1
Introduction

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1.1
Some Historical Remarks on Supramolecular Chemistry

The fundaments of Supramolecular Chemistry date back to the late 19th century, when some of the most basic concepts for this research area were developed. In particular, the idea of coordination chemistry was formulated by Alfred Werner (1893) [1], the lock-and-key concept was introduced by Emil Fischer (1894) [2], and Villiers and Hebd discovered cyclodextrins, the first host molecules (1891) [3]. A few years later, Paul Ehrlich devised the concept of receptors in his *Studies on Immunity* (1906) [4] by stating that any molecule can only have an effect on the human body, if it is bound (''Corpora non agunt nisi fixata''). Several of these concepts were refined and modified later. Just to provide one example, Daniel Koshland formulated the induced fit concept (1958) for binding events to biomolecules which undergo conformational changes in the binding event [5]. The induced fit model provides a more dynamic view of the binding event, compared with the rather static key-lock principle and is thus more easily able to explain phenomena such as cooperativity. Even the German word for ''Supramolecule'' appeared in the literature as early as 1937, when Wolf and his coworkers introduced the term ''Übermolekül'' to describe the intermolecular interaction of coordinatively saturated species such as the dimers of carboxylic acids [6].

The question immediately arising from this brief overview on the beginnings of supramolecular chemistry is: Why hasn't it been recognized earlier as a research area in its own right? Why did it take more than 40 years from the introduction of the term ''Übermolekül'' to Lehn's definition of supramolecular chemistry [7] as the ''chemistry of molecular assemblies and of the intermolecular bond'' [8]?

There are at least two answers. The first relates to the perception of the scientists involved in this area. As long as chemistry accepts the paradigm that properties of molecules are properties of the molecules themselves, while the interactions with the environment are small and – to a first approximation – negligible, there is no room for supramolecular chemistry as an independent field of research. Although solvent effects were already known quite early, this paradigm formed the basis of the thinking of chemists for a long time. However, with an increasing number of

Analytical Methods in Supramolecular Chemistry. Edited by Christoph Schalley

ISBN: 978-3-527-31505-5

examples of the importance of the environment for the properties of a molecule, a paradigm shift occurred in the late 1960s. Chemists started to appreciate that their experiments almost always provided data about molecules in a particular environment. It became clear that the surroundings almost always have a non-negligible effect. Consequently, the intermolecular interactions became the focus of research and a new area was born. With this in mind, chemists were suddenly able to think about noncovalent forces, molecular recognition, templation, self-assembly and many other aspects into which supramolecular chemistry meanwhile diversified.

The second answer is not less important, although somewhat more technical in nature. Supramolecules are often weakly bound and highly dynamic. Based on intermolecular interactions, complex architectures can be generated, often with long-range order. All these features need specialized experimental methods, many of which still had to be developed in the early days of supramolecular chemistry. As observed quite often, the progress in a certain research area – here supramolecular chemistry – depends on the development of suitable methods. An emerging new method on the other hand leads to further progress in this research field, since it opens new possibilities for the experimenters. It is this second answer which prompted us to assemble the present book in order to provide information on the current status of the methods used in supramolecular chemistry. It also shows how diverse the methodological basis is, on which supramolecular chemists rely.

1.2 The Noncovalent Bond: A Brief Overview

Before going into detail with respect to the analytical methods that are applied in contemporary supramolecular chemistry, this brief introduction to some basic concepts and research topics within supramolecular chemistry is intended to provide the reader with some background. Of course, it is not possible to give a comprehensive overview. It is not even achievable to review the last 40 or so years of supramolecular research in a concise manner. For a more in-depth discussion, the reader is thus referred to some excellent text books on supramolecular chemistry [7].

Noncovalent bonds range from coordinative bonds with a strength of several hundreds of kJ mol^{-1} to weak van der Waals interactions worth only a few kJ mol^{-1}. They can be divided in to several different classes. Attractive or repulsive interactions are found, when two (partial) charges interact either with opposite polarity (attraction) or the same polarity (repulsion). Ion–ion interactions are strongest with bond energies in the range of ca. 100 to 350 kJ mol^{-1}. The distance between the charges and the extent of delocalization over a part of a molecule or even the whole molecule have an effect on the strength of the interaction. Consequently, the minimization of the distance between two oppositely charged ions will be a geometric factor, when it comes to the structure of the supramolecular aggregate – even though there is no particular directionality in the ion–ion interaction. Interactions between ions and dipoles are somewhat weaker (ca. 50–200 kJ mol^{-1}). Here,

the orientation of the dipole with respect to the charge is important. A typical example for such an ion–dipole complex is the interaction of alkali metal ions with crown ethers. Other coordination complexes with transition metal ions as the cores are often used in supramolecular assembly. Here, the dative bond has a greater covalent contribution, which makes it difficult to clearly draw the line between supramolecular and molecular chemistry. Even weaker than ion–dipole forces (5–50 kJ mol^{-1}) are the interactions between two dipoles. Again, the relative orientation of the two interacting dipoles plays an important role.

Hydrogen bonding [9] is pivotal in biochemistry (e.g. in the formation of double stranded DNA and protein folding) and was also greatly employed in artificial supramolecules. One reason is that many host–guest complexes have been studied in noncompetitive solvents where the hydrogen bonds can become quite strong. Another, maybe equally important reason is the directionality of the hydrogen bond which allows the chemist to control the geometry of the complexes and to design precisely complementary hosts for a given guest (see below). One should distinguish between strong hydrogen bonds with binding energies in the range of 60–120 kJ mol^{-1} and heteroatom–heteroatom distances between 2.2 and 2.5 Å, moderate hydrogen bonds (15–60 kJ mol^{-1}; 2.5–3.2 Å), and weak hydrogen bonds with binding energies below ca. 15 kJ mol^{-1} and long donor–acceptor distances of up to 4 Å. This classification is also expressed in the fact that strong hydrogen bonds have a major covalent contribution, while moderate and weak ones are mainly electrostatic in nature. Also, the range of possible hydrogen bond angles is narrow in strong H bonds (175°–180°) so that there is excellent spatial control here, while moderate (130°–180°) and weak (90°–150°) hydrogen bonds are more flexible. Furthermore, one should always make a difference between hydrogen bonding between neutral molecules and charged hydrogen bonds. The latter ones are usually significantly stronger. For example, the $F{-}H\cdots F^-$ hydrogen bond has a bond energy of ca. 160 kJ mol^{-1} and thus is the strongest hydrogen bond known.

Noncovalent forces also involve π-systems, which can noncovalently bind to cations or other π-systems. The cation-π interaction [10] amounts to ca. 5–80 kJ mol^{-1} and plays an important role in biomolecules. Aromatic rings such as benzene bear a quadrupole moment with a partially positive σ-scaffold and a partially negative π-cloud above and below the ring plane. Consequently, alkali metal and other cations can form an attractive interaction when located above the center of the aromatic ring. The gas-phase binding energy of a K^+ cation to benzene (80 kJ mol^{-1}) is higher than that of a single water molecule to the same cation (75 kJ mol^{-1}). Consequently, one may ask why potassium salts don't dissolve in benzene. One answer is that the cation is stabilized by more than one or two water molecules in water and the sum of the binding energies is thus higher than that of a K^+ solvated by two or three benzenes. Another oft forgotten, but important point is the solvation of the corresponding anion. Water is able to solvate anions by forming hydrogen bonds. In benzene such an interaction is not feasible. Again, we touch the topic discussed in the beginning: the effects of the environment.

π-systems can also interact favorably with other π-systems. The interactions usually summarized with the term π-stacking are, however, quite complex. Two

similarly electron-rich or electron-poor π-systems (e.g. benzene as a prototype) tend not to interact in a perfect face-to-face manner [11], because the two partially negative π-clouds would repulse each other. Two options exist to avoid this repulsion: in the crystal, benzene forms a herringbone-packing. Each benzene molecule is thus positioned with respect to its next neighbors in an edge-to-face orientation. This causes an attractive interaction between the negative π-cloud of one benzene with the positive σ-scaffold of the other. Larger aromatic molecules, for example porphyrins, may well crystallize in a face-to-face orientation. However, they reduce the repulsive forces by shifting sideways. The picture changes significantly, when two aromatics interact one of which is electron-rich (prototypically a hydroquinone), one electron-deficient (prototypically a quinone). These two molecules can then undergo charge transfer interactions which can be quite strong and usually can be identified by a charge-transfer band in the UV/vis spectrum.

On the weak end of noncovalent interactions, we find van der Waals forces (<5 kJ mol^{-1}) which arise from the interaction of an electron cloud polarized by adjacent nuclei. Van der Waals forces are a superposition of attractive dispersion interactions, which decrease with the distance r in a r^{-6} dependence, and exchange repulsion decreasing with r^{-12}.

A particular case, finally, which perfectly demonstrates the influence of the environment, is the hydrophobic effect which relies on the minimization of the energetically unfavorable surface between polar/protic and unpolar/aprotic molecules. Hydrophobic effects play an important role in guest binding by cyclodextrins, for example. Water molecules residing inside the unpolar cavity cannot interact with the cavity wall strongly. If they are replaced by an unpolar guest, their interaction with other water molecules outside the cavity is much stronger, resulting in a gain in enthalpy for the whole system. In addition to these enthalpic contributions, entropy changes contribute, when several water molecules are replaced by one guest molecule, because the total number of translationally free molecules increases.

There are more noncovalent interactions which cannot all be introduced here. Forces between multipoles have been expertly reviewed recently [12]. Also, weak interactions exist between nitrogen and halogen atoms [13], and dihydrogen bridges [14] can be formed between metal hydrides and hydrogen bond donors. Finally, close packing in crystals is an important force in crystallization and crystal engineering. The present introductory chapter will not discuss these, but rather focus on the most important ones mentioned above.

1.3 Basic Concepts in Supramolecular Chemistry

The following sections discuss some fundamental concepts in supramolecular chemistry. The list is certainly not comprehensive and the reader is referred to textbooks for a broader scope of examples. However, the selection reveals that supramolecular research developed from its heart, i.e. the examination and understanding of the noncovalent bond, to more advanced topics which make use of that

knowledge to build large, complex architecture, to understand the action of biomolecules, to implement function into molecular devices such as sensors, to control mechanical movement, to passively and actively transport molecules, and to use supramolecules as catalysts.

Clearly, molecular recognition processes are the prototypical supramolecular reactions on which the other aspects are based. Without molecular recognition, there are no template effects, no self-assembly, and certainly no self-replication. In contrast to opinions sometimes encountered among chemists from other areas, supramolecular chemistry did not come to a halt with the examination of hosts and guests and their interactions. Sophisticated molecular devices are available which not only are based on, but go far beyond mere molecular recognition.

1.3.1
Molecular Recognition: Molecular Complementarity

After these remarks, the first question is: What is a good receptor for a given substrate? How can we design a suitable host which binds a guest with specificity? According to Fischer's lock-and-key model, complementarity is the most important factor. Most often, it is not one noncovalent interaction alone which provides host–guest binding within a more or less competing environment, but the additive or even cooperative action of multiple interactions. The more complementary the binding sites of the host to those of the guest, the higher the binding energy. This refers not only to individual noncovalent bonds, but to the whole shape and the whole electrostatic surface of both molecules involved in the binding event. Selective binding is thus a combination of excellent steric fit with a good match of the charge distributions of guest surface and the hosts cavity and a suitable spatial arrangement of, for example, hydrogen bond donors and acceptors, thus maximizing the attractive and minimizing the repulsive forces between host and guest.

Cation recognition developed quickly early on, due to the combination of the often rather well-defined coordination geometry of most cationic species and the usually higher achievable binding energies coming from ion–dipole interactions. Actually, many of the basic concepts in supramolecular chemistry have been derived from studies in cation recognition. The design of neutral hosts for neutral guests and in particular anion recognition [15] are still a challenge nowadays.

1.3.2
Chelate Effects and Preorganization: Entropy Factors

A binding event in which one complex forms from two molecules is entropically disfavored. The entropic costs need to be paid from the reaction enthalpy released upon host–guest binding. However, strategies exist which can reduce these costs to a minimum.

One approach is to incorporate more than one binding site in one host molecule. When the first bond is formed, the entropic costs of combining two molecules are taken care of. The second and all following binding events between the same two

partners will not suffer from this effect again and thus contribute more to the free enthalpy of binding. This effect is called the chelate effect and has long been known from coordination chemistry, where ethylene diamine or 2,2′-bipyridine ligands easily replace ammonia or pyridine in a transition metal complex. Bidentate binding generates rings and the chelate effect depends on their sizes. Optimal are five membered rings as formed by the ethylene diamine or bipyridine ligands discussed above. Smaller rings suffer from ring strain, larger rings need a higher degree of conformational fixation compared with their open-chain forms and are thus entropically disfavored. The latter argument can be refined. If the same number of binding sites are incorporated in a macrocycle or even macrobicycle, guest binding will again become more favorable, because each cyclization reduces the conformational flexibility for the free host and thus the entropic costs stemming from conformational fixation during guest binding. These effects have entered the literature as the macrocyclic and macrobicyclic effect. Donald Cram developed these ideas into the preorganization principle [16]. A host which is designed to display the binding sites in a conformationally fixed way, perfectly complementary to the guest's needs, will bind significantly more strongly than a floppy host which needs to be rigidified in the binding event. This becomes strikingly clear, if one compares conformationally flexible 18-crown-6 with the spherand shown in Fig. 1.1 which displays the six oxygen donor atoms in a preorganized manner. The alkali binding constants of the two host molecules differ by factors up to 10^{10}!

While discussing entropic effects, it should not be forgotten that examples exist for enthalpically disfavored, entropy-driven host–guest binding. This is possible, if the free host contains more than one solvent molecule as the guests, which upon guest binding are replaced by one large guest as discussed for cyclodextrins above. In this case, a host–solvent complex releases more molecules than it binds and the overall reaction benefits entropically from the increase in particle number.

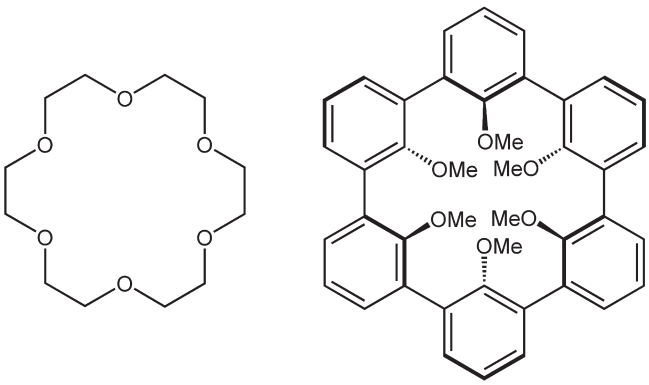


Fig. 1.1. Preorganization does matter. A comparison of 18-crown-6 and the spherand on the right with respect to alkali metal ion binding reveals that the spherand has an up to 10 orders of magnitude higher binding constant.

1.3.3 Cooperativity and Multivalency

Cooperativity and multivalency are phenomena arising in molecular recognition at hosts with more than one binding site. In order to avoid misunderstandings, one should clearly distinguish the two terms. Cooperativity describes the influence of binding a guest at the host's binding site A on the second binding step occurring at site B of the same host. Cooperativity can be positive, which means that binding strength of the second guest is increased by the first one and the sum of both binding energies is more than twice the binding energy of the first guest. Cooperativity can also be negative, if the first binding event decreases the binding of the second guest. Many examples for cooperativity are known from biochemistry, the most prominent one certainly oxygen binding at hemoglobin [17]. This protein is a $\alpha_2\beta_2$ tetramer with four oxygen binding hemes as the prosthetic groups, one in each subunit. Upon binding the first oxygen molecule to one of the heme groups, conformational changes are induced in the protein tertiary structure which also affect the other subunits and prepare them for binding oxygen more readily. From this example, it becomes clear that cooperativity does not necessarily rely on interactions between a multivalent host and a multivalent guest, but that there may well be mechanisms to transmit the information of the first binding event to the second one, even if both are monovalent interactions. The concept of cooperativity has been applied to supramolecular chemistry and was recently discussed in the context of self-assembly [18] (see below).

Conceptually related to the chelate effect, multivalency [19] describes the unique thermodynamic features arising from binding a host and a guest *each* equipped with more than one binding site. Although sometimes not used in a stringent way in the chemical literature, one should use the term "multivalency" only for those host–guest complexes, in which the dissociation into free host and guest requires at least the cleavage of two recognition sites. The concept of multivalency has been introduced to adequately describe the properties of biomolecules [20]. For example, selectivity and high binding strengths in recognition processes at cell surfaces usually require the interaction of multivalent receptors and substrates. Due to the complexity of many biological systems, limitations exist for a detailed analysis of the thermochemistry and kinetics of multivalent interactions between biomolecules. For example, the monovalent interaction is usually unknown and thus, a direct comparison between the mono- and multivalent interaction is often not feasible. The sometimes surprisingly strong increase of binding energy through multivalency is thus not fully understood in terms of enthalpy and entropy.

Recently, this concept was applied convincingly to artificial supramolecules. The examination of artificial, designable, and less complex multivalent systems provides an approach which easily permits analysis of the thermodynamic and kinetic effects in great detail. As an example, the binding of a divalent calixarene ligand bearing two adamantane endgroups on each arm binds more strongly to a cyclodextrin by a factor of 260 compared with the monovalent interaction – a much

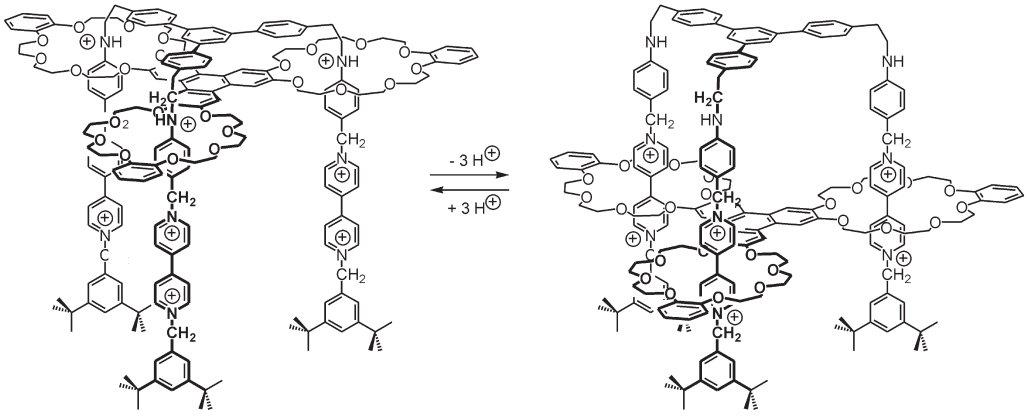


Fig. 1.2. Molecular elevator synthesized by utilizing multivalency. The position of the wheel component can be controlled by protonation/deprotonation.

higher increase than expected for merely additive interactions. If offered many cyclodextrin hosts on a surface, the binding constant again increases by 3 orders of magnitude [21]. Another example is shown in Fig. 1.2 [22]. A three-armed guest is capable of forming a triply threaded pseudorotaxane with the tris-crown derivative. Attachment of stoppers at the ends of each arm prevents deslippage of the axle components. The trivalent interaction increases the yield of the synthesis through favorable entropic contributions. At the same time, the function of a "molecular elevator" is implemented: depending on protonation and deprotonation of the dialkyl amines, the crown ethers move back and forth between two different stations along the axle.

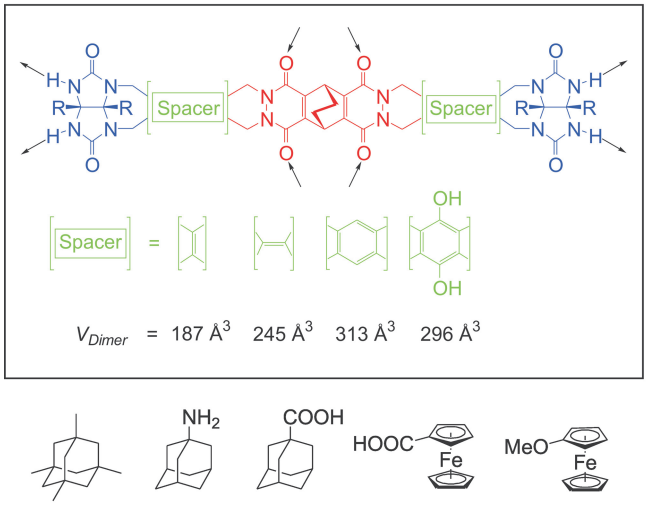
1.3.4 Self-assembly and Self-organization

Self-assembly [23] is a strategy used by supramolecular chemists to reduce the efforts required for the generation of complex structures and architectures. Instead of tedious multistep covalent syntheses, simple building blocks are programmed with the suitably positioned binding sites and upon mixing the right subunits, they spontaneously assemble without any additional contribution from the chemist. Several requirements must be met: (i) the building blocks must be mobile, but this requirement is almost always fulfilled with molecules in solution due to Brownian motion; (ii) the individual components must bear the appropriate information written into their geometrical and electronic structure during synthesis to provide the correct binding sites at the right places. Since their mutual recognition requires specificity, self-assembly is a matter of well pre-organized building blocks (see above); (iii) the bonds between different components must be reversibly formed. This means that the final aggregate is generated thermodynamically con-

trolled under equilibrium conditions. This aspect is important, because kinetically controlled processes do not have the potential for error correction and thus usually lead to mixtures. The reversibility of self-assembly processes also results in quite dynamic aggregates prone to exchange reactions of their building blocks.

Self-assembly is ubiquitous in nature [24] and often occurs on several hierarchy levels simultaneously in order to generate functional systems. For example, the shell-forming protein building blocks of the tobacco mosaic virus [25] need to fold into the correct tertiary protein structure before they can be organized around a templating RNA strand. All these processes are mediated by noncovalent forces which guide the formation of secondary structure elements on the lowest hierarchy level. These form the tertiary structure on the next level which displays the necessary binding sites for the assembly of the virus from a total of 2131 building blocks to occur as programmed on the highest level. Other examples for hierarchical self-assembly are multienzyme complexes, the formation of cell membranes with all the receptors, ion channels, or other functional entities embedded into them, or molecular motors such as ATP synthase. Self-assembly is thus an efficient strategy to create complexity and – together with it – function in nature.

Self-assembly has also been applied to numerous different classes of complexes in supramolecular chemistry [26]. Since we cannot discuss them all here, Fig. 1.3 shows only one example of a capsule reversibly formed from two identical self-complementary monomers which are bound to each other by hydrogen bonding



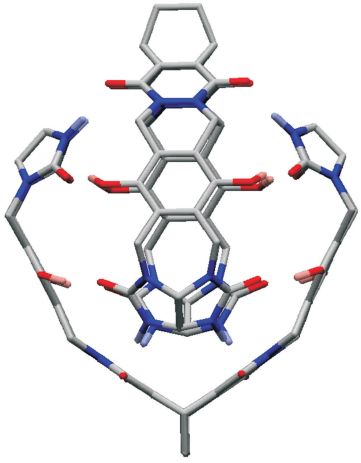


Fig. 1.3. Self-assembling "softball". Right: Computer model of the softball bearing the hydroquinone spacer (side chains are omitted). Box (left): Different monomers which form dimers with cavities of volumes between 187 and 313 Å^3 depending on the spacer length. Left: A selection of good guest molecules which can occupy the cavity inside the capsule.

[27]. The two monomers can encapsulate guests in the interior cavity of the capsule. Even more than one guest can be encapsulated, and reactions can be catalyzed inside.

Another term which is often used in the literature as synonymous with self-assembly is self-organization. However, again, we should be precise with respect to the meaning of the terms we use. One suggestion for definitions would be to distinguish processes which lead to the thermodynamic minimum and thus lead to chemical equilibria. These processes should be called self-assembly processes. On the other hand is the broad variety of spontaneous organization which occurs far away from the thermodynamic equilibrium. Many processes in living organisms are examples for self-organization in this sense. The major difference between self-assembly and self-organization is that self-assembly occurs even in a closed system while self-organization can be characterized as a steady state in which a system remains without falling to the thermodynamic minimum, because energy is constantly flowing through it. This definition has the advantage that it makes a clear difference between the two terms. This advantage however comes at the price that it is experimentally difficult to determine which is which by simple criteria.

1.3.5 Template Effects

One way to control the outcome of a reaction is templating. Like in the macroscopic world, a chemical template organizes reaction partners and thus allows the chemist to control their reactivity to achieve the formation of a desired product. However, it is almost impossible to give a concise definition of the term ''template'' [28]. Templates span the whole range from biochemistry with its complex apparatus for DNA replication [29] to the formation of structured inorganic materials [30] to the templated synthesis of macrocycles [31] to the preparation of supramolecular catalysts [32] – just to name a few examples. Nevertheless, all these have in common that a template must serve different purposes: (i) it organizes reaction partners for the formation of a desired product whose synthesis cannot be achieved in the absence of the template. Thus, a template controls reactivity and produces form; (ii) the template needs to bind to the reaction partners. Molecular recognition is thus a necessary prerequisite for template syntheses and the binding sites of the components must be complementary to each other. Usually, binding is due to noncovalent bonds, although examples for covalent templates exist; (iii) the control of reactivity and the recognition of the reaction partners imply information to be programmed into the template which is transferred to the product of the reaction.

There are different ways to categorize templates. One could for example try to distinguish template effects according to the (non-)covalent interactions involved. This classification remains ambiguous for templates operating through different forces at the same time. A maybe better way to classify templates relates to their topography. The early templated crown ether syntheses utilized alkali metal ions

around which macrocycles form with size selectivity [33]. Such templates are convex, because of their convex surface mediating the template effect. In contrast, a receptor binding two molecules which react inside a cavity is concave. This is true for many templates leading to mechanically interlocked species. One of the most prominent natural templates, i.e. single-stranded DNA, could be called a linear template according to this classification. Finally, a surface on which molecules self-assemble into an ordered array [34] may be considered as a planar template. [35].

Although there certainly is some overlap, one should distinguish between a reactant, a template, and a catalyst [36]. A strict definition would stress that the template must be removable after a successful reaction, while a reactant at least in part remains in the product. However, these definitions become blurred. For example, the synthesis of rotaxanes, catenanes, and knots [37] often relies on macrocycles which in their cavity bind an axle component in a pseudorotaxane fashion. Thus, the macrocycle acts as the template which organizes the axle in a threaded geometry. Ring closure of the axle or the attachment of stoppers lead to catenanes or rotaxanes, respectively. The macrocyclic template finally becomes part of the product according to the strict definition would be considered as a reactant rather than a template. Nevertheless, this view on the synthesis of interlocked molecules – one out of many examples is shown in Fig. 1.4 – neglects the organization of the two pseudorotaxane components which is essential for the formation of the mechanical bond. Thus, these syntheses are widely accepted as template-mediated in the chemical literature, although the use of removable transition metal ions for the synthesis of mechanically interlocked molecules [38] is probably the only true template synthesis for interlocked molecules in the strict sense. It is similarly difficult to separate templates from catalysts: on one hand, many templates do not promote catalytic reactions, because the template does not generate turnover. They need to be used in stoichiometric amounts and have to be separated from the product. On the other hand, some catalysts do not organize the reactants in space but rather change their intrinsic reactivity as for example encountered in general acid or base catalysis. Thus, they cannot be regarded as templates. These are the clear-cut cases. However, mixed forms exist, where a template is bound reversibly to the product or where a catalyst organizes the reactants with respect to their geometry. We therefore put forward a more abstract view of what a template is and consider a template as the sum of all connections between the species reacting with each other which are involved in geometrically controlling the reactivity in the desired way. It is the array of interactions and their spatial arrangement that count.

1.3.6
Self-replication and Supramolecular Catalysis

While multivalency, self-assembly, and template effects provide strategies aiming at generating more and more complex architectures, supramolecular chemistry can also be utilized for controlling reactivity and even catalyzing reactions. Closely related to organocatalysis, supramolecular catalysts [39] accelerate reactions by

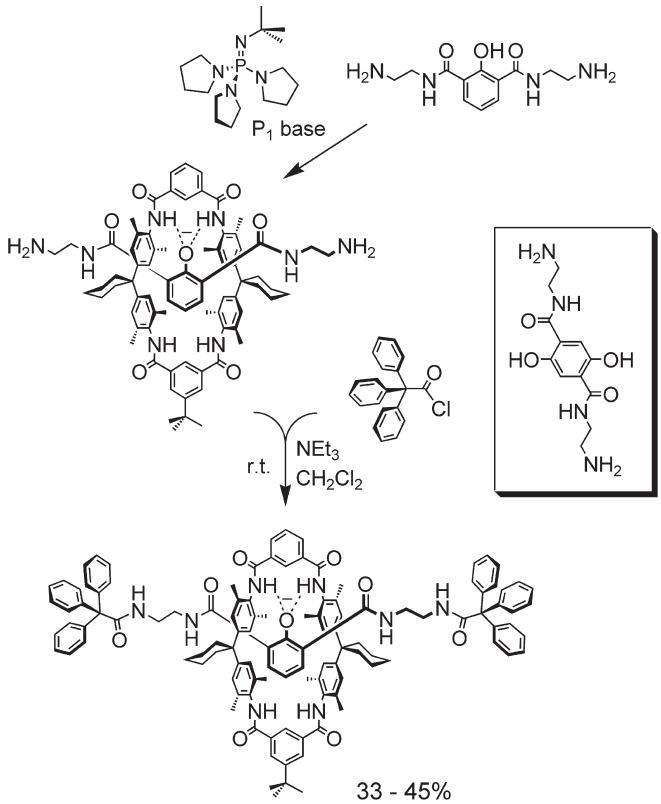


Fig. 1.4. Anion-templated rotaxane synthesis. The axle center piece is threaded through the macrocycle's cavity by hydrogen bonding. Stopper attachment to both axle ends traps the wheel on the axle. Inset: hydroquinone-based center piece which can also be used, but with lower efficiency.

lowering the barriers. The principles by which they fulfil the task are very different. Increasing the local concentration of the reactands by encapsulation is one example (see Fig. 1.3 above), increasing the intrinsic reactivity of carbonyl compounds through hydrogen bonding [40] is another and many more exist.

Originating from the question how the living organisms came into existence, self-replication is a special, but certainly intriguing case of supramolecular catalysis. If one thinks about the complex ribosome, which nowadays transscribes genetic information stored in nucleic acids into proteins, which then become involved in the duplication of DNA, it is immediately clear that this apparatus is much too complex to self-organize accidentially at the beginning of life. Instead, much simpler mechanisms must have existed in the early world. In order to find an answer, several research groups provided evidence that short DNA oligomers are indeed able to self-replicate in the presence of the appropriate template [41].

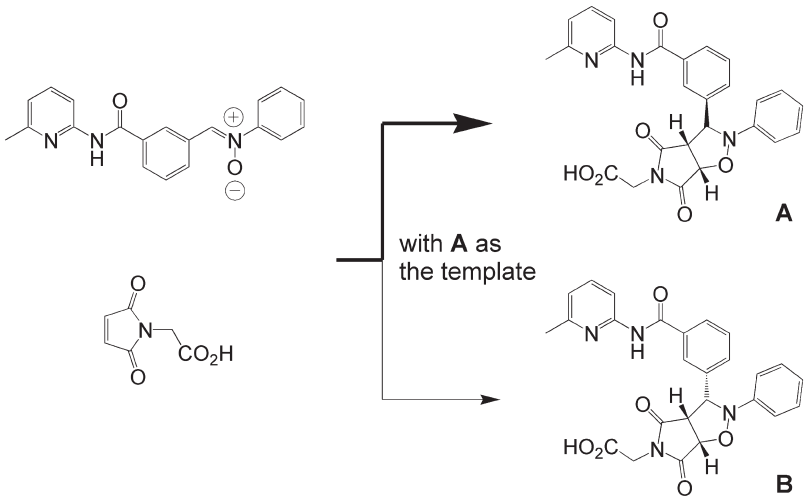


Fig. 1.5. A minimal self-replicating system. In the presence of template **A**, the two reactands on the left are organised in a way suitable for a 1,3-dipolar cycloaddition reaction. The pyridineamide part of the template recognizes the acid substituent in the reactand, while the second reactand is recognized by the carboxylic acid incorporated in the template. Particularly interesting is the fact that template **A** favors its own formation, while the other stereoisomer **B** is formed only in low amounts.

Later, suitable α-helical peptides have been shown to self-replicate as well [42]. In the context of supramolecular chemistry most interesting are however organic minimal-replicators [43] which are not based on biomolecules. Figure 1.5 shows an example for a minimal self-replicating system, which operates even in a chiroselective way. One given enantiomer of the template catalyzes its own formation, while the other enantiomer is by and large suppressed.

1.3.7
Molecular Devices and Machines: Implementing Function

Early supramolecular chemistry certainly focussed on the noncovalent bond and the beauty of structures which can be generated employing it. This is certainly the case for topologically interesting molecules such as rotaxanes, catenanes, knotanes and Borromean rings [37]. It also holds for the generation of self-assembling capsules, helicates [44], or metallo-supramolecular tetrahedra, octahedra and the like [45]. However, the focus has shifted in contemporary supramolecular chemistry towards the implementation of function into noncovalent architectures. The scope of function is broad and ranges from light-induced energy and electron transfer processes [46] and molecular wires [47] to switches [48], molecular ''motors'' [46], and devices for the active pH-driven transport of molecules through membranes. This

area is too broad to give a satisfying introduction here and thus, the reader is referred to the literature cited.

1.4 Conclusions: Diverse Methods for a Diverse Research Area

The admittedly short and simplified considerations above make clear that one aim of supramolecular chemistry is to mimic natural processes. The above sections deliberately chose examples from biochemistry as well as the multitude of artificial supramolecules in order to point to the relations which exist between the two fields. Understanding the details of noncovalent binding is much more difficult in a complex biomolecule, and thus simple model systems provide the basis for a more profound analysis. However, supramolecular chemistry goes beyond merely creating model systems for naturally occurring species. In contrast to biomolecules, supramolecular chemistry can utilize the whole range of conditions achievable, for example with respect to the use of organic solvents, in which many biomolecules would lose their integrity, because they are designed for an aqueous surrounding. Higher or lower temperatures or different pressures can also be applied. Supramolecules may even find their applications under conditions where biomolecules would not have the necessary long-term stability. The implementation of function also aims at new functions which are not realized in nature. In particular, the latter two aspects lead us to the second research area to which supramolecular chemistry contributes significantly: material sciences. Self-assembly, for example, is a strategy to create long-range order and has even been applied to particles on a micro- to millimeter scale [49].

If one thinks about function, in particular switches, logic gates, and molecular wires, it becomes clear that supramolecular chemistry is also about information processing. However, it is not only its potentially upcoming use in microelectronics: information processing begins at a much more fundamental level. Templates transfer spatial information between molecules; in order to achieve correctly self-assembling species, the building blocks of the assembly need to be programmed with the appropriate binding sites. Information transfer and information processing already starts at the molecular level.

A view back on the last few decades makes perfectly clear that supramolecular chemistry has become a highly diverse field which requires the interdisciplinary use of a huge variety of methods to answer the scientific questions addressed. Diversity however is not the only challenge for the methods that are needed. The complexity of the architectures meanwhile realized requires sophisticated structure analysis tools. The highly dynamic features of supramolecules need kinetic methods able to address many different time scales. Gathering evidence for the functions implemented is impossible without a sound methodological basis. Finally, the wish to image and influence single molecules led to the application of scanning probe microscopy to supramolecular systems. The present book intends to take this into account and to provide an overview on methods used in supramolecular chemistry – even though it is probably not possible to be comprehensive.

References and Notes

1 A. Werner, *Zeitschr. Anorg. Chem.* **1893**, 3, 267.

2 E. Fischer, *Ber. Deutsch. Chem. Ges.* **1894**, 27, 2985. Also, see: J.-P. Behr (ed.), *The Lock and Key Principle. The State of the Art – 100 Years On*, Wiley, Chichester 1994.

3 a) A. Villiers, C. R. Hebd, *Seances Acad. Sci.* **1891**, 112, 435; b) A. Villiers, C. R. Hebd, *Seances Acad. Sci.* **1891**, 112, 536.

4 P. Ehrlich, *Studies on Immunity*, Wiley, New York 1906.

5 D. E. Koshland, Jr., *Proc. Natl. Acad. Sci. USA* **1958**, 44, 98.

6 K. L. Wolf, H. Frahm, H. Harms, *Z. Phys. Chem. (B)* **1937**, 36, 237.

7 For textbooks, see: a) F. Vögtle, *Supramolekulare Chemie*, Teubner, Stuttgart **1992**; b) J.-M. Lehn, *Supramolecular Chemistry*, Verlag Chemie, Weinheim **1995**; c) H.-J. Schneider, A. Yatsimirsky, *Principles and Methods in Supramolecular Chemistry*, Wiley, New York **2000**; d) J. W. Steed, J. L. Atwood, *Supramolecular Chemistry*, Wiley, New York **2000**.

8 J.-M. Lehn, *Pure Appl. Chem.* **1979**, 50, 871.

9 G. A. Jeffrey, *An Introduction to Hydrogen Bonding*, Oxford University Press, Oxford 1997.

10 J. C. Ma, D. A. Dougherty, *Chem. Rev.* **1997**, 97, 1303.

11 C. A. Hunter, J. K. M. Sanders, *J. Am. Chem. Soc.* **1990**, 112, 5525.

12 R. Paulini, K. Müller, F. Diederich, *Angew. Chem.* **2005**, 117, 1820; *Angew. Chem. Int. Ed.* **2005**, 44, 1788.

13 P. Auffinger, F. A. Hays, E. Westhof, P. S. Ho, *Proc. Natl. Acad. Sci. USA* **2004**, 101, 16789.

14 R. H. Crabtree, P. E. M. Siegbahn, O. Eisenstein, A. L. Rheingold, T. F. Koetzle, *Acc. Chem. Res.* **1996**, 29, 348.

15 a) C. Seel, A. Galán, J. de Mendoza, *Top. Curr. Chem.* **1995**, 175, 101; b) F. P. Schmidtchen, M. Berger, *Chem. Rev.* **1997**, 97, 1609; c) P. D. Beer, P. A. Gale, *Angew. Chem.* **2001**, 113, 502–532; *Angew. Chem. Int. Ed.* **2001**, 40, 487; d) J. J. Lavigne, E. V. Anslyn, *Angew. Chem.* **2001**, 113, 3212–3225; *Angew. Chem. Int. Ed.* 2001, 40, 3119; e) J. L. Sessler, J. M. Davis, *Acc. Chem. Res.* **2001**, 34, 989; f) K. Bowman-James, *Acc. Chem. Res.* **2005**, 38, 671.

16 D. J. Cram, *Angew. Chem.* 1986, 98, 1041; *Angew. Chem. Int. Ed.* **1986**, 25, 1039.

17 W. A. Eaton, E. R. Henry, J. Hofrichter, A. Mozzarelli, *Nat. Struct. Biol.* **1999**, 6, 351.

18 G. Ercolani, *J. Am. Chem. Soc.* **2003**, 125, 16097.

19 For reviews, see: a) N. Röckendorf, T. K. Lindhorst, *Top. Cur. Chem.* **2002**, 217, 201; b) S.-K. Choi, *Synthetic Multivalent Molecules*, Wiley-Interscience, Hoboken, USA, 2004; c) A. Mulder, J. Huskens, D. N. Reinhoudt, *Org. Biomol. Chem.* **2004**, 2, 3409; d) J. D. Badjic, A. Nelson, S. J. Cantrill, W. B. Turnbull, J. F. Stoddart, *Acc. Chem. Res.* **2005**, 38, 723.

20 M. Mammen, S.-K. Choi, G. M. Whitesides, *Angew. Chem.* **1998**, 110, 2908; *Angew. Chem. Int. Ed.* **1998**, 37, 2754.

21 a) J. Huskens, M. A. Deij, D. N. Reinhoudt, *Angew. Chem.* **2002**, 114, 4647; *Angew. Chem. Int. Ed.* **2002**, 41, 4467; b) A. Mulder, T. Auletta, A. Sartori, A. Casnati, R. Ungaro, J. Huskens, D. N. Reinhoudt, *J. Am. Chem. Soc.* **2004**, 126, 6627; c) T. Auletta, M. R. de Jong, A. Mulder, F. C. J. M. van Veggel, J. Huskens, D. N. Reinhoudt, S. Zou, S. Zapotoczny, H. Schönherr, G. J. Vancso, L. Kuipers, *J. Am. Chem. Soc.* **2004**, 126, 1577.

22 J. D. Badjic, V. Balzani, A. Credi, S. Silvi, J. F. Stoddart, *Science* **2004**, 303, 1845.

23 Reviews: a) J. S. Lindsey, *New J. Chem.* **1991**, 15, 153; b) G. M. Whitesides, J. P. Mathias, C. T. Seto, *Science* **1991**, 254, 1312; c) D. Philp, J. F. Stoddart, *Angew. Chem.* 1996, 108, 1243; *Angew. Chem. Int. Ed.* **1996**, 35, 1154. (d) C. A. Schalley, A. Lützen,

M. Albrecht, *Chem. Eur. J.* **2004**, 10, 1072.

24 T. D. Hamilton, L. R. MacGillivray, *Self-Assembly in Biochemistry in: Encyclopedia of Supramolecular Chemistry*, J. L. Atwood, J. W. Steed (Eds.), Dekker, New York, 2004, 1257.

25 A. Klug, *Angew. Chem.* **1983**, 95, 579; *Angew. Chem., Int. Ed. Engl.* **1983**, 22, 565.

26 L. F. Lindoy, I. M. Atkinson, *Self-Assembly in Supramolecular Chemistry*, Royal Society of Chemistry, Cambridge 2000.

27 For a review, see: F. Hof, S. L. Craig, C. Nuckolls, J. Rebek, Jr., *Angew. Chem.* **2002**, 114, 1556; *Angew. Chem. Int. Ed.* **2002**, 41, 1488.

28 a) D. H. Busch, N. A. Stephensen, *Coord. Chem. Rev.* **1990**, 100, 119; b) R. Cacciapaglia, L. Mandolini, *Chem. Soc. Rev.* **1993**, 22, 221; c) N. V. Gerbeleu, V. B. Arion, J. Burgess, *Template Synthesis of Macrocyclic Compounds*, Wiley-VCH, Weinheim 1999; d) T. J. Hubin, A. G. Kolchinski, A. L. Vance, D. H. Busch, *Adv. Supramol. Chem.* **1999**, 5, 237; e) F. Diederich, P. J. Stang (eds.) *Templated Organic Synthesis* Wiley-VCH, Weinheim **2000**; f) T. J. Hubin, D. H. Busch, *Coord. Chem. Rev.* **2000**, 200–202, 5.

29 See, for example: D. Voet, J. G. Voet, *Biochemistry*, Wiley, Chichester 1990.

30 K. J. C. van Bommel, A. Friggeri, S. Shinkai, *Angew. Chem.* **2003**, 115, 1010; *Angew. Chem. Int. Ed.* **2003**, 42, 980.

31 B. C. Gibb, *Chem. Eur. J.* **2003**, 9, 5181.

32 J. K. M. Sanders, *Pure Appl. Chem.* **2000**, 72, 2265.

33 C. J. Pedersen, *J. Am. Chem. Soc.* **1967**, 89, 7019.

34 C. Safarowsky, L. Merz, A. Rang, P. Broekmann, B. A. Hermann, C. A. Schalley, *Angew. Chem.* **2004**, 116, 1311; *Angew. Chem. Int. Ed.* **2004**, 43, 1291.

35 J. F. Hulvat, S. I. Stupp, *Angew. Chem.* **2003**, 115, 802; *Angew. Chem. Int. Ed.* **2003**, 42, 778.

36 S. Anderson, H. L. Anderson, *Templates in Organic Synthesis: Definitions and Roles* in ref. [28e], p. 1.

37 J.-P. Sauvage, C. Dietrich-Buchecker (eds.), *Molecular Catenanes, Rotaxanes, and Knots*, Wiley-VCH, Weinheim 1999.

38 a) J.-P. Sauvage, *Acc. Chem. Res.* **1990**, 23, 319; b) D. A. Leigh, P. J. Lusby, S. J. Teat, A. J. Wilson, J. K. Y. Wong, *Angew. Chem.* **2001**, 113, 1586; *Angew. Chem. Int. Ed.* **2001**, 40, 1538; c) P. Mobian, J.-M. Kern, J.-P. Sauvage, *J. Am. Chem. Soc.* **2003**, 125, 2016.

39 a) F. Diederich, *J. Chem. Educ.* **1990**, 67, 813; b) P. Scrimin, P. Tecilla, U. Tonellato, *J. Phys. Org. Chem.* **1992**, 5, 619; c) J.-M. Lehn, *Appl. Catal. A*, **1994**, 113, 105; d) M. C. Feiters, in: *Comprehensive Supramolecular Chemistry*, Eds: J. L. Atwood, J. E. D. Davies, D. D. MacNicol, F. Vögtle, Pergamon Press, Oxford 1996, Vol. 11, p. 267; e) J. K. M. Sanders, *Chem. Eur. J.* **1998**, 4, 1378.

40 P. R. Schreiner, *Chem. Soc. Rev.* **2003**, 32, 289.

41 a) L. E. Orgel, *Nature* **1992**, 358, 203; b) T. Li, K. C. Nicolaou, *Nature* **1994**, 369, 218; c) D. Sievers, G. von Kiedrowski, *Nature* **1994**, 369, 221.

42 K. Severin, D. H. Lee, J. A. Martinez, M. R. Ghadiri, *Chem. Eur. J.* **1997**, 3, 1017.

43 a) E. A. Wintner, M. M. Conn, J. Rebek, Jr., *Acc. Chem. Res.* **1994**, 27, 198; b) A. Robertson, A. J. Sinclair, D. Philp, *Chem. Soc. Rev.* **2000**, 29, 141.

44 M. Albrecht, *Chem. Rev.* **2001**, 101, 3457.

45 J.-P. Sauvage (ed.), *Transition Metals in Supramolecular Chemistry*, Wiley, Chichester 1999.

46 V. Balzani, M. Venturi, A. Credi, *Molecular Devices and Machines – A Journey into the Nanoworld*, Wiley-VCH, Weinheim 2003.

47 L. De Cola (Ed.), *Molecular Wires* in: *Topics in Current Chemistry*, vol. 257, Springer, Heidelberg 2005.

48 B. Feringa (ed.), *Molecular Switches*, Wiley-VCH, Weinheim **2001**.

49 N. B. Bowden, M. Weck, I. S. Choi, G. M. Whitesides, *Acc. Chem. Res.* **2001**, 34, 231.