with the *aa* conformer, and the two other conformers disappear. This phenomenonon is reminiscent of Koshland's induced model for substrate binding to enzymes.[18]

To date, the majority of research carried out on the clip molecules was concerned with systems based on the diphenylglycoluril core. Very recently, we have modified the central core of the clips and synthesized new cavities derived from 2,4,6,8-tetraazabicyclo[3,3,1]nonane-3,7-dione.[19] The crystal structure of host **9** revealed that the cavity is very similar to those above, the only difference being that the carbonyl functions are pushed slightly closer together (cf. 5.2 Å for **9** and 5.52 Å for **3c**). This new host can bind resorcinol derivatives with binding constants a factor of 10 higher than those for the equivalent host **3c** (Table 1). The enhanced binding is the result of the small change in the C═O distance. In the case of resorcinol guests, the hydrogen bond strengths are enhanced due to a more optimum binding geometry. The exceptionally large binding affinity of this cavity for resorcinol guests (up to $K_a = 3.5 \times 10^6$ M^{-1}) highlights the fact that even very slight, subangstrom changes in the structure can cause surprisingly large changes in binding properties.

Baskets

To extend the diversity of binding interactions in our systems and consequently the range of substrates that can be bound, the clips were functionalized with crown ether moieties. The resulting compounds are known as "molecular baskets" due to their basket or bowl-like shape (Figure 3).[20−23]

These hosts are excellent binders for alkali metal ions (host **10b** and K^+, $K_a = 4.2 \times 10^8$ M^{-1}) and organic diammonium salts of the type $^+H_3N(CH_2)_nNH_3^+$ (host **10b** and guest $n = 6$, $K_a = 6.1 \times 10^9$ M^{-1}).[20] Not surprisingly, the basket-shaped hosts also have a strong affinity for charged aromatic compounds such as paraquat (**11a**, see X-ray structure in Figure 3) and polyparaquat derivatives (**11b**−**d**).[24] The host **10b** binds paraquat approximately 25−75 times more strongly than the bis(paraphenylene)-[34]-crown-10 macrocycle studied by Stoddart's group (K_a = 22 000 and 730 M^{-1}, respectively, in acetone). The redox activity of the complexed paraquat is significantly altered. The dication bound in **10b** is 100 mV more difficult to reduce than the free paraquat. Once reduced, however, the guest immediately falls out of the cavity. Host **10b** was also shown to "clip" onto polymeric paraquats, with association constants of 1800, 4500, and 19 000 M^{-1} for polymers **11b**, **11c**, and **11d**, respectively. The longer the spacer in the polymer, the less is the steric hindrance and the larger the binding constant. As in the case of the monomer, the electrochemical properties of the liquid crystalline, redox-active polymers **11** can be readily manipulated by the addition of host **10b**.

Basket-shaped hosts can also be synthesized containing aza-crowns and naphthalene side walls (**12**).[25,26] Like its molecular clip cousin (**7**), this host exists in three conformations, the predominant one being the *sa* conformer. Upon the addition of alkali earth metal ions such as potassium, the cavity changes its conformation into the *aa* form (Figure 4). The binding of the metal ions is a cooperative process, with the second K^+ ion binding approximately 100 times stronger than the first.

The addition of an alkali metal also makes the host molecule a better receptor for aromatic guest molecules,

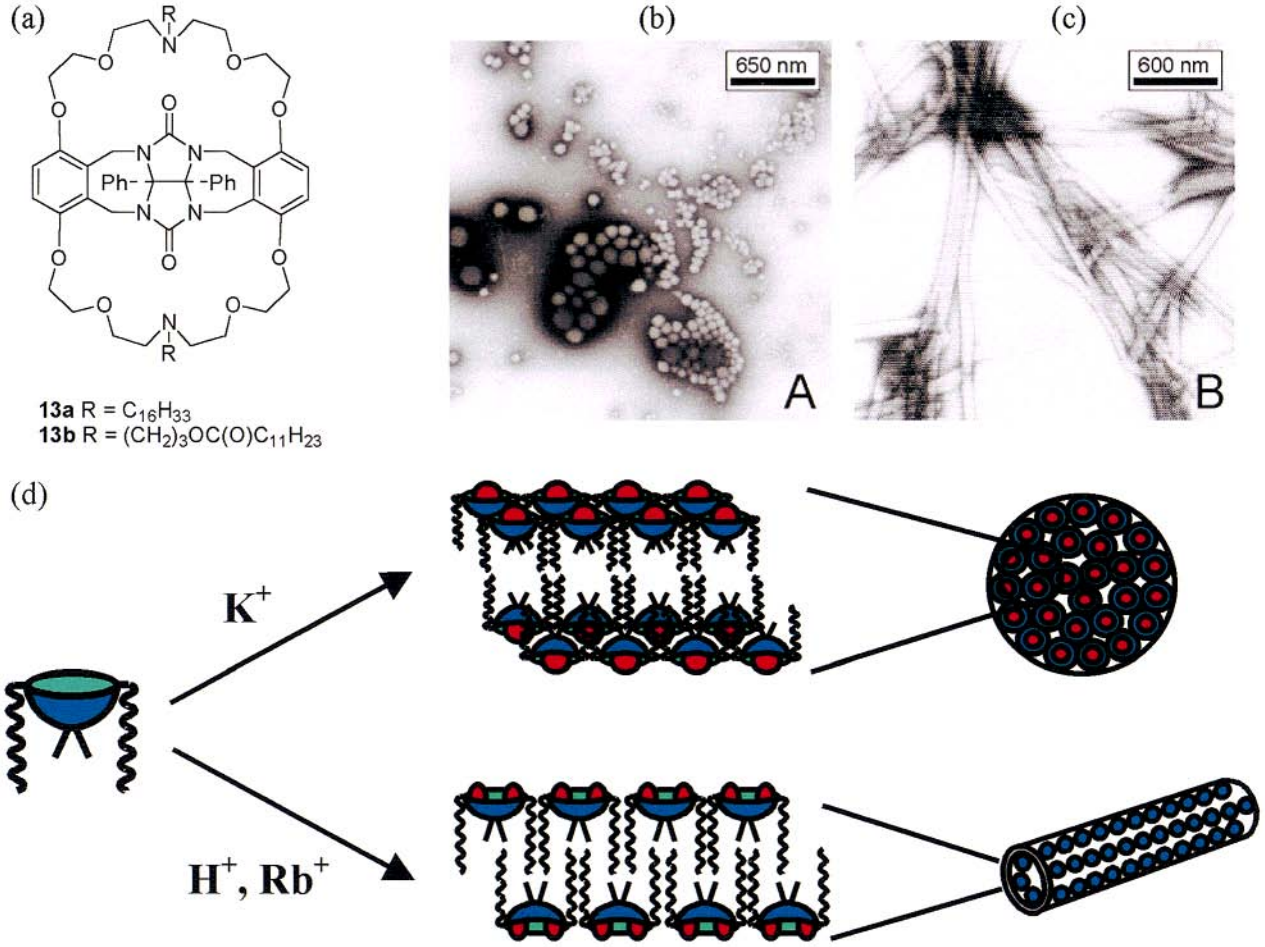


FIGURE 6. (a) Basket-shaped receptors of type **13** which aggregate to form (b) vesicles and (c) tube-like structures. (d) Schematic representation of the assembly process.

since only the *aa* conformer is present in solution. Upon the addition of a potassium salt to a solution of **12**, the binding of 1,3-dinitrobenzene increases by a factor of 2−6, depending on the solvent system (Figure 4).[26] The development from simple molecular clips to molecular baskets has resulted in a cavity which exhibits an enzymatic-like allosteric effect.

Self-Assembly

Over the past few years, the groups of Rebek and Mendoza have shown that simple derivatives of glycoluril can self-assemble by H-bonding to form a variety of cavities, i.e., tennis balls, baseballs, etc. (Figure 5).[27] The resulting cavities can, themselves, encapsulate solvent and guest molecules and enhance product formation in Diels−Alder reactions.

We have been investigating the self-assembling behavior of our molecular clips and baskets in water. Our distant goal is the construction of functional nanometer-sized architectures. The addition of long alkyl tails to aza-crown baskets results in charged amphiphilic hosts of type **13**.[28] Upon dispersal of **13a** in water, well-defined bilayer vesicular aggregates with a diameter of 1000−5000 Å were formed (see Figure 6).

The cavities were still able to bind organic guests such as magneson (4-(4-nitrophenylazo)resocinol) in water. Binding studies below the critical aggregation concentration (CAC = 2×10^{-5} M) indicated the formation of 1:1 host−guest complexes ($K_a = 1 \times 10^6$ M^{-1}). Above the CAC, guest binding still occurred, but a 1:2 complex ([G]:[H]) was formed. We like to refer to these vesicles as supramolecular "*golf balls*" [28] since only the dimples on the outside of the cavity are available for guest binding.

The aggregates formed by such amphiphilic baskets can also be tuned by the pH or the addition of metal salts. A similar basket host, **13b**, was found to give long tube-like assemblies in aqueous 0.1 M HCl and form vesicles in aqueous 0.2 M KCl or NaCl.[29] Monolayer studies showed that, in 0.1 M HCl, the basket molecule adopts an open geometry and that, in the presence of K^+ ions, a more compact, closed geometry is adopted. If larger cations such as Rb^+ or Cs^+ are used, the baskets are forced to open again, and the tube-like assembly is restored. In this way, the nano architecture can be finely tuned.

The clip-shaped hosts can, themselves, also self-assemble, forming discrete dimers in organic solution; however, this dimerization is very weak (host **3c** in $CDCl_3$, $K_d = 20$ M^{-1}). The equivalent water-soluble cavities (**14** and **15**), in contrast, have a strong affinity for self-association, forming very well-defined nanometer-sized aggregates.[30,31]

^{1}H NMR dilution studies confirmed that at aqueous

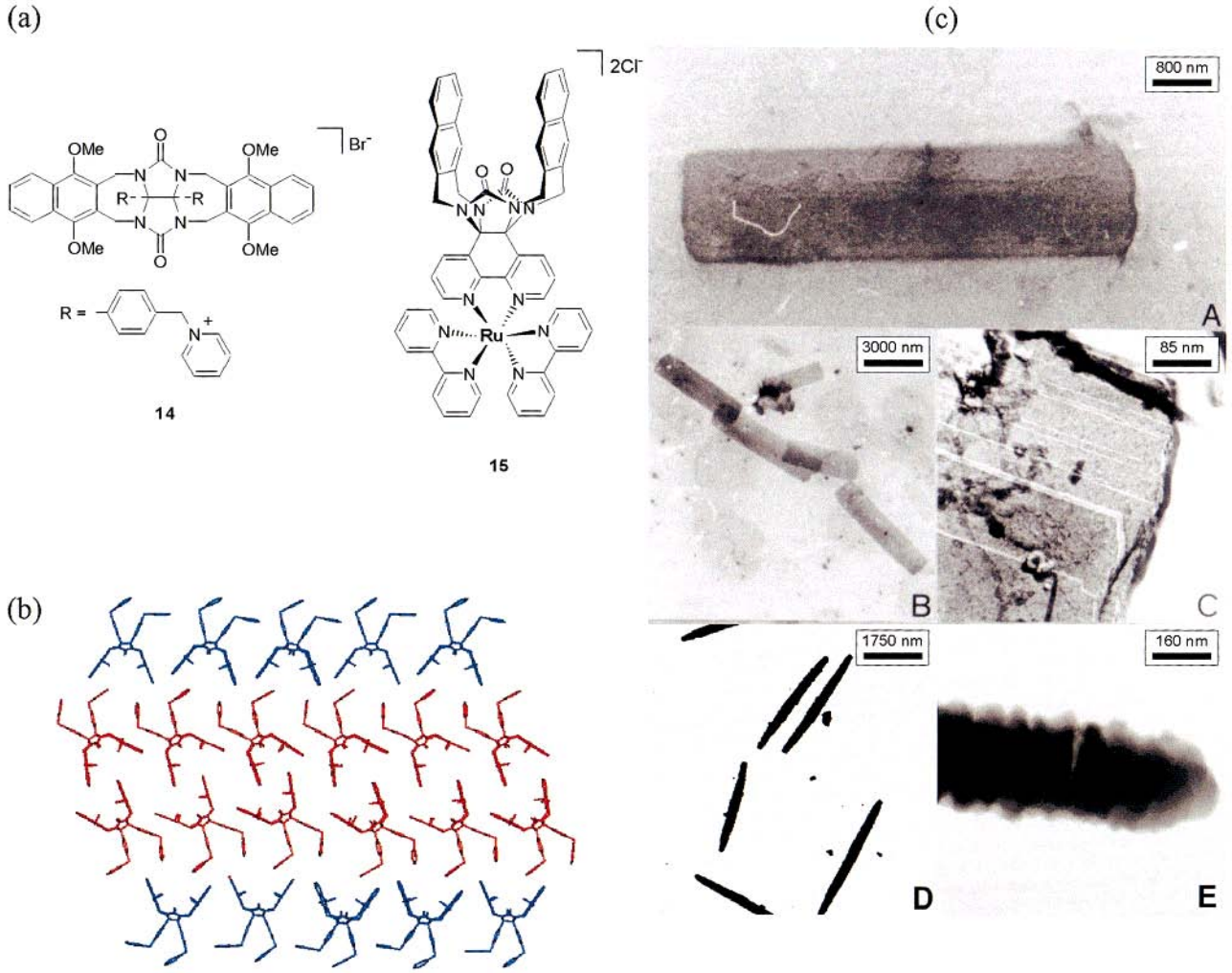


FIGURE 7. (a) Water-soluble molecular clips **14** and **15**. (b) Head-to-head and head-to-tail assembly of molecules of **14**. (c) "Razor blades" formed from **14** (A,B,C) and "cigars" formed from **15** (D,E).

concentrations >0.1−3 mmol dm^{-1}, **14** dimerizes (K_a > 5000 M^{-1}), with one clip cavity being filled by the side wall from another clip and vice versa. The observed NMR shifts suggest that two modes of self-association occur: a "head-to-head" and a "head-to-tail" mode (Figure 7). Upon increasing the concentration, an opalescent solution was formed which contained well-defined "razor blade-like" aggregates. Closer examination with electron microscopy revealed that the razor blades all had approximately the same proportions (1.2 μm × 8 μm) and were constructed from a limited number of layers (ca. 50, Figure 7). We proposed that a dimeric head-to-head seed is initially formed which acts as an initiator for further growth. Monomers attach themselves onto the pyridinium units in a head-to-tail fashion, eventually forming a multilayer structure of which the outside surface is always hydrophilic.

To study this phenomenon more closely, we synthesized another water-soluble clip which possesses a chromophoric metal site (**15**). Again, due to a predominantly solvophobic driving force, the molecules of clip **15** self-assembled, in this case to "cigar-like" aggregates (Figure 7). These nano-aggregates again had a remarkably high monodispersity in size with an aspect ratio (length/width) of 11 ± 2. What is unique about these assemblies is that the growth stops at a precise, finite size. A delicate balance between the specific molecular recognition processes present in the growth mechanism ($\pi-\pi$-stacking) and the loss in entropy upon aggregation is probably responsible for the precise shape and monodispersity of the final assembles.[32]

Bio-Inspired Molecular and Supramolecular Assemblies

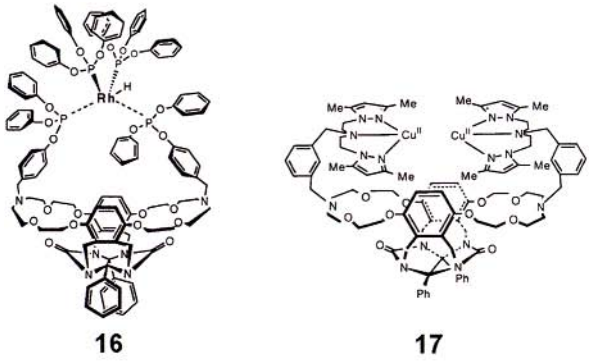
Throughout the 15 years of research into the properties of the glycoluril-based molecular cavities, we have always looked to Nature as an inspiration and guide. In particular, we have tried to design cavities which mirror the different binding processes found in enzyme binding pockets, viz., substrate selectivity, induced fit, and allosteric binding. In this regard, we have been successful, as shown above. The next stage in mimicking natural enzymes was to combine catalytically active functions with the binding ability of the molecular clips and baskets and build working catalysts.[33]

Rhodium complexes are well-known hydrogenation, hydroformylation, and isomerization catalysts. To combine this function with the diphenylglycoluril baskets, we linked a tetrakis(triphenylphosphite)rhodium(I) hydride complex to an aza-crown basket to give the host **16**.[34,35] The resulting supramolecular catalyst is able to selectively catalyze the hydrogenation of allylic aromatic guests with significant rate enhancements when compared to the corresponding catalyst without a binding site. Furthermore, the catalysis exhibits features associated with enzymatic processes, e.g., Michaelis−Menten kinetics and inhibition by alkali metal ions.

Catalysis by **16** also exhibits a unique cosubstrate activation. Upon the addition of a competitive guest such as resorcinol, remarkably the rate of hydrogenation of 4-allylcatechol was considerably enhanced, this enhancement being due to a cooperative binding which can occur between the resorcinol and the 4-allylcatechol in the large aza-crown basket.

In addition to hydrogenation catalysis, we have also studied systems which can carry out oxidation catalysis. By a synthetic methodology similar to that used for the preparation of the rhodium hydrogenation catalysts, metal-binding pyrazole ligands were attached to aza-crown baskets.[36] Upon the addition of copper(I) and copper(II) salts, metallo baskets of type **17** were formed, which despite having a tightly capped cavity were still able to complex resorcinol derivatives. With catalyst **17**, the stoichiometric oxidation of a series of benzylic alcohols to the corresponding aldehydes was studied. In the reaction, two Cu(II) centers are reduced to Cu(I), the two electrons being taken from the alcohol which is converted to the aldehyde. The rates of reaction for guests which have a high affinity for the cavity of **17** were several orders of magnitude higher than those for benzyl alcohol itself. In the case of the 3,5-dihydroxybenzyl derivative, a rate enhancement greater than 50 000 was observed.

Ideally, we would like to use molecular oxygen as the oxidant. Toward this goal, model systems have been developed which mimic hemocyanine and tyrosine hydroxylase, both naturally occurring dicopper enzymes.[37] The latter enzyme is of fundamental importance in the conversion of tyrosine to dopamine in the brain. To be able to bind molecular oxygen, the pyrazole ligands were replaced by pyridine ligands.[37] The pyridine Cu(I) host was found to form metastable O_2 adducts in CH_2Cl_2 at −85 °C, mimicking hemocyanine. The complex has a peroxo ligand in a (bent) μ-η^2:η^2 binding mode, which was confirmed by a distinctive absorption in the UV−vis spectrum. As in the case of the pyrazole-derived basket, guests can still be complexed in the cavity. In fact, the cavity is a good receptor for both tyrosine and dopamine guests (Figure 8). It was found, however, that this copper complex was unable to catalyze the oxidation of guests due to oxidative splitting of the attached pyridine ligands. Molecular modeling revealed that, in the geometry formed upon O_2 complexation, the benzylic protons linking the cavity and the pyridine functions are positioned directly next to the bound oxygen. Due to this close proximity, the cavity is oxidized in preference to the guest. However, these results are encouraging in that a mimic of hemocyanine can be formed, dopamine can be complexed, and oxidation can occur, albeit as yet only on the basket. New, more stable cavities currently being developed hold greater promise.



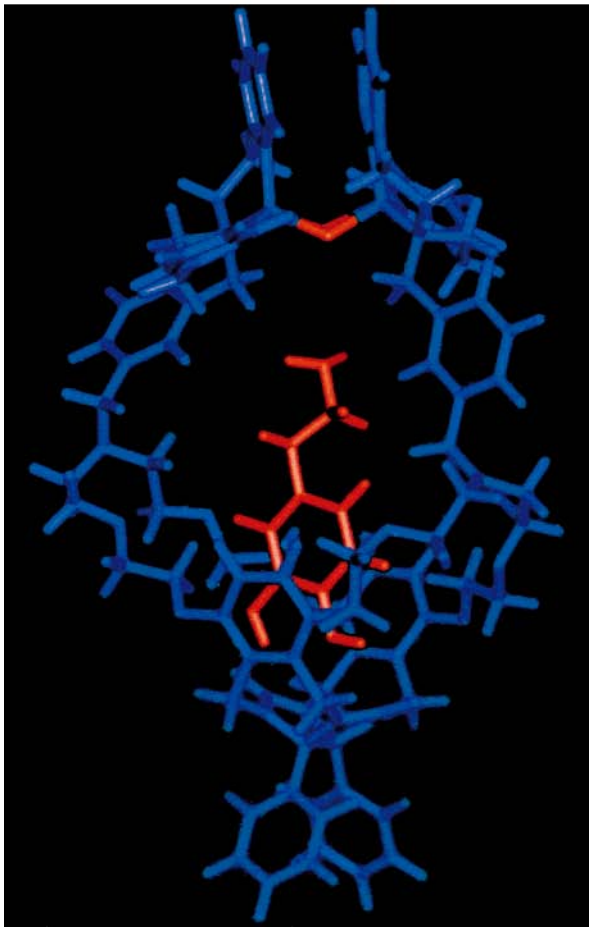


FIGURE 8. (Top) Tetrakis(triphenylphosphite)rhodium(I) hydride complex **16** and Cu(II) pyrazole basket **17**. (Bottom) Calculated molecular model representing the complex formed between dopamine and the oxygen adduct of the pyridine derivative of **17**.

Another such enzymatic system we have modeled is the ferrodoxin family, which is a class of 4Fe-4S proteins involved in biological redox processes. Two model cluster complexes based on diphenylglycoluril baskets have been constructed. In one the [4Fe-4S] is semiencapsulated by one cavity, and in the other two baskets completely

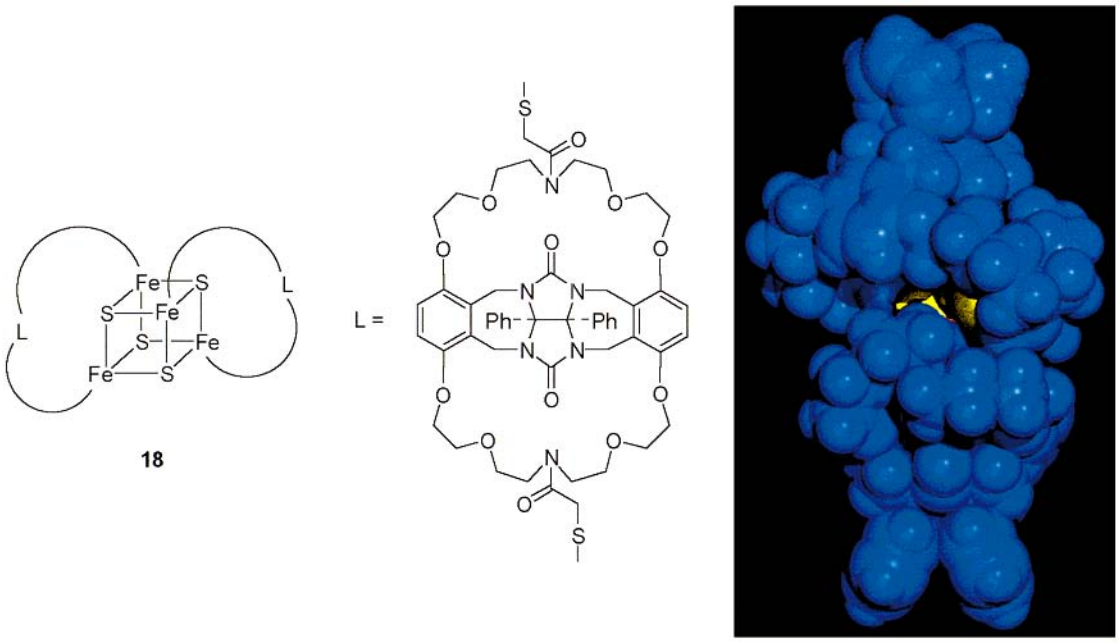


FIGURE 9. Dibasket complex **18** which fully encapsulates a [4Fe-4S] cluster, modifying its electrochemical properties.

encapsulate this core (**18**) (Figure 9).[38−42] In both systems, the redox properties of the clusters are not only altered but can also be modified by the addition of metal ions or paraquat guests which bind to the crown ether functions of the baskets, altering the shape of the complex.

Another example from Nature which greatly inspired us was a protein (Gene V protein) studied by the Biophysical Chemistry group in Nijmegen.[43] It has the shape of a very large tweezer and binds to single-stranded DNA chains, changing the physical properties of these biomolecules. Enthused by this system, we designed clip molecules (e.g., **19**) which can bind to polymers and, in an analogous manner to the protein, alter the physical properties of these macromolecules.

Molecule **19** exists predominantly in the *sa* conformation and exhibits no liquid crystalline behavior.[44,45] Upon the addition of methyl 3,5-dihyroxybenzoate, however, the host changes shape, and the resulting complex exhibits liquid crystalline properties (see Figure 10a). The versatility of the concept of supramolecular induction of liquid crystallinity can be demonstrated when multifunctional guests are used (Figure 10b).

When host **19** was added to a porphyrin modified at the meso positions with 3,5-dihydroxyphenyl groups, the resulting 4:1 complex also displayed liquid crystalline behavior. If a similar porphyrin, which cannot complex to clip **19**, was used, no mesophases were observed. This confirms that the host−guest complex is the mesogenic species (Figure 10c). Not only the material properties but also the redox properties of the porphyrin are altered. Electrochemical studies reveal that the porphyrin core is encapsulated in the 48 alkyl tails of the four receptors, causing the reduction potentials of the porphyrin to alter in a way reminiscent of certain porphyrin-containing enzymes, such as cytochrome P-450 and cytochrome *c*.

Liquid crystallinity can also be induced in polymeric systems. The complex of a copolymer of styrene and dihydroxystryrene and host **19** gave a very stable discotic mesophase between 30 and 141 °C. The molecules "clip onto" the polymer, the alkyl tails fanning out, modifying the polymer properties in a manner analogous to the Gene V protein.

We have shown above that the material and electronic properties of polymeric paraquats can be manipulated by the addition of diphenylglycoluril baskets. Unfortunately, upon formation of the active 1e-reduced species, decomplexation occurred. We therefore decided to synthesize a diphenylglycoluril clip which upon complexation with viologens forms rotaxane complexes which cannot subsequently decomplex. From the onset, it was decided to construct a "roof" on the clip which could also behave as a catalytically active site. In the resulting compound (**20**), a porphyrin roof has this function. This porphyrin clip has an extraordinary affinity for paraquat ($K_a = 6 \times 10^5$ M^{-1}). If the viologen possesses propylamine or ethanol *N*-substituents, the binding affinity between host and guest is even larger ($K_a = 9 \times 10^5$ and 7.4×10^6 M^{-1}, respectively).[46,47] Subsequent reaction of these complexes with acid chloride derivatives generated a variety of [*n*]-rotaxane species, including a polymeric rotaxane ($n \approx 15$) in which every paraquat unit possesses one porphyrin host (Figure 11). The porphyrin clip can not only bind guests, its manganese derivative is also catalytically active. This host is currently being investigated as a mimic of λ-exonuclease,[48] an enzyme system which forms rotaxane complexes with double-stranded DNA and catalytically breaks down the polymer, extruding a single DNA strand.

One final example of a bio-inspired application of our molecular clips is their use in the study of the mechanism of energy transfer in the photosynthetic system. One question unresolved is the role of intervening aromatic

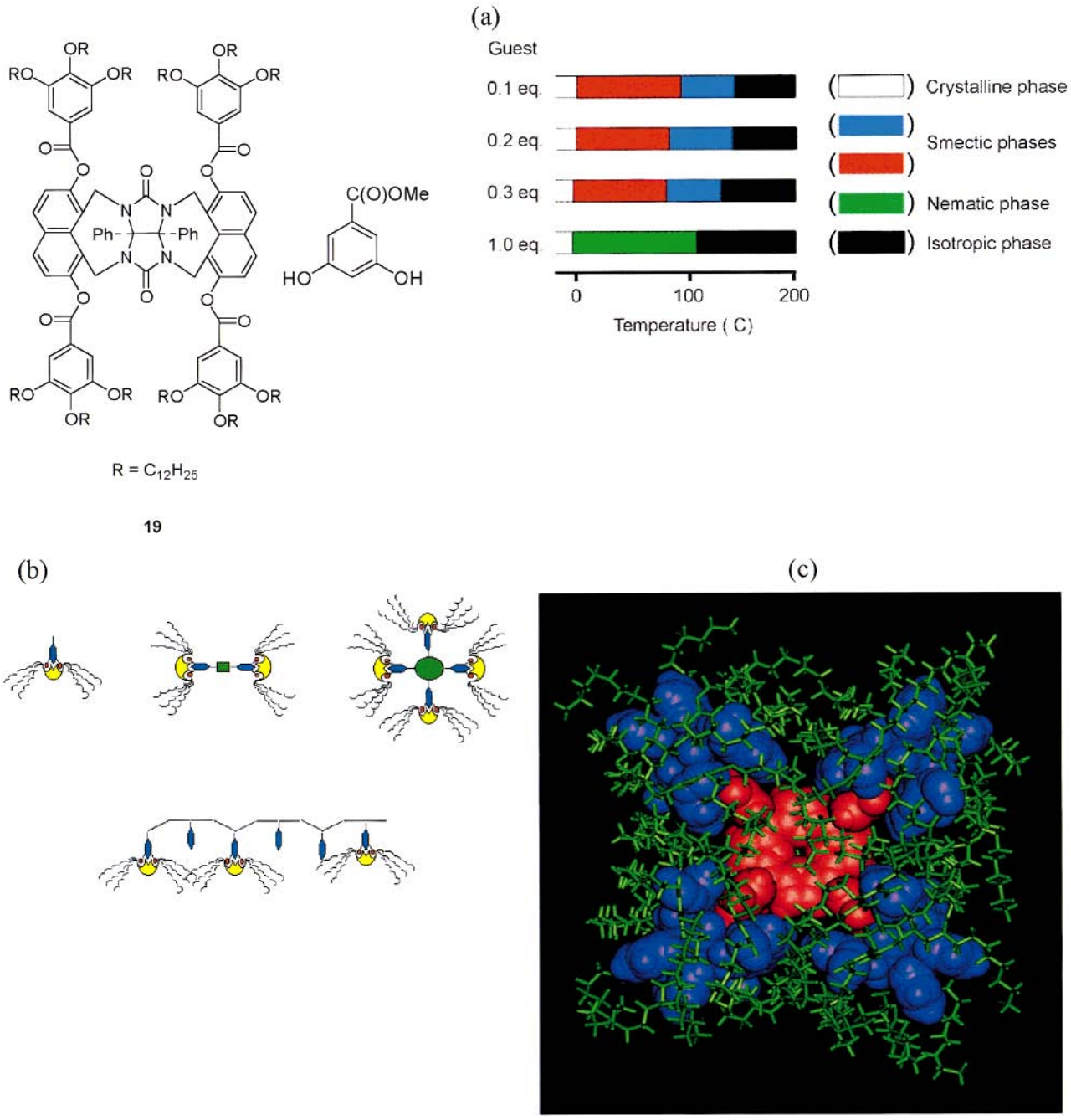


FIGURE 10. (a) (Left) Molecular basket **19**, which forms a liquid crystalline complex upon the addition of an aromatic guest. (Right) Liquid crystalline phases observed upon adding guest. (b) Schematic representation of the liquid crystalline complexes that can be obtained from molecule **19** and different guest molecules. (c) Computer-generated structure of the complex formed between tetrakis(3,5-dihydroxyphenyl)-porphyrin and four molecules of **19**.

amino acid residues in the electron transfer processes in the photosynthetic reaction centers. We specifically designed a diphenylglycoluril-based clip of which one wall is a porphyrin moiety and the other wall an aromatic donor (**21**) or acceptor (**22**) group in order to study this problem.[49]

The crystal structure of **21** revealed that this porphyrin clip is dimerized in the solid state. Its cavity is similar to that of the normal clips, with a width of 6.3 Å, ideal for sandwiching an aromatic guest. In the nonpolar solvent CCl_4, the fluorescence quantum yields of **21** and **22** were comparable to that of a simple Zn tetraphenylporphyrin (ZnTPP) molecule. In more polar solvents, the fluorescence quantum yield of **22** became much smaller due to solvent-mediated electron transfer from the porphyrin donor to the quinone acceptor (Figure 12 and Table 2). Upon the addition of an aromatic guest (hexyl 3,5-dihydroxybenzoate) to **22** in CCl_4, 80% of the fluorescent intensity of **22** was quenched due to electron transfer. Under the same conditions, this quenching was not observed for either ZnTPP or **21**. The enhanced electron transfer by the aromatic guest in our system suggests that intervening aromatic amino acid located between the bacteriopheophytin and the quinone in the natural pho-

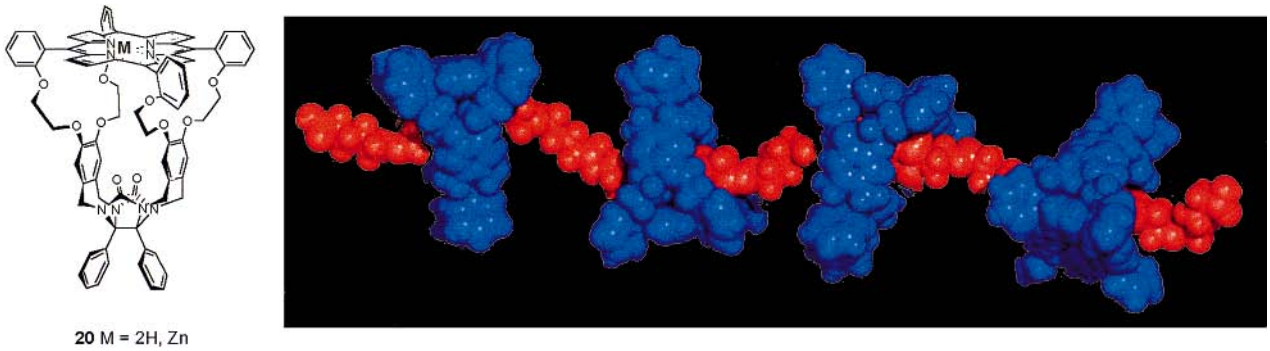


FIGURE 11. Porphyrin clip **20** and a molecular model of the polyrotaxane formed from **20** and polymeric paraquat **11d**.

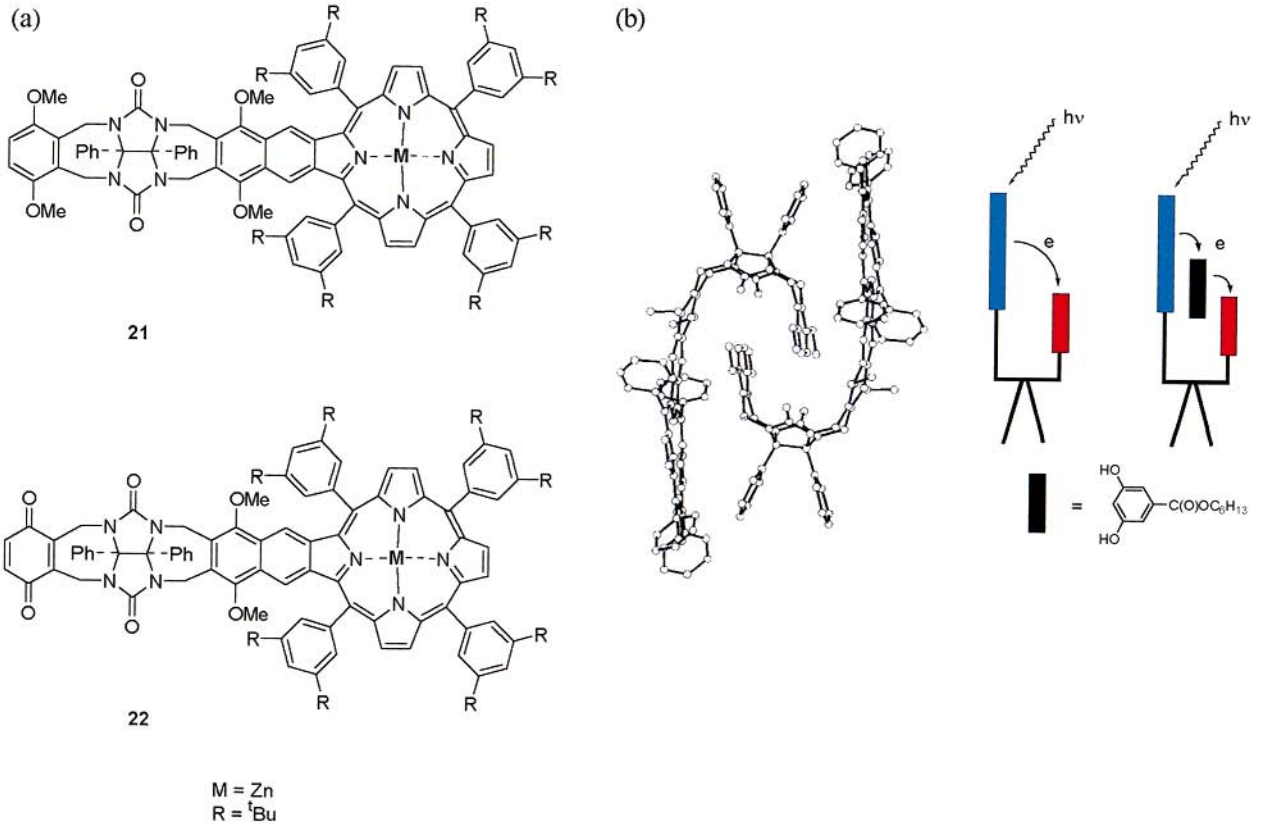


FIGURE 12. (a) Porphyrin containing clips **21** and **22** and the crystal structure of **21**. (b) Schematic representation of the mediated electron transfer which occurs upon the addition of an aromatic guest to clip **22**.

Table 2. Fluorescence Quantum Yields of Porhyrins 21 and 22 and of the Complex between 22 and Hexyl 3,5-Dihydroxybenzoate in CCl_4 and $CH2Cl_2$

	Φ		
	21	**22**	**22** + guest
CCl_4	0.020	0.020	0.0044
CH_2Cl_2	0.016	0.002	–

tosynthetic systems moieties may play a significant role in the efficiency of the energy transfer process.

Conclusion

The versatility of the molecular clips and baskets has clearly been demonstrated above. The simplest cavities have enabled us to investigate in great detail the interactions involved in host–guest complexation and have added to the considerable wealth of knowledge obtained by many other groups using different cavity systems.[8] Modifications to these hosts has further enabled us to mimic some of the characteristics found in enzymatic catalysis, i.e., substrate selectivity, induced binding, and allosteric behavior. The application of these properties has furthermore led to the controlled induction of liquid crystallinity in molecular and macromolecular systems and to the control of shape and size of self-assembled systems of nanosized dimension. The future for these receptors lies in the combination of (i) specific self-assembly and (ii) control of properties, leading to more selective catalysts and new materials. The ultimate aim is the construction of highly ordered, functional supramolecular systems. In this way, we can take one step further toward our goal of designing architectures of the same beauty as those found in Nature.

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AR9702684