1
Introduction

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1.1
Some Historical Remarks on Supramolecular Chemistry

The fundaments of Supramolecular Chemistry date back to the late nineteenth 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 [1], the lock-and-key concept was introduced by Emil Fischer [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 lock-and-key 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 wasn't it 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

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number of 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 no 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 is the methodological basis 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 of only a few kJ mol^{-1}. They can be divided into 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 circa 100–350 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 of 2.2–2.5 Å, moderate hydrogen bonds (15–60 kJ mol^{-1}; 2.5–3.2 Å), and weak hydrogen bonds with binding energies below circa 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 distinguish between hydrogen bonding between neutral molecules and charged hydrogen bonds. The latter bonds are usually significantly stronger. For example, the $F-H\cdots F^-$ hydrogen bond has a bond energy of circa 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 circa 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 do not 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 and 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, one of which is electron-rich (prototypically a hydroquinone), one electron-deficient (prototypically a quinone) interact. 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 an r^{-6} dependence, and exchange repulsion decreasing with r^{-12}.

Finally, a particular case 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 nonpolar/aprotic molecules. Hydrophobic effects play an important role in guest binding by cyclodextrins, for example. Water molecules residing inside the nonpolar cavity cannot interact with the cavity wall strongly. If they are replaced by a nonpolar 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, that is, the examination and understanding of the noncovalent bond, to more advanced topics which make use of that knowledge to build large, complex architectures, 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 are not only 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 the guest surface and the host's 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 challenges 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 Figure 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 of 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.

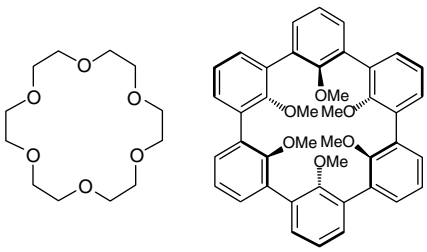


Figure 1.1 Preorganization does matter. A comparison of 18-crown-6 (a) and the spherand (b) with respect to alkali metal ion binding reveals that the spherand has an up to 10 orders of magnitude higher binding constant.

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 the 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 is certainly oxygen binding at hemoglobin [17]. This protein is an $\alpha_2\beta_2$ 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 in 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, 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 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 Figure 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
The Three "Selfs": Self-Assembly, Self-Organization, Self-Sorting

Self-assembly [23] is a strategy used by supramolecular chemists to reduce the effort required for the generation of complex structures and architectures. Instead of tedious multistep covalent syntheses, simple building blocks are programed 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); and (iii) the bonds between different components must be reversibly formed. This means that the final aggregate is generated thermodynamically controlled 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 programed on the highest level. Other examples of 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,

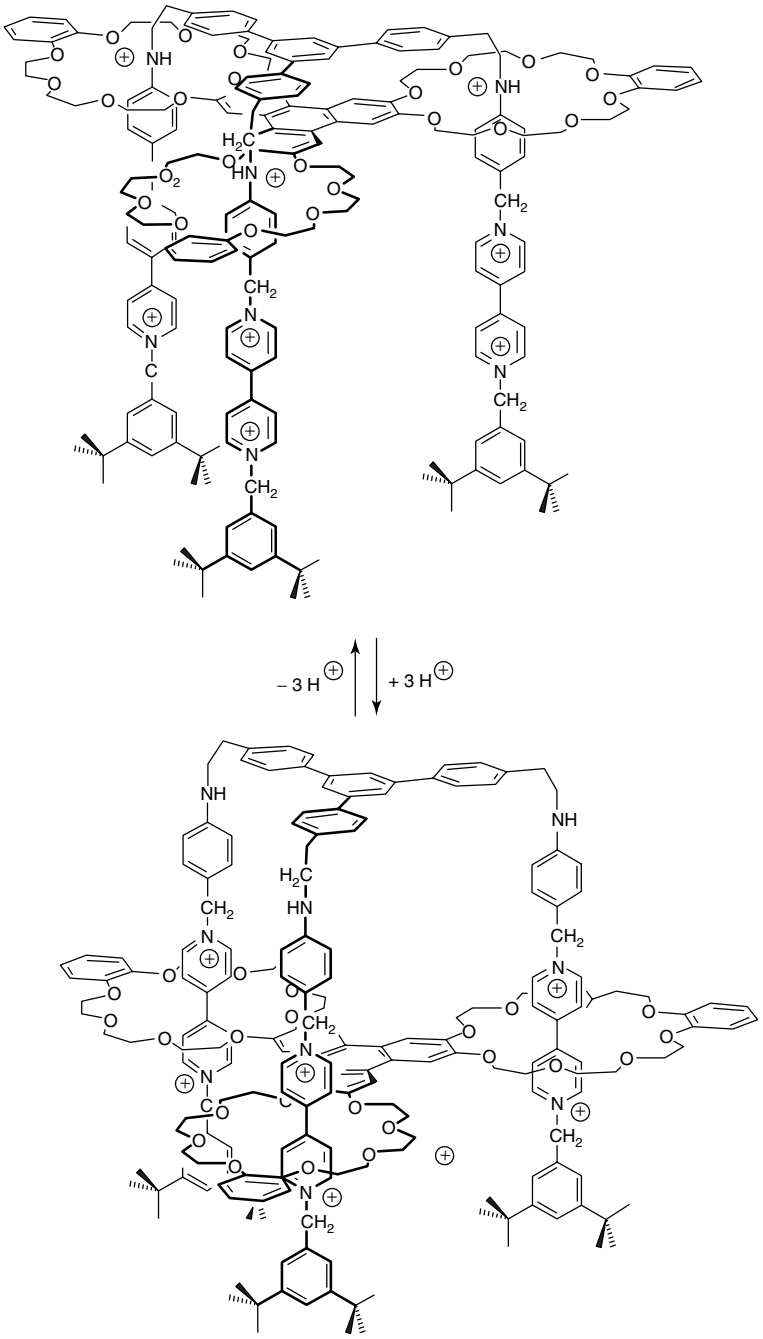
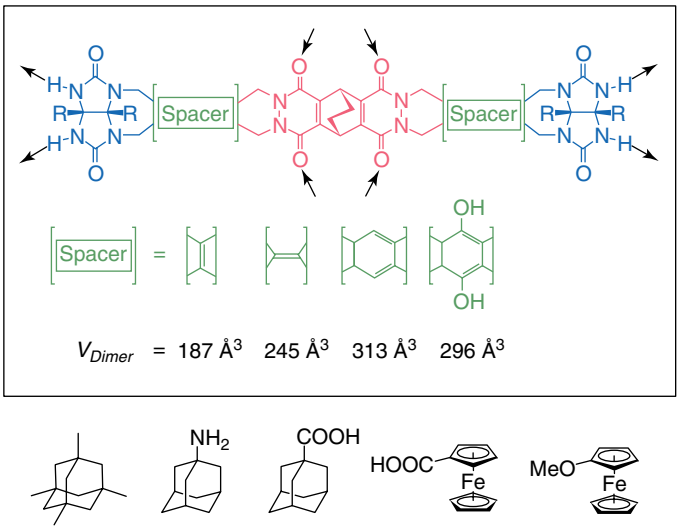


Figure 1.2 Molecular elevator synthesized by utilizing multivalency. The position of the wheel component can be controlled by protonation/deprotonation.



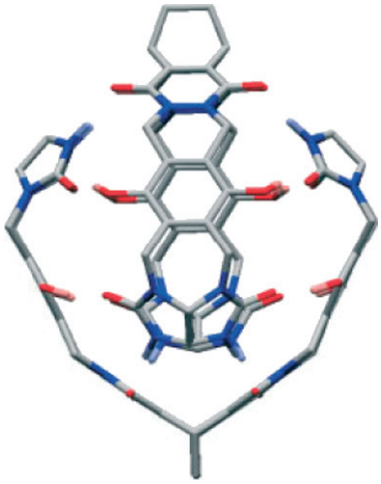


Figure 1.3 Self-assembling "softball." (a) Computer model of the softball bearing the hydroquinone spacer (side chains are omitted). (b) Different monomers which form dimers with cavities of volumes between 187 and 313 Å^3 depending on the spacer length. (c) A selection of good guest molecules which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

Figure 1.3 shows only one example of a capsule formed reversibly from two identical self-complementary monomers which are bound to each other by hydrogen bonding [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 the definitions would be to distinguish processes which lead to the thermodynamic minimum and thus lead to chemical equilibria from processes that operate far from thermodynamic equilibrium. The first kind should be called *self-assembly processes*, while the term *self-organization* might be reserved for spontaneous organization far from equilibrium. Many processes in living organisms are examples of 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. However, this advantage comes at a price, that is, it is experimentally difficult to determine which is which by simple criteria.

But, for a moment, let us come back to the tobacco mosaic virus (TMV) and ATP synthase. What is the difference between them? The virus is composed of 2130 *identical* protein building blocks surrounding the genetic information, while ATP synthase is constructed from many *different* subunits, which all need to find their correct positions in the whole assembly in order to result in a functional assembly. Therefore, the amount of information which needs to be programed into the building blocks is quite different. Each protein building block in the TMV needs to be programed so that the next building block is attached in the right way. In contrast, the building blocks in ATP synthase need many different, orthogonal binding sites which are able to ensure that only the correct building block attaches and none of the many other building blocks. The orthogonality of the binding sites thus leads to a selection process which can be called *self-sorting*.

Supramolecular chemists have started to use self-sorting [28] as a strategy to generate complex architecture. There are some discussions about the exact meaning of ''self'' in the literature. On the one hand it is defined as the ability to efficiently distinguish between self and non-self. On the other hand ''self'' means that there is no additional external input required, because the specific information for the sorting process is encoded in the molecules themselves. In analogy to self-assembly, reversible interactions between the buildings blocks are required to enable error corrections during this process [29].

Different types of self-sorting can be distinguished [30]: One speaks of *narcissistic* self-sorting, when the molecules are self-complementary and form complexes only with identical copies of themselves. The molecules are thus able to distinguish self from non-self. The other type of self-sorting can be realized with molecules **A** and **B**, which form complexes with **C** and **D**, when **A** prefers **C** over **D** and **B** binds more tightly to **D** than to **C**. In this case of so-called *social* self-sorting, only two complexes are formed almost independent from the stoichiometry of the components: **A•C** and **B•D**. Most of the self-sorting systems known so far in supramolecular chemistry belong in this category. However, there is a second kind of social self-sorting, in which the stoichiometry is important: Let us assume that

both, **A** and **B** prefer **C** over **D**, and that the binding energy difference between **A•C** and **A•D** is significantly higher than that between **B•C** and **B•D**. If all four components are added in equimolar amounts, **A** will form a complex with **C** and more or less completely consume **C**. Then, **B** is left with **D** and the mixture again contains almost only **A•C** and **B•D**. One recent example of this type involves two different cucurbit[*n*]urils ($n = 7, 8$) [31].

Integrating two orthogonal binding sites into one key component allows the chemist to program the assembling molecules. A larger, geometrically well-defined supramolecular architecture can thus be made. Examples of this are known from metallo-supramolecular chemistry, where isosceles trapezoids have been assembled from five different components in a well-defined way [32]. Another example is multiply threaded crown ether/ammonium pseudorotaxanes, in which the orientation of all building blocks is programed into the assemblies through the concept of *integrative* self-sorting [33].

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*" [34]. Templates span the whole range from biochemistry with its complex apparatus for DNA replication [35], to the formation of structured inorganic materials [36] to the templated synthesis of macrocycles [37], to the preparation of supramolecular catalysts [38] – to name just 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 of covalent templates exist. (iii) The control of reactivity and the recognition of the reaction partners imply information to be programed 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. Maybe a 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 [39]. 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, that is 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 [40] may be considered as a planar template [41].

Although there is certainly some overlap, one should distinguish between a reactant, a template, and a catalyst [42]. 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 [43] 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 and, according to the strict definition, would be considered as a reactant rather than a template. Nevertheless, this view of the synthesis of interlocked molecules – one out of many examples is shown in Figure 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 in the chemical literature as template-mediated, although the use of removable transition metal ions for the synthesis of mechanically interlocked molecules [44] is probably the only true template synthesis for interlocked molecules in the strict sense. It is similarly difficult to separate templates from catalysts: on the 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 [45] accelerate reactions by lowering the barriers. The principles by which they fulfill the task are very different. Increasing the local concentration of the reactants by encapsulation is one example (see Figure 1.3 above), increasing the intrinsic reactivity of carbonyl compounds through hydrogen bonding [46] is another, and many more exist.

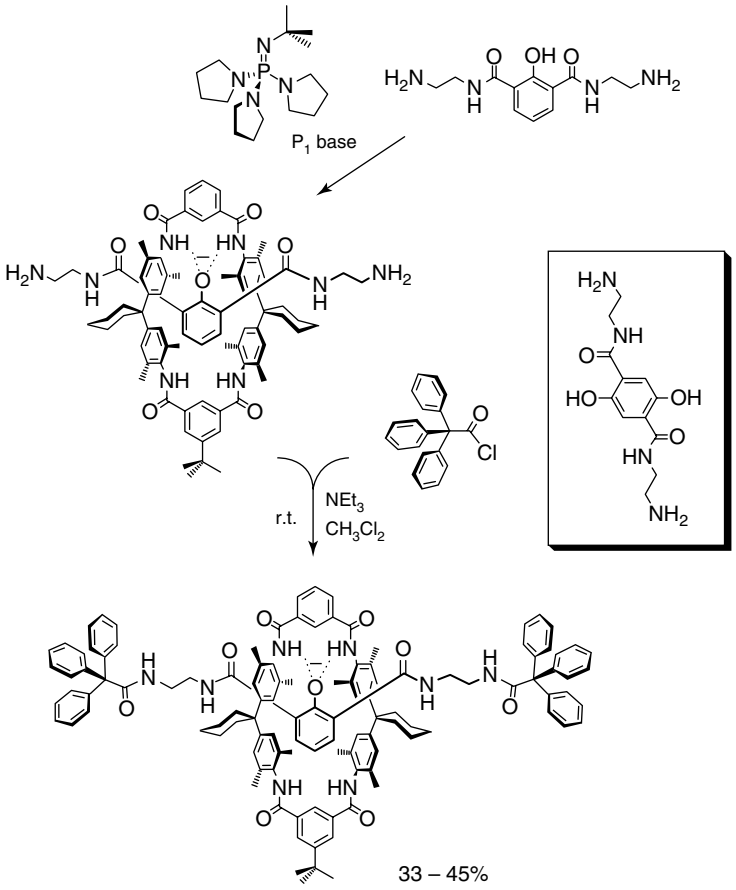


Figure 1.4 Anion-templated rotaxane synthesis. The axle center piece is threaded through the macrocycle's cavity by hydrogen bonding. Stopper attachment to both axle ends traps the wheel on the axle. Inset: hydroquinone-based center piece which can also be used, but with lower efficiency.

Originating from the question as to how 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 transcribes 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 accidentally 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 [47]. Later, suitable α-helical peptides were also shown to self-replicate [48]. In the context of supramolecular chemistry, however, most interesting are organic

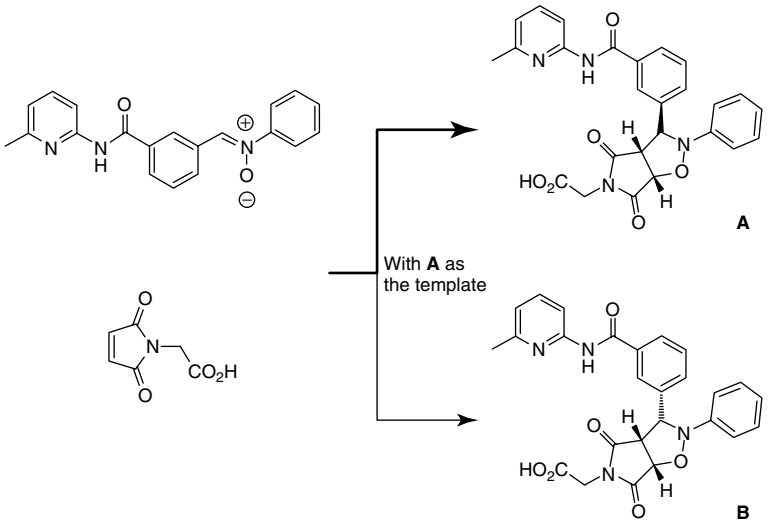


Figure 1.5 A minimal self-replicating system. In the presence of template **A**, the two reactands on the left are organized in a way suitable for a 1,3-dipolar cycloaddition reaction. The pyridineamide part of the template recognizes the acid substituent in the reactand, while the second reactand is 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.

minimal-replicators [49] 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 focused on the noncovalent bond and the beauty of structures which can be generated by employing it. This is the case for topologically interesting molecules such as rotaxanes, catenanes, knotanes, and Borromean rings [43]. It also holds for the generation of self-assembling capsules, helicates [50], or metallo-supramolecular tetrahedra, octahedra, and the like [51]. However, the focus has shifted in contemporary supramolecular chemistry toward the implementation of function into noncovalent architectures to achieve one of the aims of supramolecular chemistry: to develop organized functional units of molecular dimension, to interpret, store, process, and transmit information in the same way, as is already done in the complex machinery of natural systems [52].

Interlocking compounds such as rotaxanes, pseudorotaxanes, and catenanes play central roles in designing such synthetic molecular machines.

A special feature of pseudorotaxanes is their ability to dissociate/associate selectively into their free building blocks by appropriate external stimuli. This

opens up the possibility to achieve large movement amplitudes in relatively small molecules, which are mainly due to the formation and the release of noncovalent bonds between the components. However, not only are classical threading and dethreading of the axle into and out of the host molecule possible, but also more complex movements like the exchange of the guest or host molecule can be realized. This requires an external stimulus to be able to weaken the noncovalent interactions that hold the supramolecular complex, and thus to ''turn off'' the binding interactions, or, in the opposite case, to strengthen them in order to ''turn them on'' [53]. Mandolini *et al.* succeeded in designing a molecular plug/socket-system based on the reversible acid/base-driven threading/dethreading motions in a hydrogen pseudorotaxane, which emits light as a readout signal. The individual components in this case are a crown ether and an amine that are present side by side in neutral state solution without forming a complex. When acid is added, the protonated amine forms a pseudorotaxane with the macrocycle, which leads to an efficient photoinduced energy transfer from the binaphthyl unit of the crown ether to the anthracenyl group incorporated within the dialkylammonium ion [54]. Another interesting function is displayed by the processive pseudorotaxane from Rowan *et al.*, which works in a similar way to the DNA polymerase. In this case, a macrocycle catalyst moves along a threaded polybutadiene while oxidizing the double bonds into the corresponding epoxides in the presence of an oxygen donor [55]. The investigation of such systems is not only an end in itself but provides useful basic knowledge for the synthesis of complex supramolecular devices on the basis of rotaxanes or catenanes. The most important dynamic properties of rotaxanes are the rotation of the macrocycle around the axle and the translational motion (shuttling) along the axle. This ''shuttling,'' that is, the movement in a permitted direction of a particularly large amplitude, is in many ways similar to the restricting of the movement of biological motors by a rail [56]. A molecular shuttle, in which the shuttling rate can be controlled through deprotonation and protonation, provides an example in which the speed of the macrocycle motion can be precisely adjusted [57]. Nevertheless, a simple shuttling that is only driven by background thermal energy cannot do any useful work. Therefore the implementation of two or more different binding sites which are controllable by external stimuli is required. A targeted turning-on or turning-off of these sites allows control of the location of the macrocycle.

Popular stimuli are processes such as protonation/deprotonation, as used for the molecular elevator shown in Figure 1.2. In the deprotonated state, the crown ether stays preferably at the paraquat station. Upon protonation, the tris-crown ether moves up and complexes to the ammonium ion [22].

Moreover, photo- and electrochemical processes [58] have been very successful in many cases of reversible switching as, for example, in the case of the molecular muscle from Stoddart *et al.* Driven by external electrochemical impulses, the distance between a pair of mechanical mobile rings on a single dumbell can be reduced from 4.2 to 1.4 nm and vice versa, which mimics the contraction and extension of a skeletal muscle [59]. Similar strategies have been used by Sauvage *et al.* to generate switchable rotaxanes and catenanes, where metal complexes were

used as building blocks and a switching takes place by redox processes at the metal centers [60]. Stimuli-responsive molecular shuttles that function through metal templates [61] or via reversible formation of covalent bonds such as Diels–Alder and retro Diels–Alder reactions [62] have also been reported. Based on switchable rotaxanes, so-called molecular valves can be synthesized. In this case, rotaxanes were immobilized on the surface of a porous silica gel while, for example, a dye is embedded in the pores of the silica gel. This dye cannot escape since the wheel of the rotaxane is near the silica surface. Only when the macrocycle is displaced by an external stimulus will the pores open allowing the enclosed dye molecules to escape [63].

As with rotaxanes, stimulated structural changes can be used for catenanes in order to vary the movement of the components relative to each other. Such switchable catenanes can, in principle, be regarded as molecular rotors, provided that a rearrangement is always in the same direction and does not only represent a swing motion [64]. Such a positional switch was realized by Leigh *et al*. The idea was to introduce three binding sites located on a larger ring, and the ability to control the affinity of a smaller wheel to the individual stations sequentially, to move the smaller wheel in discrete steps between these binding sites in one direction. In fact, the small ring in this [2]catenane moves with high positional integrity but without control over its direction of motion. Only with the implementation of a fourth binding site and the use of a second smaller wheel, was a unidirectional motion around the larger ring induced, since the two rings in the [3]catenane mutually block each other's movement to ensure an overall stimuli [65].

A very different approach to molecular rotary engines was realized by Kelly *et al*. as far back as 1999 with the synthesis of the first chemically driven, unidirectional motor in a molecular ratchet consisting of a three-bladed triptycene rotor and a helicene stator rotating against each other around the C–C-single bond connecting both parts. In contrast to other rotors known at that time, the rotation expired not only spontaneously but could be controlled chemically by reaction with phosgene. Although this system is only capable of performing a unidirectional 120° rotation, it has all the features of a functional, chemically driven rotary motor [66]. Feringa *et al*. reported the creation of a light-driven monodirectional molecular rotor able to undergo a complete 360° rotation. This system is made up of a bis-helicene connected by an alkene double bond displaying axial chirality and having two stereocenters, which are essential for the observed unidirectional behavior of the molecular motor. One cycle of unidirectional rotation involves four discrete isomerization steps: Light-induced cis/trans double bond isomerization brings the system into a strained state, which relaxes by continuing the rotary motion in the same direction through thermally induced relaxation into a less strained state. Repeating this sequence a second time brings the system back to the starting structure [67]. Immobilization of these rotor molecules on carriers can enable the conversion of rotation into mechanical work, as in case of the Feringa-nanomotor which – embedded in a liquid crystal film – is able to rotate microscale objects placed on the film that exceed the size of the motor molecule by a factor of 10 000 [68].

The examples shown here can only give a small impression of the diverse and exciting field of implementing function in supramolecular chemistry and there are more intriguing examples for molecular devices. Many other functions have also been implemented in synthetic supramolecules. This area is simply too broad to give a complete introduction and thus we can only refer the interested reader to the literature [69].

1.3.8 Extended Assemblies: Liquid Crystals and Supramolecular Gels

Dynamic soft materials, such as liquid crystals and gels, are becoming increasingly important. Although they are not as durable as ceramics, metals, or plastic, they still provide highly interesting properties, for example, the ability to be controlled by external stimuli, and thus they open the way to completely new functional materials [70].

Liquid crystals are among the most important anisotropic molecular materials and they are well known because of their application in advanced technologies such as high-resolution, energy-saving flat screen monitors [71]. The basis for such applications can be found in the liquid crystals' unique characteristics. They are composed of so-called mesogens and represent a state between solid and liquid due to the fact that their order is higher than in liquids, but lower than in solids. In addition to some aspects of the solid and liquid state, liquid crystals often have quite novel properties. Their order behavior can be influenced and controlled by external stimuli such as normal magnetic or electric fields, or just by a temperature change. Their optical activity, which is often of a magnitude far beyond the activity of solids, liquids, or gases, enables investigation and control by light [72].

Many well-defined supramolecular mesogenic structures have been discovered. The use of noncovalent interactions, like H-bonding or dipole–dipole interactions, led to many new possible structures in liquid crystals, often based on relatively simple synthetic building blocks. Noncovalent interactions can stabilize the mobile liquid crystalline states and can also be broken or changed by external influences. For example, by the addition of ions, the hydrogen bond pattern can change, which leads to a change in the aggregate structures [70]. These special properties of supramolecular liquid crystals open up entirely new prospects for a broad field of applications [73]. To mention them all would go beyond the scope of this introduction, but Figure 1.6 gives a very good insight into the various structures and uses of liquid crystals.

Supramolecular gels have received substantial recent attention as a fascinating case of self-assembly and phase separation [74]. The *gel state* is defined as ''a two-component, colloidal dispersion with a continuous structure with macroscopic dimensions that is permanent on the time scale of the experiment and is solid-like in its rheological behavior'' [75]. For years, the structure of such systems has typically been formed by cross-linked covalent polymers, which are able to swell by taking up a large amount of solvent that outweighs their own mass [76]. Lately, however, there has been an increased interest in gelation systems based

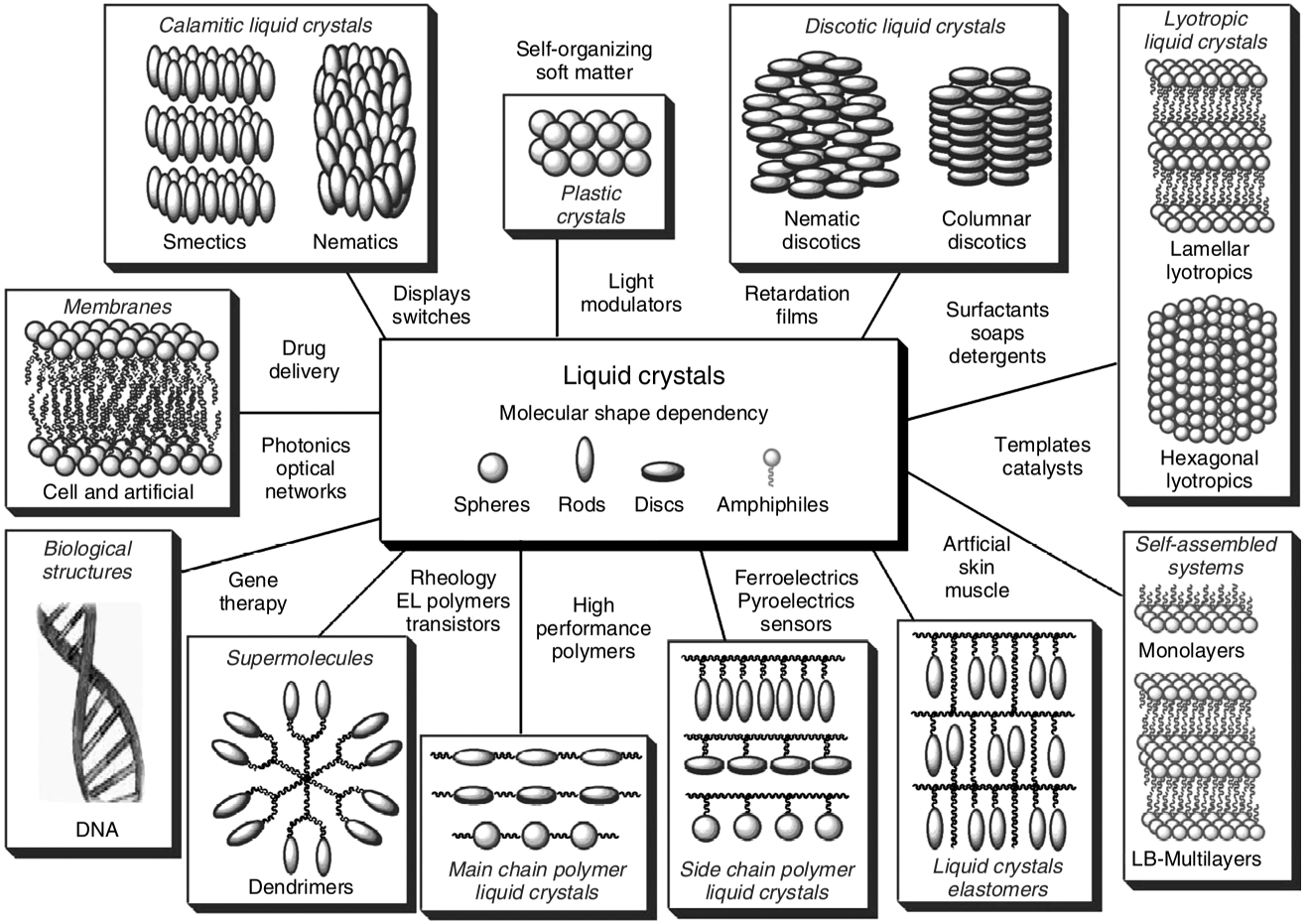


Figure 1.6 Overview of the various structural and application possibilities of liquid crystals. Reproduced from Ref. [73] with kind permission of Wiley-VCH.

on low-molecular-weight building blocks, which self-assemble through noncovalent interactions into supramolecular three-dimensional networks, the so-called supramolecular gels. In contrast to polymeric gels, these consist of small covalent building blocks with a defined chemical structure. The noncovalent bonds connecting them can be modified by the environment to control the macroscopic characteristics of the gel. These supramolecular aggregates can be dissolved by simply adding a co-solvent, by mechanical pressure or by heating [77]. The ability to control this interplay of multiple weak and reversible interactions provides the opportunity to create new tunable soft matter with specific properties, which has the potential to act as a chemical sensor and biodegradable material in drug-delivery [74]. Thus, drugs embedded in a gel, which would be stable under normal physiological conditions, can, for example, be released at the target area in the body by a particular stimulus. Decisive for the formation of a supramolecular gel is the ability of the building blocks to aggregate into one-dimensional fibers by noncovalent interactions such as hydrogen bonding and $\pi-\pi$-stacking. Interconnection of these fibers builds up a three-dimensional network trapping the solvent inside its cavities. A popular approach is the use of cavitands, such as cyclodextrins, calixarenes, and cucurbiturils, because these are able to form stable host–guest complexes. Harada *et al.* showed that several host–guest motifs form gels using cyclodextrins [78]. Supramolecular hydrogel could be synthesized from a guest-modified cyclodextrin dimer (CD) without a polymer backbone. The CD forms supramolecular, linear fibrils together with the divalent guest molecules. Hydrogen bonds between the CDs ensure the cross-linking between the individual fibers. By adding competitive guest molecules, the gel formation can be reversed and a sol is then formed. Another possibility to form supramolecular gels is self-inclusion. A cyclotriveratrylene (CTV) platform symmetrically end-substituted with pendent primary amines or nicotamic substituents induces self-assembly in a large variety of solvents, forming robust and opaque gels. Because of the shallow bowls of CTV derivatives one molecule stacks inside the bowl of the next one to form one-dimensional fibers, which are held together by $\pi-\pi$-stacking. These fibers then further self-assemble into large networks [79].

Another class of gels that have been receiving more and more attention is that of the metallogels, in which ligands and metal ions function as complementary building blocks in a hierarchical self-assembly process. The interplay between metal–ligand interactions and self-assembly processes, and the related transmission of magnetic, catalytic, and redox characteristics from the metal centers to the gel offer new possibilities to create ''intelligent'' gels that can easily be modified and can profit from the characteristics of the metal complexes [80]. There are, for example, thermo-reversible, switchable gels with adjustable, magnetic, optical, and rheological features, in which the gelator undergoes a spin-crossover which results in a change in the gel's color [81]. Metallogels can be especially interesting for their use in luminescence technology, photovoltaics, and photocatalysis because metal chelates often show long-lasting excited triplet states. Aida *et al.* were successful in synthesizing a gelling agent based on a trinuclear gold(I) pyrazolate metallacycle, with which phosphorescence can be observed during the gel phase. By doping and

dedoping with Ag(I), a reversible red–green–blue luminescence can be induced and controlled [82].

Also, the potential of metallogels to act as catalysts became more interesting after Xu *et al.* reported the first example of a catalytic coordination polymer, formed using a Pd(II) metal center and multidentate ligands. The Pd(II) moieties catalyze the oxidation of benzyl alcohol to benzaldehyde with a turnover twice that of $[Pd(OAc)_2]$ under similar reaction conditions [83]. Controlling reversible sol–gel phase transitions in metallogels provides further interesting opportunities. Lee *et al.* describe a reversible gel–sol switching via a simple counteranion exchange. Depending on the nature of the anions, the cationic Ag(I) coordination polymers adopt two distinct conformations: a folded helical structure (gel) and an unfolded zigzag conformation (sol) [84]. Another elegant route to control the sol–gel phase-transition phenomenon is triggered by thermal and chemical stimuli, such as the change in the redox state of the metal [85]. Even the control of gel formation by means of ultrasonic treatment is known [86].

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 aqueous surroundings. 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 [87].

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 programed

with the appropriate binding sites. Information transfer and information processing already starts at the molecular level.

A view back over 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 of the methods used in supramolecular chemistry – even though it is probably not possible to be comprehensive.

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