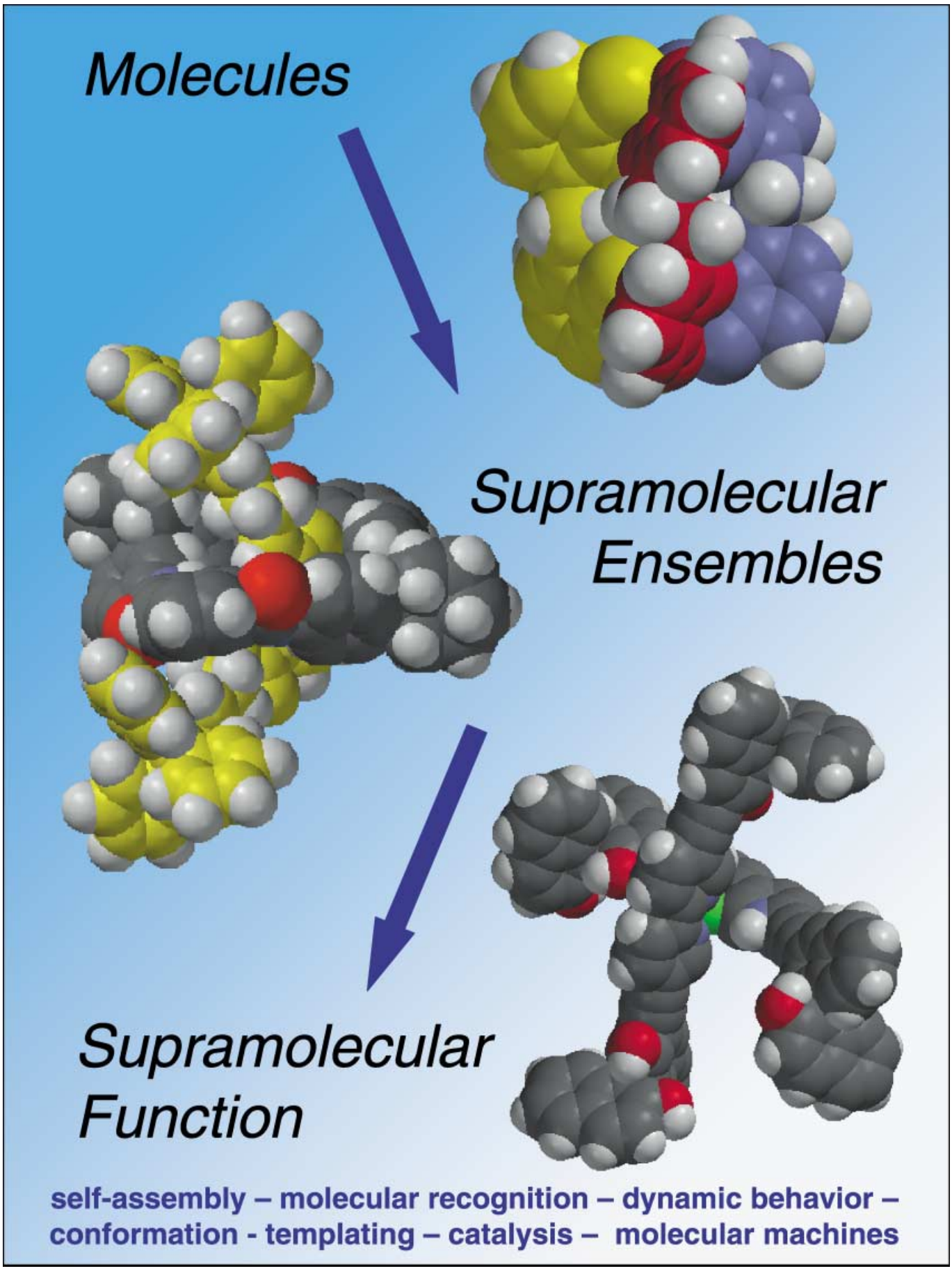

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Approaching Supramolecular Functionality

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Dedicated to Professor Fritz Vögtle on the occasion of his 65th birthday

Abstract: Functional molecules require a high degree of complexity which is difficult to achieve by covalent synthesis. This article discusses supramolecular approaches to the creation of larger architectures through noncovalent bonds, self-assembly, and template strategies. It highlights selected examples for the structural and conformational control of function and attempts to identify difficulties and challenges which may arise in future.

Keywords: conformational control · molecular devices · self-assembly · supramolecular chemistry · template effects

Introduction

Biological systems (e.g., DNA, enzymes, or other proteins) are highly advanced and very efficient functional molecular devices which are built from smaller and simpler components by aggregation through noncovalent interactions. An exact spatial positioning of suitable functionalities as well as the ability to undergo well-defined dynamic structural rearrangements is essential for their function as molecular information storage devices, as molecular machines, and as selective catalysts. In order to mimic biological devices or even to develop new functional molecules a high degree of complexity is mandatory. One may even speculate whether nature would have achieved its extreme efficiency if biomolecules were smaller and simpler than they are. In particular, the fine tuning that finally optimizes function requires a number of parameters for detailed adjustments. For any artificial device,[1] the necessary degree of complexity thus requires the design and preparation of large molecules with numerous functional groups. Despite the admirable power of covalent organic synthesis[2] and its astonishing successes, the enormous effort associated with it represents a severe limitation for the generation of artificial functional devices.

The application of noncovalent synthesis, for example, the substitution of covalently-assembled structure-determining elements by structurally analogous metal coordination complexes, can significantly lower the preparative efforts necessary for the formation of sophisticated architectures.[3] This is shown, for instance, in Figure 1, where a central 9,9′-spirobifluorene unit of tetra(2,2′-dihydroxy-1,1′-binaphthyl) **1** is substituted by a copper(I) or silver(I) bis(2,2′-bipyridine) complex.[4] This strategy not only simplifies the synthesis of such a complex structure, but also offers the possibility to access a broader diversity of geometrically and/or electronically different aggregates simply by exchanging the metal ion for one that has a different charge and/or prefers another coordination number and/or geometry other than Cu^+ or Ag^+ ions.

Thus, the following sections will focus on the use of noncovalent forces for organizing (supramolecular) architectures of complex species, for directing reactivity, and hence for controlling function.

Noncovalent Interactions, Self-Assembly, and the Importance of Template Effects

Noncovalent interactions generally are much weaker than their covalent counterparts. Usually, strong binding is only observed if multiple interactions cooperate. Consequently, most supramolecular complexes are reversibly formed and are prone to dynamic processes. This is a prerequisite for the self-assembly[5] of defined aggregates that occurs under thermodynamic control. Due to the reversibility of noncovalent bond formation many supramolecular aggregates should be considered as highly dynamic units.

Different types of noncovalent interactions can influence the aggregation of molecules, and different bond energies

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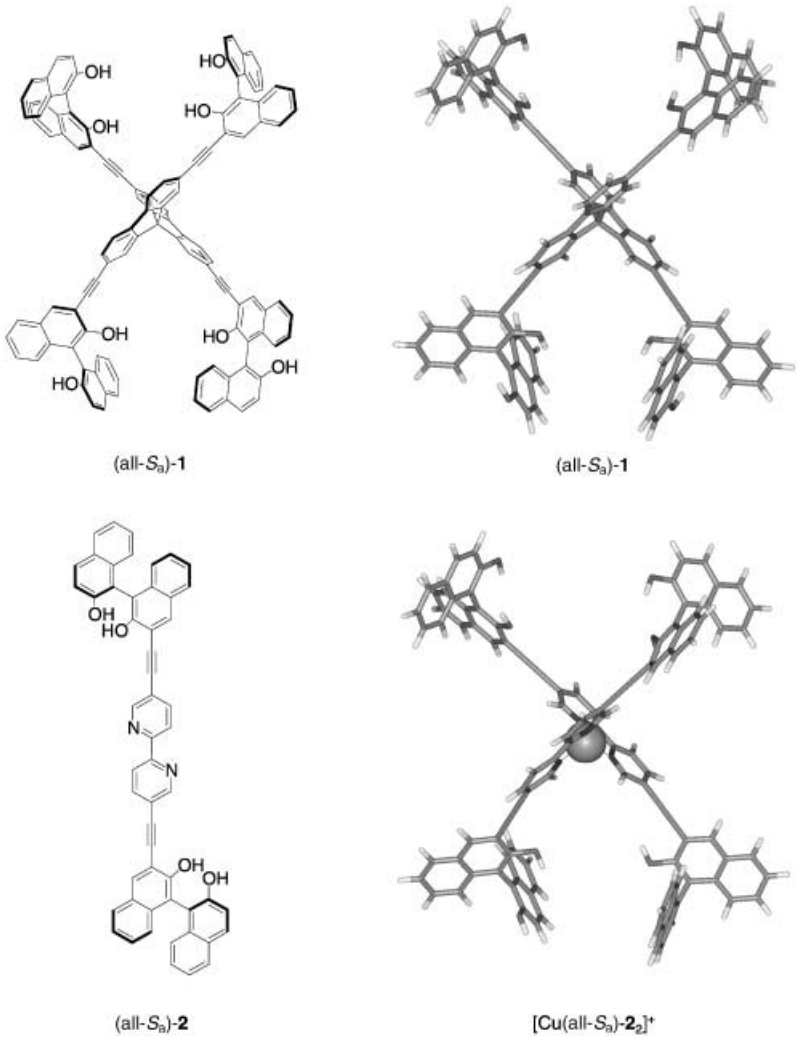


Figure 1. MM2-minimized structure of tetra(2,2′-dihydroxy-1,1′-binaphthyl)-substituted 9,9′-spirobifluorene (all-S_a)-**1** (top) and MMFF-minimized structure of its analogous [Cu{(all-S_a)-**2**}$_2$]$^+$ complex (bottom).

allow a gradual cooperation of effects with different strengths giving rise to systems with a hierarchical order of degrees of complexity (hierarchical self-assembly).[6] The different interactions can support each other in a cooperative fashion[7] and either lead to positive or negative allosteric effects.[8]

However, for thermodynamic control of self-assembly processes, not only the strength or weakness of bonding interactions is mandatory. The directionality and the rigidity of the building blocks also play a pivotal role. Figure 2 shows a schematic representation of different possible assembly modes, which are often in competition with each other. On the one hand, a nonspecific formation of oligomeric aggregates (e.g., glasses and the like) is presented. On the other hand, well-defined structures are obtained in a specific self-assembly process. In an *ideal* system, the change of enthalpy is only due to the formation of new bonds, which remains the same irrespective of the formation of a small well-defined aggregate or the formation of oligomers and polymers. Therefore, entropy takes control over the reaction path and favors the formation of a maximum number of species. On the other hand, in a *non-ideal* system, strain can be built up within either oligomeric or discrete species, in particular when rigid subunits are chosen. Here, enthalpy comes into play again and the fine balance between enthalpic and entropic effects finally governs the direction of the assembly process.

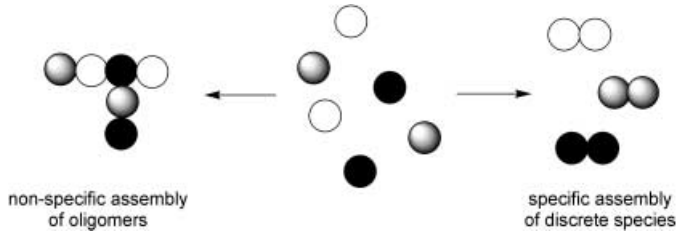
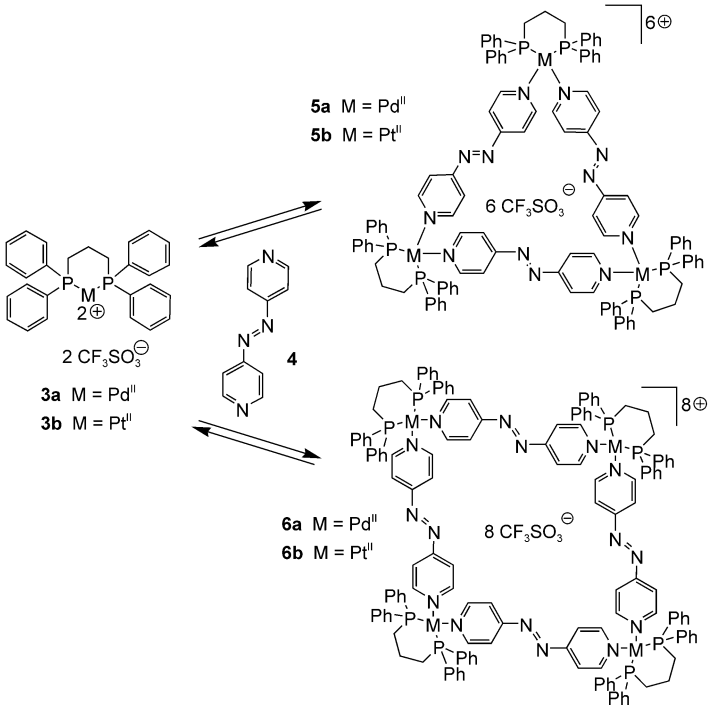


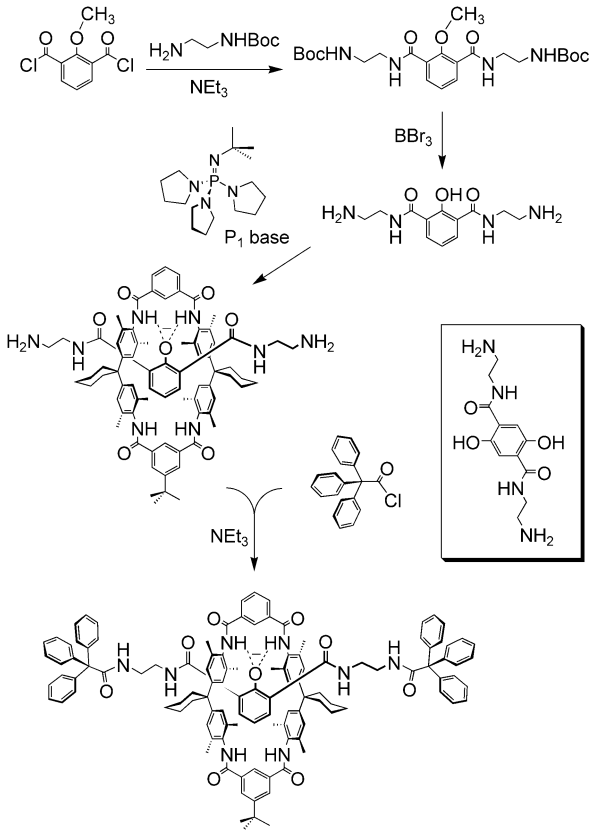
Figure 2. Reversible binding allows the molecules to bind and dissociate and thus to correct errors leading to higher energy assemblies. Such processes thus have low barriers and are thermodynamically controlled.

A recent example for this balance between the enthalpic contributions of strain and the entropic advantage of forming a larger number of species is the self-assembly of molecular triangles *and* squares[9] from azopyridine **4** and [Pd^{II}(dppp)] or [Pt^{II}(dppp)] complexes **3a**,**b** (Scheme 1).[10] Although the coordination geometry around the metal centers and the structure of the azopyridine ligand **4** would speak in favor of the exclusive formation of squares **6a**,**b**, which is indeed realized for 4,4′-bipyridine as the bidentate bridging ligand, a mixture of triangles **5a**,**b** and squares **6a**,**b** was identified by ^{1}H, ^{31}P, and DOSY NMR spectroscopy and ESI-FTICR mass spectrometry. This can be understood, if a lower rigidity of azopyridine **4** relative to 4,4′-bipyridine is assumed; this lowers the strain imposed on the triangle. While in the bipyridine case, the strain is higher and the enthalpic contributions govern the exclusive formation of squares, for azopyridine the entropically favorable formation of triangles overcompensates strain.

Specificity is an important goal in the application of self-assembly to the formation of defined supramolecular structures that can also be favored over non-specific oligomers, if "secondary effects" stabilize one defined species over all others. Typical "secondary effects" are again based on weak noncovalent interactions, for example, solvation effects,



Scheme 1. Self-assembly of molecular triangles **5a**,**b** and squares **6a**,**b** from azopyridine **4**.



Scheme 2. A modified anion template effect that serves for the synthesis of rotaxanes with functional groups in the axle center piece. The inset shows a hydroquinone center piece which can be used similarly.

steric constraints, or π-stacking as in double-stranded DNA. Templates[11] represent a particular type of such secondary effects in that the geometry of the assembly receives structural information from its environment (the template) rather than its own properties. Nevertheless, the control of mixture compositions by templating is a tempting challenge and the design of suitable templates is by no means trivial.

A problem which can be solved by designing suitable template effects is the threading of an axle through a macrocycle, which after attachment of stoppers leads to a rotaxane structure or gives rise to a catenane upon cyclization of the thread. Thus, in elegant approaches different kinds of templating were used by Stoddart, Sauvage, and Vögtle for the preparation of mechanically linked supermolecules.[12] A more recent example is the modified anion template effect that permits the synthesis of rotaxanes with phenolic OH groups in the axle center piece (Scheme 2).[13] These functionalities are controlled by pH changes and one may well take advantage of them in order to control the motion of the wheel around or along the axle.

Another illustrative example is the template-directed formation of dinuclear triple-stranded cryptand-type helicates like **7** and **8**[14] from alkyl-bridged dicatechol or di(8-hydroxyquinoline) ligands, respectively; these form according to the principles of dynamic combinatorial chemistry.[15] Initially, molecular diversity is generated by nonspecific formation of oligonuclear coordination compounds. Due to the noncovalent nature of the coordinative bonds between the building blocks, all species of the library are in equilibrium with each other under the appropriate conditions. Addition of a template selects the most appropriate "receptor" present in this mixture and shifts the library composition towards the desired host–guest complex by enthalpic stabilization. In Figure 3, the solid-state structures of helicate-type complexes **7** and **8** are shown; these were obtained by this principle and possess cations as the templating species bound in their interior.

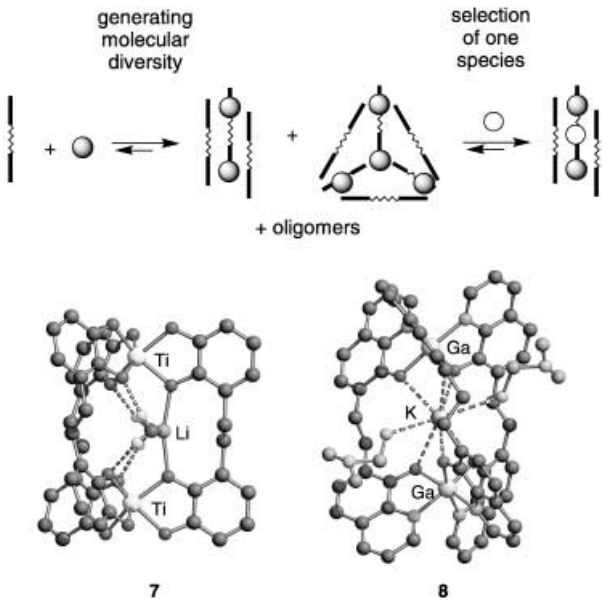


Figure 3. Dynamic combinatorial chemistry—template-directed formation of dinuclear triple-stranded cryptand-type helicates **7** and **8**.

Structural Control of Function

After this brief discussion of ways to generate large and complex architectures from much simpler building blocks, the question arises how structure and function are related. A large variety of functional units could be discussed here,[1] among them optically active building blocks, such as ruthenium–bipyridine complexes or porphyrins, electroactive groups, such as ferrocene or quinones, functional groups useful for supramolecular catalysis,[16] and many more. However, since we deal with supramolecular approaches to functionality in this article, we will focus on host–guest chemistry, molecular motion, and the stabilization of specific conformations here. These functions, for example, the recognition of a guest in a receptor, seem to be rather simple, but their successful implementation is still a challenge. Furthermore, they may be part of a functional chain in that, for example, guest binding may act as an input signal to induce and mediate another process that is either suppressed or only possible when no guest is present. Thus, it is of prime importance to be able to tailor hosts and supramolecular catalysts. Both are related to each other, because a receptor binds a guest molecule in one of its minima on the potential-energy surface (PES), while supramolecular catalysts must be hosts with a higher affinity for the transition structure of the desired reaction than to the reactant and product. This is beautifully illustrated by hydrogen-bonded capsules[17] that are capable of binding guests with a high degree of selectivity[18] and have also been shown to promote and catalyze Diels–Alder reactions.[19] Consequently, the same principles govern both types of functional molecules, they are just applied to different species on the PES. One of them is the principle of preorganization.[20] High binding constants and selectivity are achieved when the binding sites of a host are as complementary as possible to those of the guest. However, since the match between host and guest usually is not perfect, it is often advantageous if the host has limited flexibility to adjust to the guest (or the transition structure).[21]

Another important structural problem is the assembly of chiral hosts for chiral recognition and, again, helicates may serve as examples to illustrate this point. The stereochemistry of helicate-assembly versus formation of the achiral *meso*-helicate ("side-by-side" complex) is influenced by the rigidity of the ligands, by templating effects, or by chiral substituents at the ligand. A systematic approach to the diastereoselective formation of helicates ($\Lambda\Lambda$ and $\Delta\Delta$) or *meso*-helicates ($\Lambda\Delta$) is to use alkyl-bridged ligands. Due to the preferred zigzag-conformation of the alkyl-spacer, ligands with an odd number of methylene-units in the bridge lead to the *meso*-helicate; while ligands with an even number of CH_2 units are well predisposed for the formation of the helicate (Figure 4).[11,22]

Enantiomerically pure helicates are obtained when chiral substituents are introduced either at the termini or in the spacer of the ligand. In particular, the latter strategy offers the opportunity to obtain supramolecular structures that bear chiral cavities with inwardly directed functionalities which could be used for further purposes, such as molecular recognition or supramolecular reactivity. However, in order to avoid problems arising from the orientation of the ligands in these helicates, which would result in an almost uncontrollable number of possible stereoisomers, the use of dissymmetric ligand units is especially advantageous. This could be shown with 2,2′-dihydroxy-1,1′-binaphthyl-centered bisbipyridine ligand **11** (Figure 5), which undergoes diastereoselective self-assembly upon coordination to suitable transition-metal ions to form enantiomerically pure dinuclear double- and triple-stranded helicates.[23] Whereas the

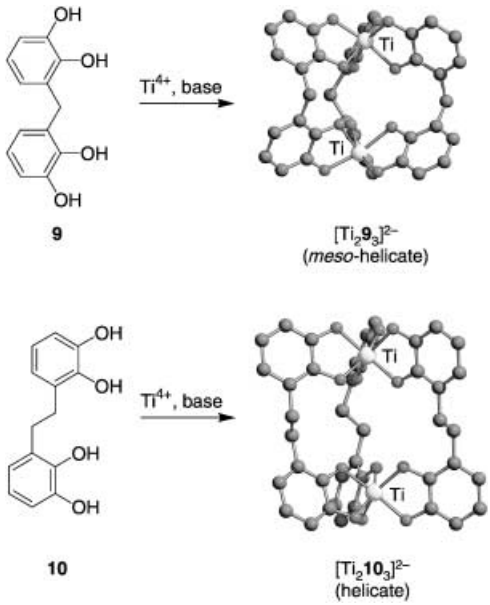


Figure 4. Stereoselectivity of dinuclear metal coordination complexes—helicate assembly versus formation of the achiral *meso*-helicate.

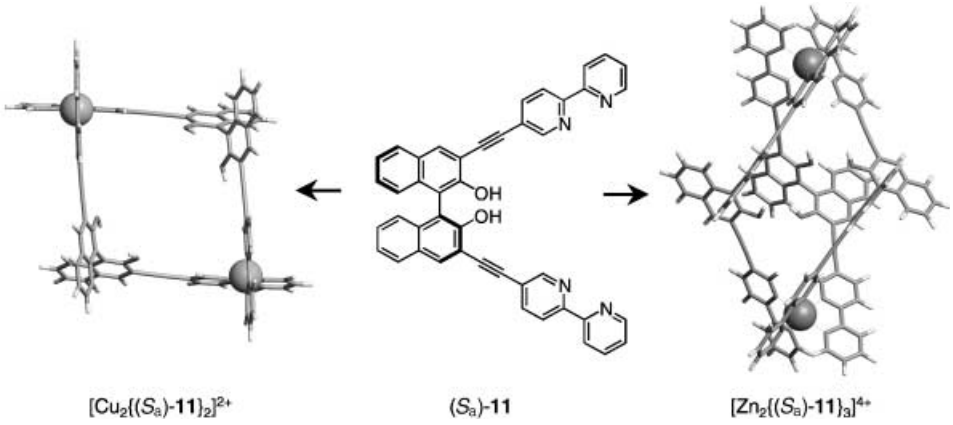


Figure 5. Enantiomerically pure double- and triple-stranded helicates $[Cu_2\{(S_a)\text{-}\mathbf{11}\}_2]^{2+}$ (left) and $[Zn_2\{(S_a)\text{-}\mathbf{11}\}_3]^{4+}$ (right) (MMFF-minimized structures) with inwardly directed functional groups.

ligand itself proved to be ineffective for the recognition of monosaccharide derivatives, the double-stranded dinuclear silver(I) helicate could be demonstrated to bind these molecules under identical conditions in qualitative NMR-based binding studies.

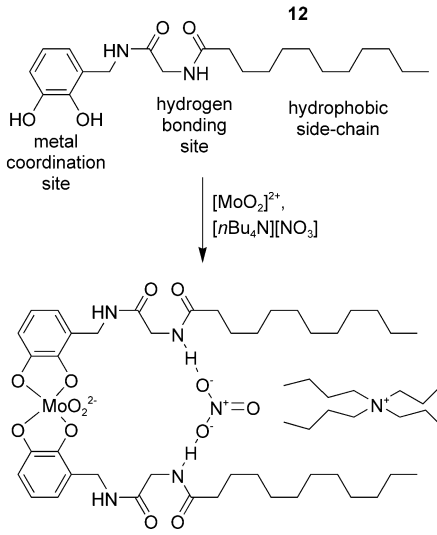
Conformational Control of Function

An organized flow of signals is required in order to control function. Signal transduction at a molecular level can be afforded by messenger molecules, a principle which is often realized in biology. However, there are different ways to obtain controlled function, one of which employs conformational changes that are a result of the action of an external signal. One example for such a system is the biconformational perhydroanthracene described by Koert et al.[24] The preferred conformation of the perhydroanthracene permits the formation of an excimer of two incorporated pyrene units upon irradiation with light. Light emission from the excimer occurs. After Zn^{II} addition, a conformational flip is induced by complexation of the metal to two bipyridine units at the opposite site of the molecule. Excimer formation is prevented and light emission occurs from the pyrene monomers.

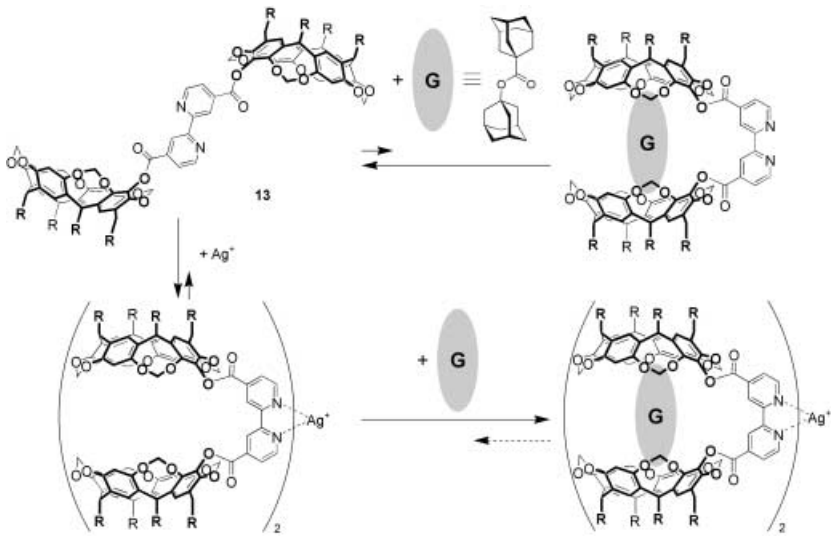
Of course not only the properties of a molecule, but also those of a supermolecule highly depend on the conformation that is adopted. For example, a cryptand-type helicate with ethylene-linked bis(8-hydroxyquinoline) ligands (as shown in Figure 3) can adjust its size to effectively bind either small sodium or larger potassium cations ("induced fit").

Multiple binding sites that can undergo different noncovalent supramolecular interactions in a hierarchical way can lead to the formation of well-defined aggregates. An example, in which allosteric behavior between different domains of a compound can be observed, is shown in Scheme 3. The catechol derivative **12** possesses one catecholate–metal binding site, a hydrogen bonding site (amides), and one hydrophobic side-chain. Addition of a source of *cis*-dioxomolybdenum(VI) dications leads to a mixture of isomeric dicatecholmolybdenumdioxo complexes, which upon addition of tetrabutyl ammonium nitrate transforms into one defined species. This compound is stabilized by allosteric action of the strong metal coordination together with the weaker hydrogen bonding between nitrate and amide and probably hydrophobic interactions between the side-chains and the tetrabutyl ammonium ion.[25]

A triggered conformational rearrangement can be used to switch on or off some function that is intrinsically embedded in different parts of a molecule, but which have to be specially arranged in space for an optimized cooperative action. Bis(resorcin[4]arene)-substituted 2,2′-bipyridine **13** is a good example for such a heterotropic positive cooperative allosteric receptor.[26] Its recognition behavior towards nonpolar substrates like the adamantyl ester of adamantane carboxylic acid can be changed dramatically upon coordination of a transition-metal ion as an effector or modulator to the 2,2′-bipyridine unit, which serves as the allosteric center. As depicted in Scheme 4, the free ligand is not able to bind the substrate because the two resorcinarene units of the receptor are not able to take part in simultaneous attractive interactions with a single guest molecule. However, the binding of the metal ion switches the conformation in a way that a hemicarcerand-like structure is obtained in which both resorcinarenes can cooperatively participate in the recognition



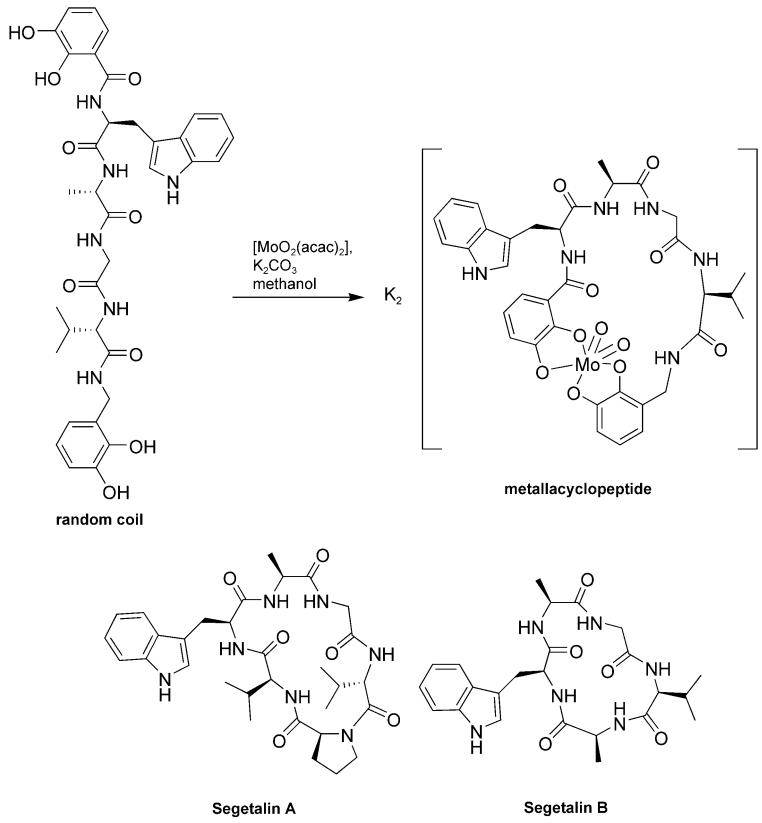
Scheme 3. Dicatecholmolybdenumdioxo complex as an allosteric ion pair receptor.



Scheme 4. Allosteric recognition behavior of bis(resorcin[4]arene) **13**.

of one substrate molecule mainly through CH–π interactions and solvophobic effects.

Noncovalent interactions can be used to switch on and off other functions or activities. For example, short linear peptides, which are terminated by catechol units, form metallacyclopeptides in the presence of *cis*-dioxomolybdenum(VI). A conformationally undefined random coil peptide can be fixed in a well-defined turn- or loop-type structure by metal coordination to the catechols (Scheme 5). One of the major challenges then is to prepare such compounds that possess no or low biological activity in the uncomplexed state, but upon addition of metal ions obtain a rigidified structure with enhanced biological activity. Therefore, the active Trp-Ala-Gly-Val-sequence of the natural products segetalin A and B[27] was introduced as the spacer in a dicatechol derivative. Complexation with $[MoO_2]^{2+}$ leads to the metallacyclopeptide, with the peptide front fixed in a similar conformation as is found in the bioactive natural compounds.[28]



Scheme 5. Mimicking the active part of the Segetalins A and B by fixation of a peptide loop.

As a final example for conformational control of function, rotaxanes and catenanes may serve to illustrate how external stimuli can be converted into molecular motion. Several groups attempted to construct artificial molecular motors on the basis of rotaxanes, the macrocyclic wheel being the stator and the axle representing the rotor. Similarly, one wheel of a catenane can move through the cavity of the other. With respect to the external stimuli that induce such motion in a controlled way, chemical signals, light, or electrons can be used, for example, to modulate hydrogen-bonding abilities[29] or the preferred coordination number of a metal ion.[30]

Other applications in nanoscale electronics can be envisaged. A molecular shuttle with two different states—despite of all technical difficulties involved in writing and reading information into or from one molecule—may be considered as one bit of a miniaturized computer chip.[31] If the switching between two states can be controlled by two different stimuli, logic gates can be constructed that combine two different input signals to one output. Such electronic devices at a molecular level are one of the chemists' potential answers to the visions of Feynman's bottom-up approach.[32] Since the ongoing reduction of the size of conventional electronic devices (the top-down approach) has limitations that cannot be overcome with current technology, it seems promising to start with molecules and construct electronic devices at a nanometer level.

In order to reach these ambitious goals, it is necessary to obtain information about the kinetic and thermodynamic stability of these noncovalently assembled systems first. One approach is the systematic investigation of deslipping processes of rotaxanes to learn more about the effects of small structural variations.[33] Indeed, in molecules as large and flexible as rotaxanes, whose components are merely bound by mechanical trapping, even the smallest possible steric changes influence their properties: If one replaces a stopper group by a deuterated stopper group, the labeled stopper deslips more quickly through the wheel (Figure 6).[34] The reason for the approximately 10% faster rate of the deuterated stopper is the vibrational amplitude of the C–D bond, which is smaller than that of the C–H bond and thus makes the labeled stopper appear smaller than the unlabeled counterpart. This example illustrates how important even subtle effects may become, when a fine tuning of molecular machines is attempted.

Conclusion

"Supramolecular functionality" is not only a vision for the future, but many systems are already known in which some kind of supramolecular function is working. As impressive examples, molecular containers should be mentioned here. In the interior of the covalently linked carcerands of Cram

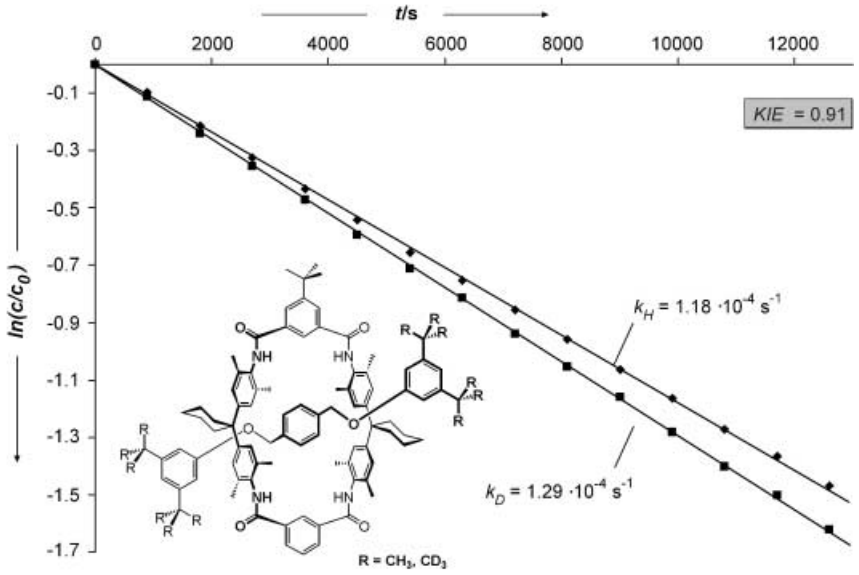


Figure 6. Plot of $\ln(c/c_0)$ against time (s) for the determination of the rate constants of deslipping of the deuterated and non-deuterated rotaxanes shown below. The kinetic isotope effect KIE is inverse and the value of approximately 0.9 indicates that the deuterated rotaxane deslips at a 10% higher rate than its unlabeled analogue.

and Warmuth, highly reactive species are stabilized at room temperature.[35] Rebeks hydrogen-bonded containers act as a kind of "molecular reaction vessel" and promote cycloadditions and other reactions,[19,36] and a very similar function is observed within the coordination compounds described by Fujita.[37] Three different types of assembly modes (covalent versus hydrogen-bonding versus metal coordination) lead to supramolecular ensembles, which owing to noncovalent binding of species are able to support or to suppress chemical reactions.

We have argued here that self-assembly and template effects are efficient means for the generation of complex structures, and this is certainly true if compared to covalent synthesis of similar architectures. With respect to function, however, a great challenge remains: most self-assembled structures known so far have rather simple building blocks that are in one or another way repeated within the architecture. This yields complex structures, but it does not necessarily end up with complex function. In particular, for functional chains that can sense an external stimulus (input) leading to a reaction within the chain (computing) which creates an externally measurable signal (output), complexity means to incorporate a variety of *different* subunits with different functional groups into one assembly at exactly the required positions. Complexity thus not only requires control over the repetition pattern of the assembly, but also control over, for example, sequence information. With systems of hierarchical self-assembly, the first steps in this direction have been made. Clearly, a ranking of different noncovalent forces with well-defined bond strengths helps to mediate such higher-order self-assembly. Nevertheless, much is left to be investigated in this respect.

Another problem is that of nanofabrication.[38] In particular, sizes between about 10 nm, which can easily be achieved by molecules and smaller aggregates, and 70 nm, which can be accessed with (although rather expensive) photolitography methods, need to be successfully addressed and need new technologies for implementing function.

Acknowledgments

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