

# Supramolecular chemistry—general principles and selected examples from anion recognition and metallosupramolecular chemistry

Markus Albrecht

Received: 24 January 2007 / Revised: 23 May 2007 / Accepted: 25 June 2007 / Published online: 24 July 2007  
© Springer-Verlag 2007

**Abstract** This review gives an introduction into supramolecular chemistry describing in the first part general principles, focusing on terms like noncovalent interaction, molecular recognition, self-assembly, and supramolecular function. In the second part those will be illustrated by simple examples from our laboratories. Supramolecular chemistry is the science that bridges the gap between the world of molecules and nanotechnology. In supramolecular chemistry noncovalent interactions occur between molecular building blocks, which by molecular recognition and self-assembly form (functional) supramolecular entities. It is also termed the “chemistry of the noncovalent bond.” *Molecular recognition* is based on geometrical complementarity based on the “key-and-lock” principle with nonshape-dependent effects, e.g., solvatization, being also highly influential. *Self-assembly* leads to the formation of well-defined aggregates. Hereby the overall structure of the target ensemble is controlled by the symmetry features of the certain building blocks. Finally, the aggregates can possess special properties or *supramolecular functions*, which are only found in the ensemble but not in the participating molecules. This review gives an introduction on supramolecular chemistry and illustrates the fundamental principles by recent examples from our group.

**Keywords** Supramolecular chemistry · Molecular recognition · Self-assembly · Noncovalent interaction · Supramolecular function

M. Albrecht (✉)  
Institut für Organische Chemie,  
Rheinisch-Westfälische Technische Hochschule Aachen,  
Landoltweg 1,  
52074, Aachen, Germany  
e-mail: markus.albrecht@oc.rwth-aachen.de

## Introduction

Supramolecular chemistry is a young discipline, which investigates (supra)molecular phenomena in between the traditional fields of chemistry (organic, inorganic, and physical chemistry). As a matter of course it is strongly influenced by other natural (biology and physics) and material sciences (engineering).

Supramolecular chemistry is often defined as “the chemistry beyond the molecule” or “the chemistry of the noncovalent bond” (Lehn 1988, 1994, 1995). This means that not only an isolated molecule (either as a single species or as bulk material) but also the assembly of at least two molecules is studied (Steed and Atwood 2000; Beer et al. 1999; Ariga and Kunitake 2006). *Molecular recognition* between the molecular building blocks is important to enable an effective aggregation by *noncovalent interactions*, which in reversible *self-assembly* processes leads to stable and well-defined supramolecular species. Aggregation of the components might result in new properties, which are expressed in a supramolecular function (Lehn 1995; Vögtle 1992). By the use of this principle to construct large ensembles of molecules, supramolecular chemistry bridges the gap between the picometer dimensions of molecules and the nanoworld. Therefore, the understanding of its fundamental basics is crucial for a successful chemical “bottom-up” approach toward nanotechnology (Whitesides et al. 1991).

Essential biological processes, e.g., reproduction, signal transduction, biocatalysis, information storage, and processing, are all based on supramolecular interactions between molecular components. Enzymes, viruses, membranes, and many other complicated structures with biologically relevant functions are mainly built up by

simple self-assembly processes (Klug 1983; Urich et al. 2006). The processes can be mimicked in small artificial supramolecular derivatives.

The interaction of enzymes with a substrate relies on molecular recognition and is based on the complementarity of noncovalent binding sites. The double-stranded DNA is a striking example of two linear strands, which can bind to each other through complementary hydrogen bonding in addition to stabilizing  $\pi$ - $\pi$  interactions. Here the system possesses a high content of information that is stored, replicated, and processed (Watson and Crick 1953).

Nature's examples in supramolecular chemistry are much more advanced than the simple model systems developed by men (Greig and Philp 2001). However, artificial models help us to gain a deeper understanding of basic mechanisms and to develop more complicated systems in the future.

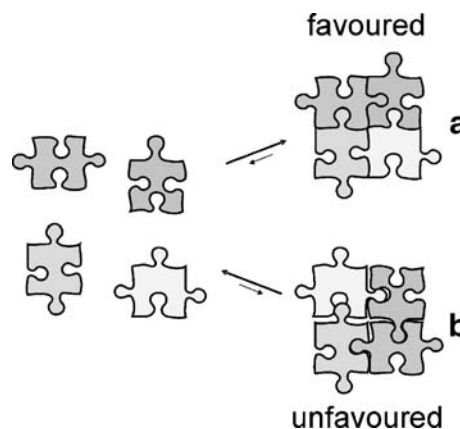
The terminology of supramolecular chemistry, as we know it today, was defined starting in the 1970s and the new concepts were introduced by many different working groups. In 1987 the Nobel prize in chemistry was awarded to C. J. Pedersen, D. J. Cram, and J.-M. Lehn for "pioneering an important contribution in the field of molecular recognition by nonnatural receptors." At that time supramolecular chemistry has been accepted as an interdisciplinary but independent field of contemporary research.

In the following, the reader will be made familiar with the fundamental principles and terminology of supramolecular chemistry. The terms *noncovalent interaction*, *molecular recognition*, *self-assembly*, and *supramolecular function* will be introduced. In the second, more specific part the described principles will be illustrated using examples from our group in the fields of anion recognition, helicate chemistry, molecular containers, and enzyme mimicry. Due to the immense variety of publications on supramolecular chemistry during the last 40 years, this review will focus on some selected major contributions and on work from our own laboratories.

## Part I

### General principles

*Noncovalent interactions*, *molecular recognition*, and *self-assembly* are keywords that have to be considered when we are discussing the principles of supramolecular chemistry. Figure 1 demonstrates the meaning of those three "keywords" giving a jigsaw puzzle as model from the macroscopic world: The pieces of the puzzle fit together, if they are complementary in shape (*molecular recognition*) and if this process is reversible (*noncovalent interactions*,



**Fig. 1** Schematic representation of the *self-assembly* of a supramolecular aggregate **a** by *molecular recognition* and *noncovalent interactions* between molecular building blocks. Poor complementarity of the building blocks will destabilize the obtained aggregate **b**, while the binding between complementary units leads to strong aggregation in the case of **a**. On a molecular level the thermodynamically most favored species, the most stable one, will be obtained in a thermodynamically controlled system. Therefore, in a reversible process, **b** can be converted into the preferred **a**

dynamics) the best-fitting result is favored. By connecting all the pieces of the jigsaw puzzle in the correct way (*self-assembly*) the final object is obtained (A). Wrong connections lead to an unfavored and thus more instable entity (B), which is eventually disconnected again to arrange the pieces correctly. If the pathway for the connection of the building blocks is controlled by the stability of the final product (thermodynamic control) the assembly and disassembly will shift an equilibrating mixture toward only one, energetically most stable, aggregate (Lehn 1995; König 1995).

Although recently some millimeter-dimensioned self-assembly processes were investigated (Whitesides and Boncheva 2002), "self-organization" does not work in the macroscopic world for the puzzle. The pieces of the jigsaw puzzle will never find each other by only mixing and shaking them. Error correction of mismatching units through spontaneous displacement will not be possible.

However, on a molecular level reversible binding between the components and movement by diffusion (either in a solution or on a surface) can lead to the self-assembly of the corresponding "molecular puzzle."

### Noncovalent interactions

Noncovalent interactions between molecular building blocks are crucial for the reversible formation of supramolecular aggregates. Although the term "*noncovalent interaction*" is not well defined, it is generally understood as a bonding interaction that cannot be described in terms of the classical "electron sharing between two atoms by the

overlap of two atomic orbitals to form molecular orbitals.”

Noncovalent interactions vary between very weak (binding energy 1–10 kcal/mol), like solvent effects (e.g., hydrophobicity), dispersion, dipole–dipole, cation– $\pi$  interactions, or  $\pi$ – $\pi$  stacking and quite strong (electrostatic, coordinative interactions; 10–90 kcal/mol) (König 1995; Goshe et al. 2002).

They might be roughly classified in the following categories:

- (1) The weak *van der Waals* interaction is formed due to attractive dispersive and/or inductive forces.
- (2) Relatively strong *electrostatic* interactions are caused by the attraction between differently charged ions or dipoles. Its strength highly depends on the polarity of the surrounding medium and the solvation of the ions themselves.
- (3) Binding occurs in *charge transfer* interactions by energy transfer between energy-rich and energy-poor components (e.g., between two aromatic systems [ $\pi$ – $\pi$  stacking] or metals and ligands).
- (4) The “classical” *hydrogen bonding* describes the contact between positively polarized (“acidic”) hydrogen and an electron pair donor atom. Hydrogen bonds can be linear, bent, or bifurcated. Although the binding energy of a single hydrogen bridge is low, the combination of several of them leads to an accumulation of bond energy and thus multiple-hydrogen-connected arrays usually show a high stability.
- (5) In the context of supramolecular chemistry *metal coordination* is considered as a “noncovalent” interaction, although it often possesses a strong covalent component in the binding. Hereby it is important that the ligand–metal interaction is “stable” but “labile.” This is the case for certain 3D elements but also for alkaline, earth alkaline, or lanthanide metal cations, which mainly bind due to electrostatic and dipole–dipole interactions. Supramolecular chemistry involving metal coordination is also termed *metallo-supramolecular chemistry* (Constable 1991).
- (6) Recently *reversible covalent bonds* like esterification, imine, or disulfide formation were introduced in supramolecular chemistry in the context of dynamic combinatorial chemistry. A dynamic library of compounds (molecular diversity!) is formed in a first reaction. In a successive selection step one of the species from this library is enriched in the equilibrating mixture (Lehn 1999; Corbett et al. 2006).

It was pointed out that the selected species does not have to be the most stable one, but the energy balance of the whole system must be minimized (Grote et al. 2003).

The reversibility of bond formation is essential for molecular recognition and self-assembly. If an error occurs in a molecular recognition process it can be corrected by dissociation of the “mismatching” pair of building blocks. In case of nonreversibility it would propagate in the assembly of bigger aggregates and thus, would disturb the specific formation of well-defined species.

Very often different noncovalent interactions act in concert, and a hierarchy can be discussed for the build up of aggregates depending on the strength and the sequence of the interactions (Würthner et al. 2003).

### Molecular recognition

The formulation of fundamental principles of molecular recognition goes back to the early 20th century, when Emil Fischer and Paul Ehrlich introduced the terms “lock and key principle” (Fischer 1894) and “receptor/substrate” (Ehrlich 1906). Molecular recognition is the specific interaction between two molecules, which are complementary in their geometric and electronic features (like two fitting pieces of a jigsaw puzzle). The lock and key principle describes the fit of a rigid substrate to a rigid receptor analogous to a key and a lock. This is a highly simplified model and cannot be strictly compared to actually occurring molecular recognition events. Molecules often possess some dynamic behavior with different fast equilibrating conformations. Flexible molecular species interact with each other and adopt only one out of several possible geometries. The classical lock and key principle describes the interaction of components due to their shape and rigidity (preorganization). This model takes only the enthalpic driving force for binding into account, while entropy is ignored. However, to understand the specificity of molecular recognition and the strength of binding between complementary partners, both enthalpic and entropic contributions have to be considered. In contrast to many examples from classical “covalent chemistry,” entropy is an important factor in molecular recognition and supramolecular chemistry (Schneider 1991).

The lock and key principle laid the foundation for host–guest chemistry. Starting with Pedersen’s observation that the formation of crown ethers is templated by metal cations and that vice versa the cations can be selectively complexed by the ethers, a diverse research field developed. The selective binding of molecular guests by a host depends not only on the complementarity of the species. Crown ethers usually adopt a conformation in which the oxygen donors are directed “outward” to interact with polar solvents. Upon addition of a cation a structural change has to occur with the donor atoms now pointing toward the encapsulated metal ion. Thus the lock and key principle is not a rigid model, but it has to be

considered in the context of “induced-fit-mechanisms” (Pedersen 1988).

Host–guest chemistry has become a broad discipline in which not only the binding of cations but also of neutral molecules or anions is investigated. The binding of ion pairs is especially attractive to extract toxic wastes or to enrich desirable (valuable) products from mixtures. In addition the host–guest chemistry has some great influence on modern sensor technology. As examples, ion selective electrodes or sensors for poisons or explosives have to be mentioned here.

In biological systems, host–guest chemistry is crucial for the interaction between biomolecular species. Simple systems (like the crown ethers) model specific features of the natural examples (e.g., ion selectivity) but do not give an insight into the complicated processes, which occur, e.g., upon interaction between proteins. Often several binding events occur simultaneously and lead to very strong aggregation. This multivalent behavior can also be found in simple supramolecular systems (Badjić et al. 2004).

If several events take place at once, conformational changes at the host or the guest may influence each other, leading either to a stronger or a weaker interaction. The enhancement of the complex formation is termed “positive cooperativity,” while a reduction of the binding represents “negative cooperativity.” Successive interactions of one host with two (or more) guests in an allosteric process can even trigger the second binding by the first one (Rebek et al. 1981). This is frequently found in enzymes, where the complexation of a host species at a remote site switches a reaction center on or off (Williams et al. 2004).

Molecular recognition is a keyword in supramolecular chemistry, which is related to the early host–guest chemistry of simple crown ether or cryptand-type molecules, but it has an implication on biochemical events, which happen upon interaction between a receptor and a substrate. While the lock and key principle offers a simple understanding of molecular recognition, actually occurring binding is much more complicated, which is due to dynamic processes leading to adaptive effects like cooperativity or allosterism.

### Self-assembly

Recognition between molecules leads to an aggregation, which finally results in an ensemble that is composed of two or more discrete units (Philp and Stoddart 1996; Lawrence et al. 1995). If mixing of the components spontaneously affords only one well-defined product, the process is called self-assembly. According to an early definition by Lindsey, we have to distinguish between different classes of self-assembly processes. In supramolecular chemistry *strict self-assembly* seems to be the most important one, but *directed (templated) self-assembly* processes are also frequently found. *Strict self-assembly*

means that a self-assembly process directly proceeds toward the formation of a well-defined aggregate. In *directed self-assembly* this process is controlled/influenced by some additional species, e.g., templates (Lindsey 1991). This means, in an idealized case self-assembly follows a “cooperative” or allosteric process. The aggregate finally obtained is the thermodynamically most stable within a series of different possible species of different structures and compositions (Hamacek et al. 2005a, b).

The overall shape of self-assembled aggregates highly depends on the geometry of the single components. Huge container-type molecules, which more or less represent Platonic or Archimedean solids, can be designed by symmetry considerations using incommensurate binding sites or geometries of the building blocks (Scherer et al. 1999). Thus, many containers were obtained by self-assembly (MacGillivray and Atwood 1999). The influence of symmetry on self-assembly of different architectures is even precedent in the biological world (e.g., symmetry-driven formation of viruses) (Caulder and Raymond 1999).

Self-assembly processes are controlled by “thermodynamics.” Following the Gibbs–Helmholz equation ( $\Delta G = \Delta H - T\Delta S$ ) the enthalpic ( $\Delta H$ ) and the entropic term ( $-T\Delta S$ ) have to be considered for the total free energy of the system (Schneider 1991). In an idealized case the aggregation of two (or more) molecular units should be driven by a change of enthalpy, which represents the deliberation of bond energy by formation of new bonds. Entropy, on the other hand, should disfavor the aggregation because only one species is formed out of many, leading to a highly organized and thus disfavored aggregate. However, in a real system the environmental conditions (e.g., solvent) have to be considered too. Thus, an oligomerization process can become entropically favored due to the dissociation of solvent molecules, which are bound to the single units and are stripped off during aggregation (for an example, see “Part II”). The enthalpic contribution is reduced and now only represents the difference between the binding of solvent molecules and the complementary moieties (Schalley et al. 2004).

Very often the thermodynamic differences between possible assemblies are subtle. To get only one well-defined species, secondary stabilizing effects (e.g., templating, conformational restrictions, etc.) are important as additional driving forces.

As mentioned before, self-assembly of molecular species bridges the gap between the molecular world and nanotechnology. Starting with small building blocks, aggregation can lead to up to several 100th of nanometer-sized domains, which show special properties. Hereby the symmetry of the small building blocks influences the structure of the ensemble and the features of the bulk material (Percec et al. 2000).

Molecular recognition and self-assembly not necessarily has to take place in the condensed phase but also can occur between different phases or on surfaces (either of a liquid, of solid material, or on a membrane) (Ariga and Kunitake 1998).

### Topologically interesting molecules

Mechanically interlocked molecules like rotaxanes (a ring fixed on a terminally blocked axis), catenanes (two intertwined rings), and also molecular knots (e.g., trefoil knots) are considered as supramolecular species. In the case of knots interlocking leads to intramolecular conformational fixation of a macrocycle but not to an intermolecular interaction between different molecules (Safarowsky et al. 2000; Amabilino and Stoddart 1995).

### Supramolecular chemistry: the science of information encoding and processing

Supramolecular chemistry is often termed the “molecular science of information encoding and processing.” This expression describes the high information content (electronic features and geometry) that is encoded in the molecular building blocks to get high selectivity in a molecular recognition event. The recognition corresponds to the information processing leading to a new aggregate with the information of the single building blocks and of the whole ensemble stored in it. Finally, this might lead to a functional system, which eventually allows the reading of the information.

A high degree of information has to be embedded in all molecules, which are involved in selective chemical reactions (covalent or noncovalent). However, in supramolecular chemistry the reversibility of the interactions allows us to develop systems, which can be switched and thus can be written, read, or erased. The information in supramolecular systems should be discussed in the context of information technology but it is also important as a tool for development of new functional materials or molecular machines through self-assembling (Lehn 1990, 2000).

## Part II

### Selected examples

Supramolecular chemistry matured over the last 40 years to an exciting highly influential interdisciplinary but independent field of research. Many examples of artificial receptors for molecular recognition and self-assembly processes are found in the literature. In this section, some basic principles are demonstrated by selected examples from our group,

which were investigated recently. However, the reader should have in mind that outstanding work has been performed in this field by many excellent research groups all over the world.

### Molecular recognition: optimizing a receptor for spherical anions

The synthesis of crown ethers as selective receptors for cations in the early 1960th by Pedersen has founded modern supramolecular chemistry (Pedersen 1988). The first artificial receptors for anions were also discovered at that time (Park and Simmons 1968). However, the latter field did not develop as fast as the chemistry of cations. This can be explained by the fundamentally different binding features of anions in comparison to metal cations. Based on Alfred Werner’s coordination chemistry (Werner 1893) and Emil Fischer’s lock and key principle (Fischer 1894) cations can be selectively bound by designing structurally well-preorganized receptors, which recognize a metal cation by its size, shape, coordination chemistry, and hardness or softness. The binding of the metal is significantly driven by the formation of stronger bonds and thus by a change of enthalpy ( $\Delta H$ ).

Anions, on the other hand, are bigger with a more diffuse charge distribution. They do not form strong bonds with the receptor but are attracted due to relatively weak dipole–dipole or electrostatic interactions. Hydrophobic effects in the sense of the Hofmeister series play a role for selectivity. The contribution of the enthalpy ( $\Delta H$ ) to binding of anions is much lower than in case of cations and therefore the entropic contribution ( $-T\Delta S$ ) to the free energy ( $\Delta G$ ) becomes prevalent.

Another difference is the lack of preferred coordination geometries. Even the tetrahedral sulfate or the trigonal planar nitrate anions are more or less spherical objects. This again is due to the nondirected electrostatic attraction between the receptor and the anion.

In nature, enzymes are found, which specifically bind anions and membrane channels with high selectivities for anions exist. Thus, anion recognition and transport has a significant impact on biological, medical, or pharmacological processes (Dutzler et al. 2002).

Many artificial anion receptors are based on cationic species, which provide a binding site for the anion in addition to an electrostatic attraction (ion pairing). However, neutral molecules can also bind anions, if, e.g., acidic (positively polarized) hydrogen atoms are available. Those are able to form hydrogen bonds to the anion or at least contribute by their dipole to the binding (Bianchi et al. 1997).

The halides are very simple spherical anions, which possess different size, basicity, and hydrophobicity. The

latter characteristics are important for selectivity in the anion binding.

The quinoline derivatives **1** and **2a/b** shown in Fig. 2 seem to be suitable receptors for halide anions. In both derivatives, two acidic protons form intramolecular hydrogen bonds to the pyridine nitrogen atom and therefore are preorientated for an attractive interaction with anions. Receptor **1** binds chloride at room temperature in chloroform in a 1:1 ratio with very low association constant of  $K_a = 76 \text{ M}^{-1}$ . However, the observation of this binding event indicates that at least some weak interaction occurs between anion and receptor. The weakness of binding is explained by reduction of the formal positive charge at hydrogens by intramolecular hydrogen bonding of the OH and the NH to the pyridine lone pair.

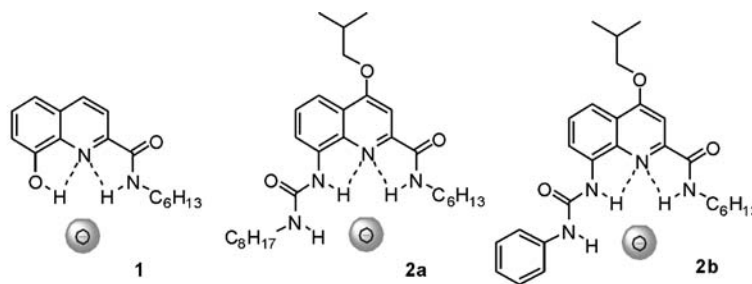
In contrast to **1**, receptor **2a** possesses an additional hydrogen bond donor orientated toward the anion binding site. This one is not involved in hydrogen bonding and can strongly bind an anion, which is located “in front” of the receptor. Consequently,  $K_a$  increases (determined by NMR). The receptor shows some selectivity for the binding of chloride over bromide over nitrate due to their different sizes (see Fig. 2). In case of fluoride the high basicity causes fast proton exchange. Therefore, the binding of this anion cannot be followed by NMR spectroscopy. However, fluorescence titrations show that receptors like **2** are especially appropriate for the binding of  $\text{F}^-$ .

Table 1 reveals a methodological problem in the determination of anion-binding constants. A discrepancy between the data detected by NMR and fluorescence

spectroscopy is observed (see Table 1 for receptor **2a**). The reason for this is the self-aggregation behavior of the receptor at high concentrations. Therefore, the NMR data recorded at relatively high concentrations result only in a  $\Delta K_a$  between self-aggregation and anion binding. Concentration-dependent measurements show that the fluorescence spectroscopic investigations provide more reliable data than NMR because low concentration requirements prevent the aggregation (Albrecht et al. 2005a).

Compound **2a** is an obvious example how a receptor for anions should be designed. In contrast to metal cation binding the receptor does not need a specific geometry, but it has to provide some positively polarized space where the anion can be fixed. In the presented case selectivity is shown for the molecular recognition of spherical anions due to difference in size and basicity. The small fluoride anion fits well into the relatively small cleft of the receptor and due to its substantial basicity is strongly attracted. The reported association constants in chloroform are not high, but this example shows how anion recognition can be realized with simple artificial receptors. To enhance the affinity of a receptor like **2** for anions, different approaches can be envisaged. For example, the acidity of the NH of the urea, which is not involved in intramolecular hydrogen bonding, can be increased. Replacing the octyl substituent of **2a** by a phenyl group (**2b**) leads to a higher acidity (and higher positive local charge) at this group, and anions bind more strongly ( $K_a(\text{CHCl}_3) = 10.380 \text{ M}^{-1}$  for chloride and  $150.000 \text{ M}^{-1}$  for fluoride determined by fluorescence spectroscopy) (Albrecht et al. 2007a).

**Fig. 2** Schematic representation of anion receptor interactions as they are found in the binding to the quinoline receptors **1** and **2a/b**. The association constants  $K_a$  of receptor **2a/b** with different anions were determined at 296 K in chloroform with concentrations of 0.0125 M (NMR) or 1  $\mu\text{M}$  (fluorescence)



Anion	$K_a$ with <b>2a</b> (NMR)	$K_a$ with <b>2a</b> (fluorescence)	$K_a$ with <b>2b</b> (fluorescence)
$\text{F}^-$	Not determined	$14.400 \text{ M}^{-1}$	$150.000 \text{ M}^{-1}$
$\text{Cl}^-$	$1.000 \text{ M}^{-1}$	$3.100 \text{ M}^{-1}$	$10.380 \text{ M}^{-1}$
$\text{Br}^-$	$500 \text{ M}^{-1}$	$640 \text{ M}^{-1}$	$1.887 \text{ M}^{-1}$
$\text{NO}_3^-$	$420 \text{ M}^{-1}$	$400 \text{ M}^{-1}$	$1.672 \text{ M}^{-1}$

**Table 1** Anion-binding constants of receptors 2a and 2b determined by NMR or fluorescence spectroscopy

Anion	$K_a$ with 2a (NMR) ( $M^{-1}$ )	$K_a$ with 2a (fluorescence) ( $M^{-1}$ )	$K_a$ with 2b (fluorescence) ( $M^{-1}$ )
$F^-$	Not determined	14.400	150.000
$Cl^-$	1.000	3.100	10.380
$Br^-$	500	640	1.887
$NO_3^-$	420	400	1.672

Starting with a simple molecule 1, an efficient receptor for anions 2a can be designed. Electronic modification of the basic molecular skeleton leads to the derivative 2b, which shows an impressive selectivity and affinity for the fluoride anion.

Although the described investigation presents a very basic study, the recognition of anions is highly connected to separation and sensor technology and to pharmacological problems. Therefore, more reliable systems for selective and efficient binding of anions have to be found.

The chemistry of anion recognition became a topic of major interest and many valuable achievements are expected in the near future.

#### Hierarchical self-assembly of helicate-type complexes

The term helicate was introduced by J.-M. Lehn in 1987 and describes di- or oligonuclear coordination compounds with two or three linear organic ligands wrapping around the metals and thus are forming a double- or triple-stranded helix (Lehn et al. 1987). Due to their simplicity, helicates became a class of model compounds that enable studies to gain a deeper understanding of fundamental principles of metallosupramolecular chemistry. Stereochemical or regiochemical problems are addressed and mechanistic investigations are performed, which finally lead to the development of functional helicates. Those that act as optical nanodevices, bind to DNA or form mesophases. In the latter case hierarchical organization of the self-assembled helicates into mesostructured higher-order aggregates leads to the special property (formation of liquid crystalline phases) (Piguet et al. 1997; Albrecht 2001).

Herein a more simple example for “hierarchical self-assembly” (Sun et al. 2001) will be discussed. It uses a helicate-type system as model for thorough investigations in the solid state, in solution, and in the gas phase. (For supramolecular interactions at gas/liquid interfaces, see, e.g., Ariga and Kunitake 1998).

3-Carbonyl-substituted catechol derivatives (3, aldehyde, ketones, esters, but not amides) possess two different binding sites for metal ions. One is the catecholate unit,

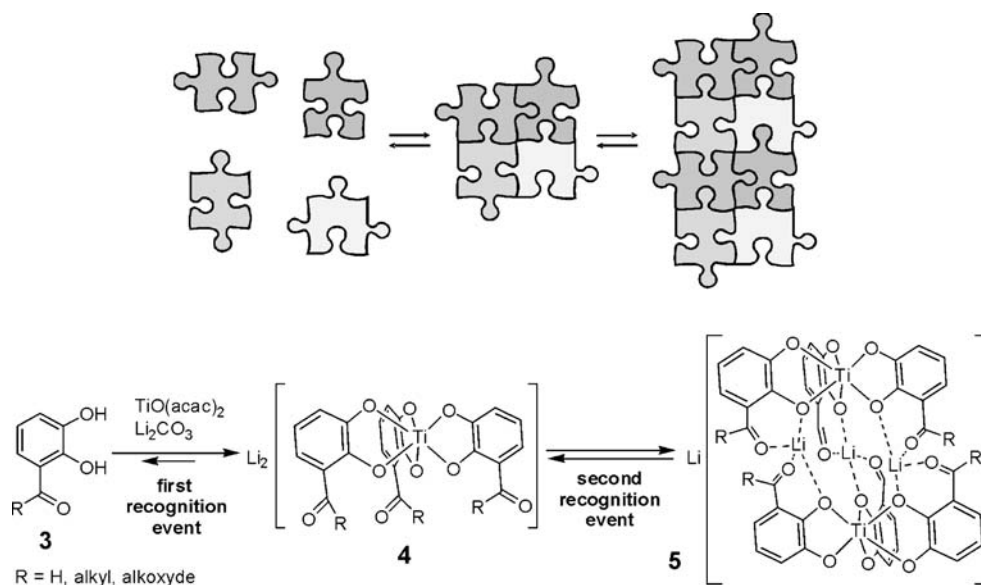
which itself was intensely investigated due to its unique metal coordinating ability and due to its presence in naturally occurring chelating agents—the siderophores (Carrano and Raymond 1978; Hider and Liu 2004). The second binding site is formed by the catecholate oxygen in 2-position and the carbonyl. It corresponds to a salicylate unit. The catecholate and the salicylate binding sites can be distinguished by different metals because of their different geometric and electronic features. The catecholate unit forms a five-membered chelating ring and possesses a highly negative charge (2-) while the mononegatively charged (1-) salicylate moiety affords a six-membered ring.

3-Carbonyl-substituted catechol ligands 3 lead in classical Werner-type coordination chemistry to *tris*(catecholate) titanium(IV) derivatives 4. The observed complex formation can be interpreted as a first recognition event between the catecholate ligands and titanium(IV) ions (selecting the catecholate over the salicylate). In the presence of lithium cations (but not sodium or potassium) a second recognition event occurs. The lithium cations bind to the salicylate as chelating unit. Dimerization takes place by coordination of two such sites to the lithium cations affording the triple-stranded helicate-type complex 5 as it is shown in Fig. 3. The first step of the dimerization process is thermodynamically straightforward and affords the triscatecholate 4. In the second step the dimerization occurs. However, in solution, both the dimeric 5 and the monomeric species 4 are observed at room temperature (by NMR). This allows the simple determination of the dimerization constant  $K_{dim}$  for the formation of the dinuclear titanium(IV) complex.

The dimerization equilibrium in solution is highly dependent on a series of different factors: (1) the donor ability of the carbonyl substituent at the ligand, (2) the solvent, and (3) the charge of the monomeric triscatecholate complex.

- (1) The donor strength of lone pairs at the carbonyl group decreases in the series ester > ketone > aldehyde. Therefore, ligands 3 with ester moieties are much better in coordinating lithium cations than the corresponding aldehydes. The obtained dimers are much more favored with the esters. Accordingly, dimerization constants are observed in methanol at room temperature of  $K_{dim}=25.600 M^{-1}$  (R=OMe),  $715 M^{-1}$  (R = Et), and  $10 M^{-1}$  (R=H). While in case of an ester mainly the dimer is observed, it is the minor species with an aldehyde.
- (2) A strong competitor for the formation of the dimer by lithium coordination is the coordination of the alkali cations by the solvent molecules. Good donors lead to the disruption of the dimer by dissolution of the  $Li^+$  ions. Only monomeric species are observed in DMSO for the aldehyde derivative. In a weakly coordinating

**Fig. 3** Schematic representation (*top*) and an example (*bottom*) of hierarchical self-assembly. In a first recognition event a non-covalently linked aggregate is formed, which in a second recognition step further aggregates to a bigger entity. The number of levels of hierarchy correlates with the complexity of the system



solvent, like acetone, the same compound is dissolved to form an equilibrium with the dimer being the dominating species ( $K_{\text{dim}}=1.330 \text{ M}^{-1}$ ).

- (3) Mononuclear triscatecholate titanium(IV) complexes bear the charge of 2<sup>−</sup> and therefore the bridging lithium cations are not only bound by donor–acceptor interaction but are additionally attracted by the negative charge. Substitution of the central titanium (IV) by gallium(III) leads to triscatecholate complex units, which possess the negative charge of 3<sup>−</sup>. The lithium now is even more attracted and for the aldehyde derivatives the dimerization constant in methanol at room temperature increases from  $K_{\text{dim}}=10 \text{ M}^{-1}$  (M=Ti) to  $K_{\text{dim}}=200.000 \text{ M}^{-1}$  (M=Ga).

The observations show that in the described hierarchical self-assembly process subtle factors can influence the equilibria and shift them toward one or the other species.

Temperature-dependent NMR measurements of the monomer–dimer equilibrium give some insight in the thermodynamics of the dimerization process. It was found out that the dimer formation by aggregation of two triscatecholate metal complex units and three lithium cations is enthalpically and entropically favored. The entropic driving force can be understood if the solvent molecules are taken into account. Approximately four solvent molecules are deliberated from the first ligand sphere of each lithium by incorporation of the cation into the dimer (Albrecht et al. 2005b).

In the solid state, dimeric species 5 are always observed for the titanium complexes in the presence of lithium cations. Only in the case of related *cis*-dioxomolybdenum (VI) complexes the monomeric building block  $[(3)_2\text{MoO}_2]^{2-}$  was analyzed by X-ray diffraction as a DMF-bridged

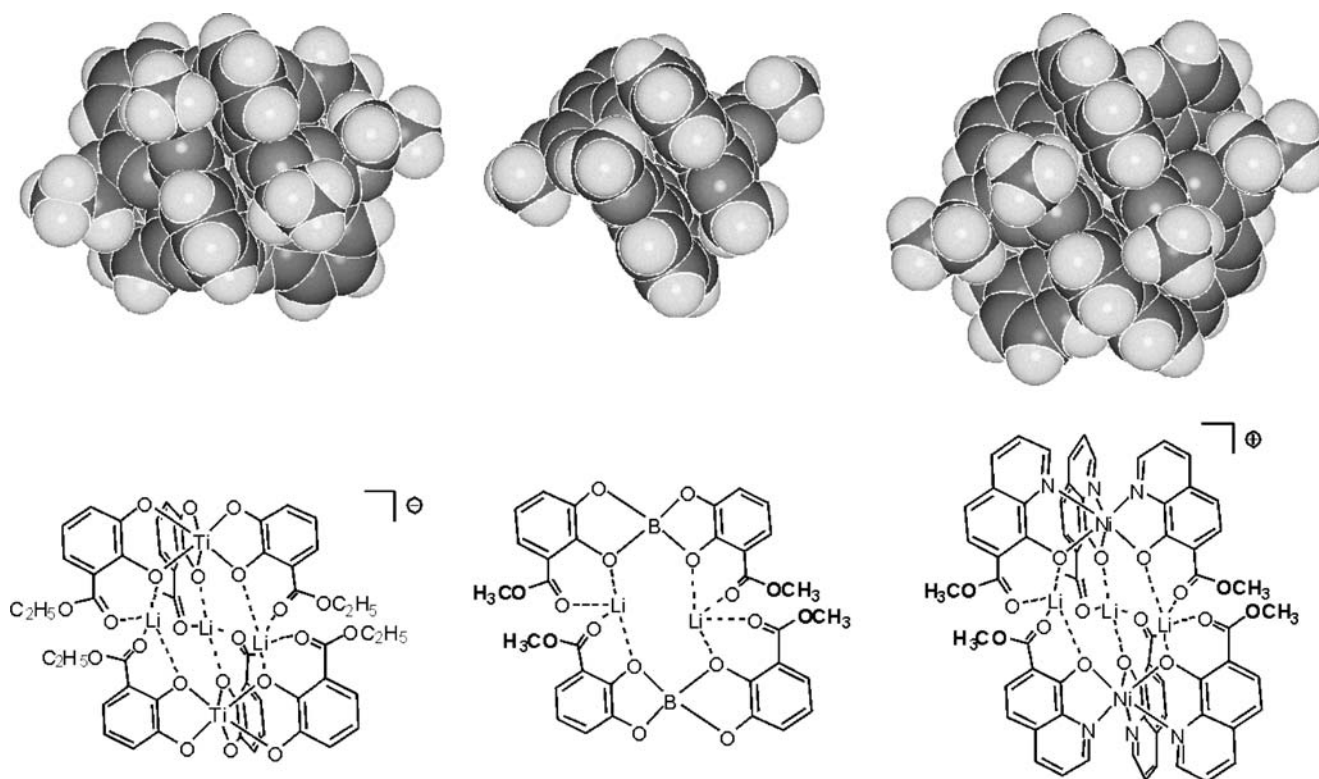
coordination polymer. In case of the molybdenum complexes dimerization takes place with only two ligands 3 per monomeric building block. However, additional lithium cation bridging occurs by involvement of the molybdenum oxo units (Albrecht et al. 2006a).

Electrospray ionization (ESI) Fourier transform ion cyclotron resonance mass spectrometry (MS) reveals a high stability of the dimers in the gas phase. Investigations of the exchange of monomeric complexes and ligands in the dimer show that the ligand exchange proceeds on a slow time scale while the exchange of complex units is fast. This again shows the hierarchy in the assembly of the complexes with a strong metal-to-ligand interaction and a weaker tendency for the formation of the dimers (Albrecht et al. 2005b).

The described example of hierarchical formation of helicate-type complexes seems to be unique. However, the principle can be used in a more general way. Figure 4 shows a collection of X-ray crystal structures, which reveal that triple- and double-stranded lithium-bridged coordination compounds are formed depending on the metal center. Furthermore, the assembly is not only restricted to catecholate derivatives in combination with early or main group metal cations. For example, the introduction of 8-hydroxyquinoline units allows the formation of related complexes with late transition metals (Co<sup>2+</sup>, Ni<sup>2+</sup>, and Zn<sup>2+</sup>). However, for the hierarchical assembly of dinuclear complexes of the described type the complementarity of the accessible geometry at the two binding sites at the ligand and the intrinsic geometry preferences of the metals are crucial (Albrecht et al. 2007b).

As a restriction for the formation of dimers it was found that the monomeric trischelate metal complex units have to bear a negative charge to strongly attract the bridging lithium cations. Neutral or cationic building blocks do not add this





**Fig. 4** Results of X-ray structure analyses showing triple-stranded (*left*) and double-stranded (*center*) complexes with catecholates and titanium(IV) or boron(III) as central “metal” units. On the right a related triple-stranded nickel(II) complex is shown in which the

catechol ester ligands are substituted by related 8-hydroxyquinoline derivatives. The overall charge of the complexes is  $-1$  (*left*),  $0$  (*center*), and  $+1$  (*right*)

electrostatic stabilization and therefore corresponding dimers are not stable. However, dinuclear complexes finally obtained can be positively or negatively charged and neutral (Albrecht et al. 2007b).

Although this example of hierarchical self-assembly is rather simple, it gives some insight into the formation of supramolecular aggregates. Further functionalization of the side chains of the complexes should lead to compounds able to shift the monomer–dimer equilibrium and therefore allow a switching (e.g., on/off) of their properties.

#### Self-assembly of molecular containers for host–guest chemistry

In the previous section a supramolecular system was described, which should allow an “outside” functionalization of supramolecular aggregates to introduce some special properties. On the other hand, supramolecular chemistry also enables the easy assembly of container molecules, which provide internal space to study host–guest chemistry, mediate chemical reactions, or perform catalytic processes (Fiedler et al. 2005; Fujita et al. 2005; Lützen 2005).

Approaches to get container molecules by self-assembly are mainly based on symmetry arguments. Hereby the

building blocks have to provide some geometrical features, which define the edges or the faces of a container.

The use of four triangular ligands is a simple approach in which they can be connected by four  $C_3$ -symmetric building blocks (e.g., an octahedrally coordinated metal ion) at the corners. As a result a tetrahedron will be formed (Albrecht 1999).

Compounds 6 represent appropriate ligands. They can easily be prepared by condensation of rigid triangular triamines with 2,3-dihydroxybenzaldehyde in high yields (Albrecht et al. 2004a).

The size of the ligands determines the size of the supramolecular tetrahedron, which will be produced upon metal coordination. A measure for this is the distance between two hydrogen atoms located in 4-positions of two former 2,3-dihydroxybenzaldehyde units. In ligand 6a the distance is 2.01 nm while the bigger 6b shows a length at the edge of 2.77 nm. Simple mixing of the ligands 6 with titanium(IV) ions and alkali metal carbonate ( $M = \text{Li}, \text{Na}, \text{K}$ ) in a ratio of 4:4:4 results in the spontaneous and quantitative formation of the molecular tetrahedra  $M_8[(6)_4\text{Ti}_4]$ .

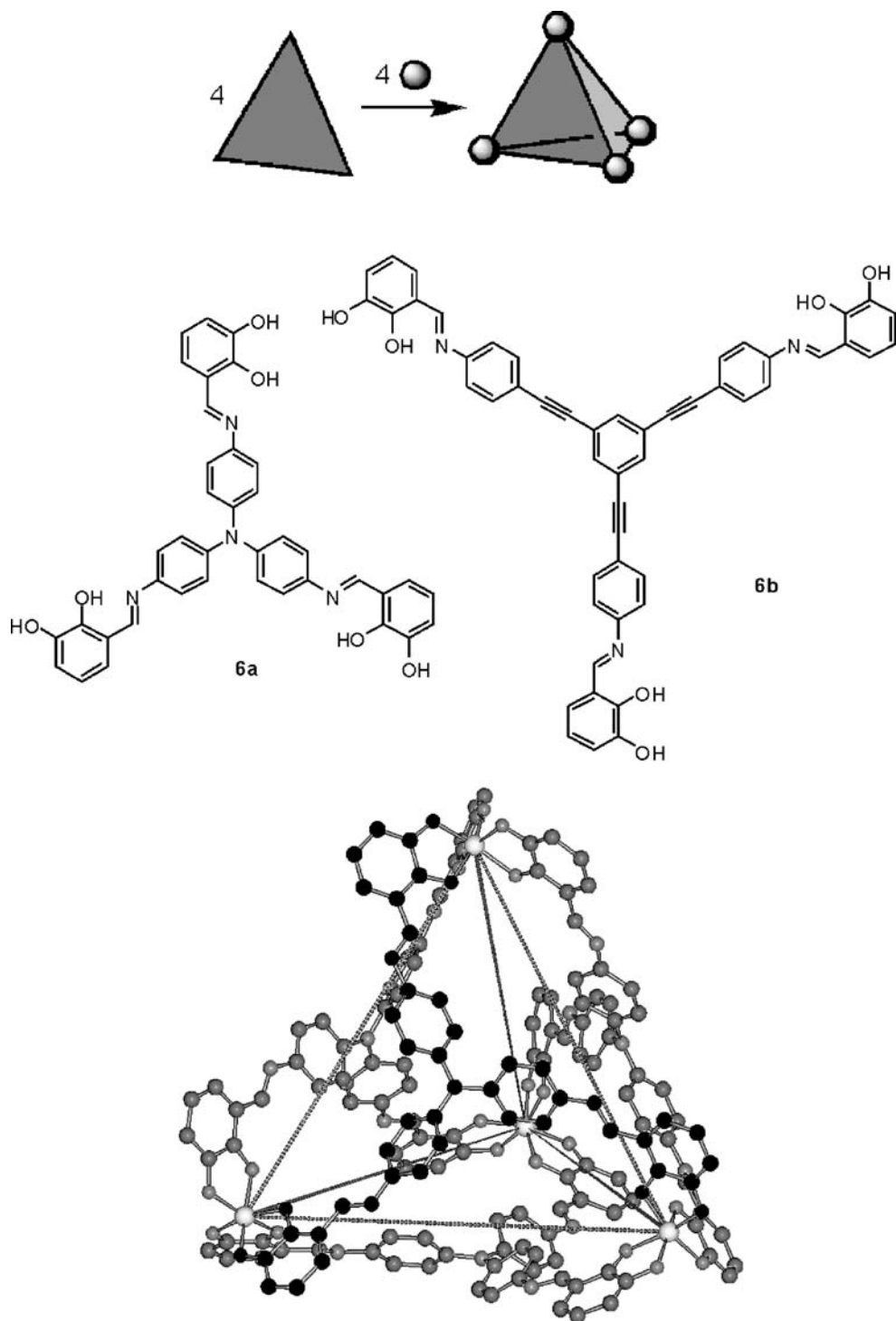
In Fig. 5 (bottom) the structure of the anion  $[(6a)_4\text{Ti}_4]^{8-}$  is shown, as it is found in the solid state. As expected, the titanium(IV) ions are located at the corners of a molecular

tetrahedron with the ligands spanning the faces. The distance between the metal ions is approximately 1.7 nm. Thus, a huge internal cavity is formed, which in the crystal contains four of the potassium counter cations and 12 DMF molecules (Albrecht et al. 2003).

To investigate the exchange of the internal guest species by organic substrates, cationic anilinium derivatives were added to the molecular tetrahedron  $\text{Li}_8[(6a)_4\text{Ti}_4]$ . Upon

addition of only one equivalent of anilinium chloride, the NMR spectrum of the container becomes unstructured and only broad signals are observed. This is due to incorporation of one guest species in the interior. Hereby the symmetry of the tetrahedron is broken. Upon addition of an excess of anilinium chloride a well-structured spectrum is observed again showing the high symmetry. The four lithium cations in the interior are substituted by four of the

**Fig. 5** Representation of triangular triscatechol ligands **6a** and **6b**, which are predisposed to form metallocupramolecular tetrahedral. The structure of the octaanionic complex  $[(6a)_4\text{Ti}_4]^{8-}$  derived by X-ray analysis is shown (*bottom*)



organic cations and the symmetry is restored (Albrecht et al. 2006b).

The next step will be not only to introduce organic guests but also to perform some chemical reactions in the cavity, as it was demonstrated with other container molecules (Lützen 2005).

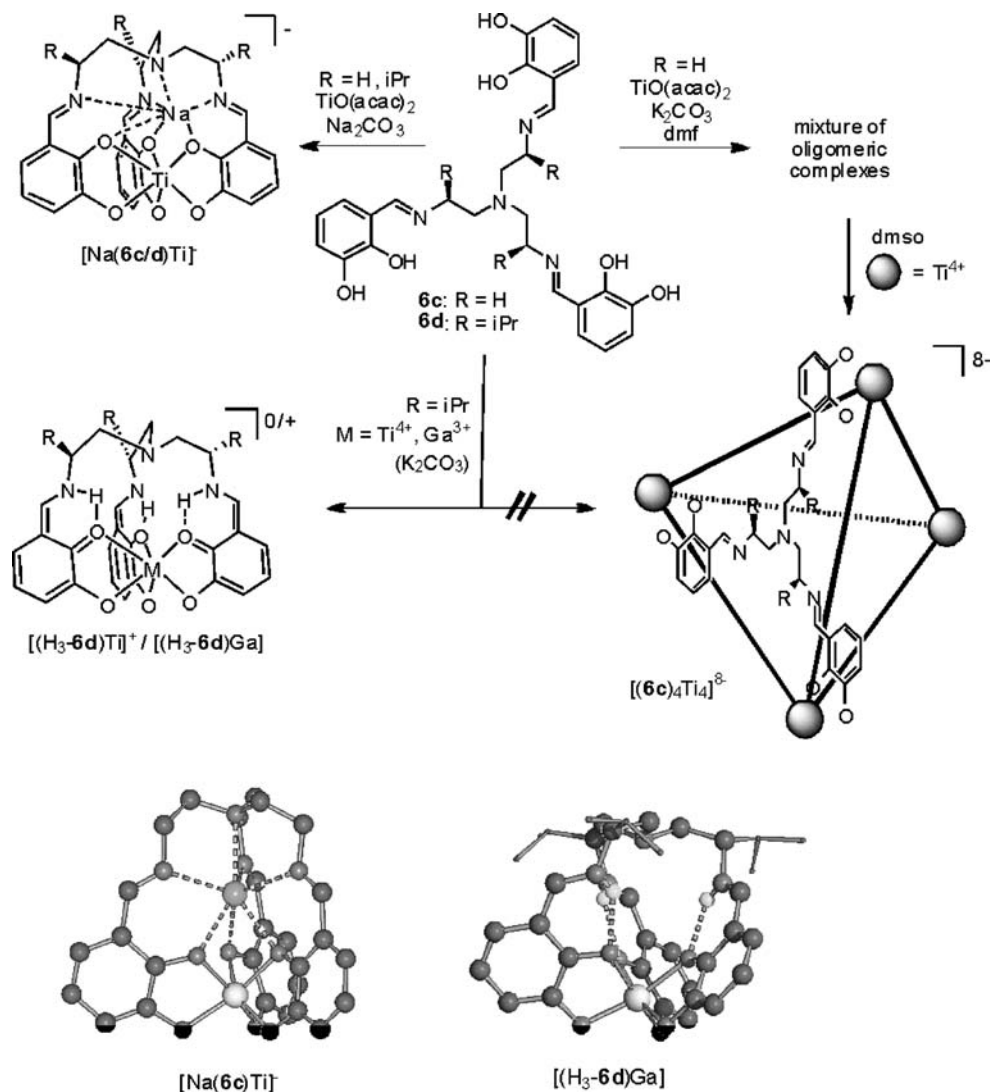
In most studies on metallocupramolecular container molecules rigid building blocks are used for the assembly. The question arises if flexible well-designed ligands can also lead to related architectures. Therefore, the imine ligands **6c** and **6d** were prepared and used in coordination studies (Fig. 6).

Reaction of the ligands **6c** or **6d** with titanium(IV) ions in the presence of sodium carbonate leads to mononuclear titanium(IV) complexes with the tripodal ligand capping the metal and encapsulating a sodium cation. The sodium cation is an important template to compensate the repulsion between the electron pairs at the imine nitrogens and the internal catechol oxygen atoms. In a similar coordination

study with ligand **6c** in the presence of potassium carbonate in DMF, only mixtures of oligomeric complexes are observed. Potassium is too big to be bound in the cavity and therefore cannot act as template. However, dissolving this mixture of oligomers in DMSO leads to one species within a couple of hours. ESI MS shows that a tetrahedral complex  $[(6c)_4Ti_4]^{8-}$  is formed. The reason for this is the strong ion solvating ability of DMSO, which removes coordinating potassium from the oligomer. Repulsion of the above-mentioned electron pairs leads to the spreading out of the ligand **6c** and to its preorganization to form the tetrahedron (Albrecht et al. 2004b).

Attempts to form related tetrahedra of gallium(III) or titanium(IV) ions with the chiral substituted ligand **6d** were unsuccessful. Steric interaction of the bulky isopropyl groups prevents the spreading out of the ligand and only a mononuclear complex is observed. In the absence of sodium cations the repulsion between imine and oxygen electron pairs is compensated by incorporation of three

**Fig. 6** Formation of mononuclear and tetranuclear complexes from flexible tripodal ligands and solid state structures obtained by X-ray structural analysis



protons (e.g., from solvent molecules). However, this should lead to a strong repulsion between three  $H^+$ . The system prevents this by adopting an isomeric form, which strongly disturbs the aromatic system and can be discussed as an enaminone/*o*-quinomethine structure (Albrecht et al. 2007c).

The described results show that the formation of big supramolecular aggregates is predictable if rigid building blocks are used. On the other hand, using flexible moieties, self-assembly processes highly depend on a subtle interplay of steric and electronic factors. The understanding of the general principles of container assembly is important to develop novel supramolecular host–guest systems.

#### Enzyme mimicry: self-assembled receptors for small reactive molecules

It is a challenge to follow nature's example and to use self-assembled supramolecular structures for the stabilization of reactive species or for the control of chemical reactivity.

Here, an example is discussed, where a reaction proceeds not in the interior of a container, but in a pocket, which is formed by two metal ions and two bridging amino acid-derived ditopic ligands. In some respects this example can be described as metalloenzyme mimicry. (Lippard and Berg 1994).

To mimic metalloenzyme action, ligands were prepared, which contain two binding sites for metals and amino acids or small peptides as spacers (Albrecht et al. 2001a). If the spacer is short (one or two amino acid residues) the ligands bind to two different metal ions. With longer spacers the ligands are able to form a turn structure and the terminal units are coordinating to only one metal center. This behavior is of interest for the stabilization of peptide turn structures, but it does not provide an entry into the control of reactivities (Albrecht and Stortz 2005).

A fascinating chemistry was developed based on simple amino acid-bridged catechol ligands **7**. Those form dinuclear titanium(IV) complexes in which two ligands **7** bridge two metal centers and still provide coordination sites for two coligands (e.g., methanolate or hydroxide from a solvent). Due to the chirality at the metal centers and to the directionality of the ligands, seven different isomers of, e.g.,  $[(7)_2(OCH_3)_2Ti_2]^{2-}$ , are formed. However, long-term NMR studies show that a thermodynamically favored isomer can be obtained as the dominating species (Albrecht et al. 2001b).

First structural informations for the solution species of  $[(7)_2(OCH_3)_2Ti_2]^{2-}$  were obtained by NMR and polarographic studies combined with computational considerations (Fig. 7).

Finally, the structure of the thermodynamically favored isomer of  $[(7)_2(OCH_3)_2Ti_2]^{2-}$  was found out by a confor-

mational analysis of several of the complexes using Ramachandran's method. Therefore, dihedral angles  $\Phi$  and  $\Psi$  of the amino acid spacers determined by X-ray were measured and Ramachandran conformational analysis was performed.

X-ray structures are obtained for some of the complexes  $[(7)_2(OR)_2Ti_2]^{2-}$  (R = Me, H) with respectively alanine, phenyl alanine, leucine, or valine residues in the spacer. In case of valine the achiral mesocomplex is obtained. To some content epimerization took place during synthesis of the ligand.

The Ramachandran plot (Fig. 8) shows that most derivatives adopt conformations typical for amino acid residues of right handed  $\alpha$ -helical peptides (Ala, Leu, Phe-2, (*S*)-Val).

Two of the obtained data points (Phe-1, R-Val) are found in the region of left-handed helical conformations. For the *R*-valine-bridged ligand this is the favored arrangement. However, it is unusual for the *S*-phenyl alanine derivative. *S*-Amino acids prefer to adopt a right-handed helical conformation due to sterical interactions between the side chain and the amino acid backbone. A left-handed turn leads to repulsion between the substituent at  $\alpha$ -C and the amino acid backbone. A closer look at the X-ray structures shows that the ligands, which possess the right-handed helical twist, are bound with their more rigidly connected N-terminal ligand moiety to the  $\Lambda$ -configured metal center of the mesotype complex. On the other hand, the N termini of the left-handed twisted ligands bind to a  $\Delta$ -configured metal. Thus,  $\Lambda$ -configuration at the N terminus induces the preferred right-handed helicity at the amino acid residue while  $\Delta$ -configuration at the N terminus leads to the unfavored left-handed twist.

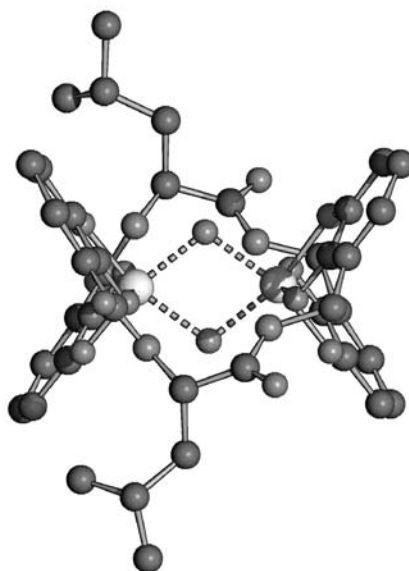
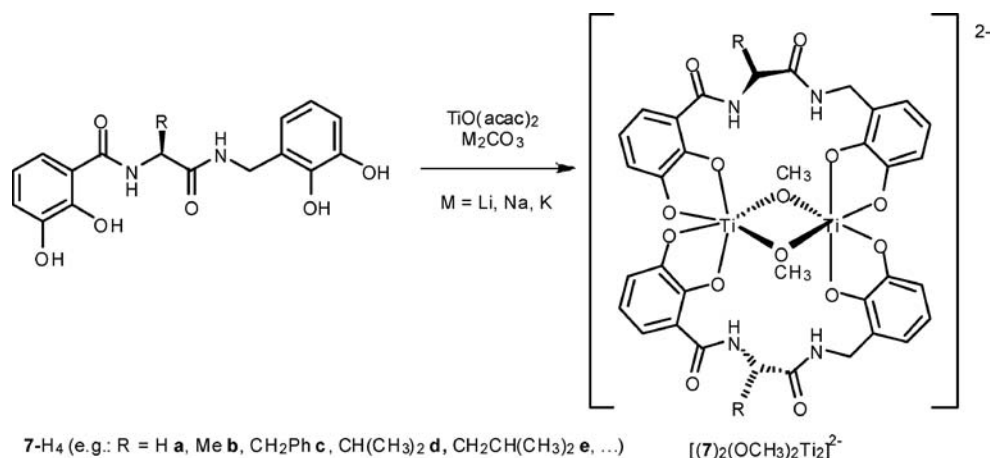
To get the thermodynamically preferred species, both ligand strands should bind with their N termini to the  $\Lambda$ -configured metal center of the mesotype dinuclear complex to adopt the more favored right-handed helical conformation (Albrecht et al. 2001c).

Complexes like  $[(7)_2(OCH_3)_2Ti_2]^{2-}$  show some structural similarity to the reactive sites of metalloenzymes with dinuclear metal centers. The two metals are separated by approximately 5.6 Å, as it is found in naturally occurring dinuclear complex units. The whole ensemble is embedded in a pocket formed by amino acid residues and there are some coligands present. In natural systems such coligands can be substituted by reactive species, and chemical reactions proceed in the ligand sphere of the complex.

However, to introduce specific reactivity in compounds like  $[(7)_2(OCH_3)_2Ti_2]^{2-}$ , some requirements have to be fulfilled:

- More reactive coligands have to be introduced to perform reactions.

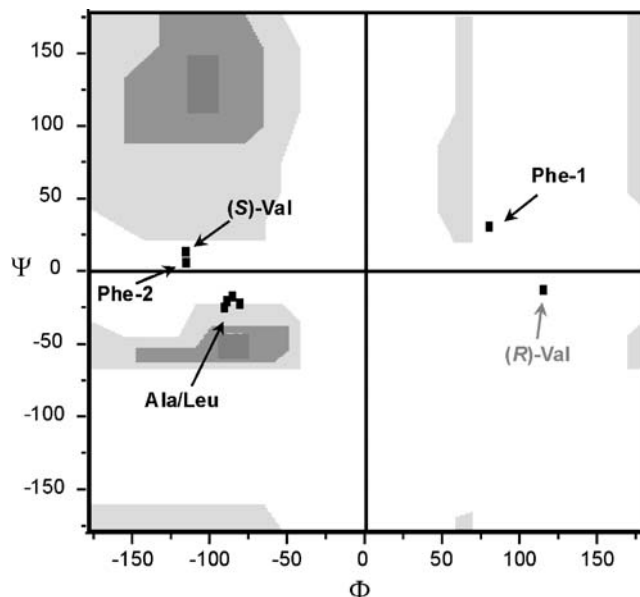
**Fig. 7** Formation of double stranded dinuclear complexes  $[(7)_2(\text{OCH}_3)_2\text{Ti}_2]^{2-}$  and the solid state structure of the thermodynamically favored isomer of the leucine derivative  $[(7e)_2(\text{OH})_2\text{Ti}_2]^{2-}$  (H atoms are omitted for clarity)



- The coligands should not be derived from the solvent to get reactions at the coordinated ligands and not at the solvent.
- Only one of the isomers of the dinuclear complexes should be present to perform a well controlled reaction.

Ways had to be found to prepare the dinuclear complexes in a fashion, which introduces reactive coligands, enables the solvation of the complexes in “innocent” (unreactive) solvents, and which yields only the thermodynamically favored species. This was in the reported case achieved by synthesis of the complexes in acetonitrile as solvent in the presence of tetrabutyl ammonium hydroxide as base and with stoichiometric amounts of appropriate alcohols as coligands. Addition of ether results in precipitation of the dinuclear complexes as predominantly the most favored isomer (Albrecht et al. 2005c).

In an orientating study a phenyl alanine-bridged coordination compound was used to perform a Diels–Alder reaction in the coordination sphere of the complex units.



**Fig. 8** Ramachandran plot for the conformational analysis of the amino acid residues of  $[(7b-e)_2(\text{OR})_2\text{Ti}_2]^{2-}$

Reaction of cyclopentadiene with monoacryl–glycolate, which is bound in the pocket of the dinuclear titanium complex, followed by hydrolysis of this complex yields the Diels–Alder product in an exo to endo ratio of 7:1. However, Diels–Alder reactions are well known to be endoselective, and a control experiment of “free” cyclopentadiene results in the product in an exo to endo ratio of 1:4 (Clapham and Shipman 1999). Therefore, selectivity of this reaction in the ligand sphere of the titanium(IV) complex is inverse compared to the one without coordination to this unit. The reason for this behavior is illustrated in Fig. 9 (bottom). Cyclopentadiene can more easily approach the dienophile in the cavity with the small methylene unit pointing into the cleft provided by the amino acid spacers of the ligand. This leads to the formation of the exo Diels–Alder product.

This example shows that supramolecular coordination compounds (like  $[(7)_2(\text{OCH}_3)_2\text{Ti}_2]^{2-}$ ) can act as reaction centers similar to metal complex units in metalloenzymes. The special structures of the aggregates influence chemical reactions, which proceed in the coordination sphere of the supermolecules. This is an entry into a field of new chemical reactions in which self-assembly is used to

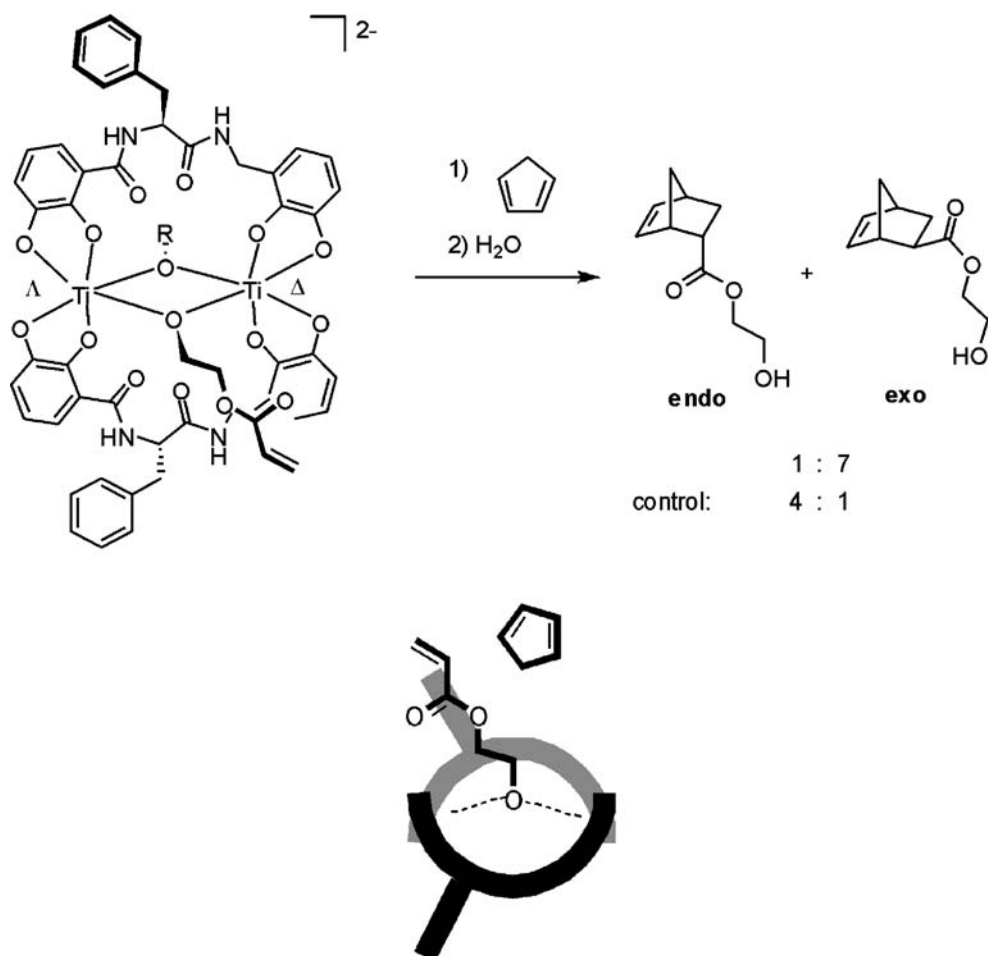
provide cavities for the efficient control of reaction pathways.

## Conclusion

In this review, general principles of supramolecular chemistry were introduced and the key terms *noncovalent interaction*, *molecular recognition*, and *self-assembly* were described. Those three basic supramolecular principles were discussed in the more general context, providing insights in thermodynamic requirements and energetics of dynamic processes. The latter are crucial for selectivity in molecular recognition and for specificity in self-assembly. In addition, the term “supramolecular function” was introduced as an important motivator to study supramolecular chemistry and to develop new materials based on this.

In the second part of the review, very basic examples were described to illustrate the fundamental principles *noncovalent interaction*, *molecular recognition*, and *self-assembly*. Those simple models show the enormous potential of supramolecular chemistry to act as a mediator between chemistry and nanotechnology and to synthesize

**Fig. 9** Example of an endo-selective Diels–Alder reaction, which becomes exoselective in the coordination sphere of a dinuclear titanium(IV) complex. The control experiment was performed with free acryl glycolate



molecules, which possess new properties or show novel reactivities.

**Acknowledgement** I thank all my coworkers and all the collaborating scientists who were involved in the works described and which are mentioned in the reference section. Funding for our work is generously provided by the DFG (especially within the priority program SPP 1118) and by the Fonds der Chemischen Industrie.

## References

- Albrecht M (1999) Into the next dimension: nanometer-sized, oligonuclear coordination compounds with  $C_3$ -symmetric ligands. *Angew Chem Int Ed* 38:3463–3465
- Albrecht M (2001) “Let’s twist again”—double-stranded, triple-stranded and circular helicates. *Chem Rev* 101:3457–3498
- Albrecht M, Stortz P (2005) Metallacyclopeptides: artificial analogues of naturally occurring peptides. *Chem Soc Rev* 496–506
- Albrecht M, Napp M, Schneider M (2001a) The synthesis of amino acid bridged dicatechol derivatives. *Synthesis*:468–472
- Albrecht M, Napp M, Schneider M, Weis P, Fröhlich R (2001b) Kinetic versus thermodynamic control of the self-assembly of isomeric double-stranded dinuclear titanium(IV) complexes from phenylalanine-bridged dicatechol ligands. *Chem Commun* 409–410
- Albrecht M, Napp M, Schneider M, Weis P, Fröhlich R (2001c) Dinuclear titanium(IV) complexes from amino acid-bridged dicatechol ligands: formation, structure, and conformational analysis. *Chem Eur J* 7:3966–3975
- Albrecht M, Janser I, Meyer S, Weis P, Fröhlich R (2003) A metallosupramolecular tetrahedron with a huge internal cavity. *Chem Commun* 2854–2855
- Albrecht M, Janser I, Fröhlich R (2004a) Synthesis of triscatechol derivatives—building blocks with an idealized  $C_3$ -symmetry for metallo-supramolecular chemistry. *Synthesis* 1977–1982
- Albrecht M, Janser I, Runsink J, Raabe G, Weis P, Fröhlich R (2004b) Selecting different complexes from a dynamic combinatorial library of coordination compounds. *Angew Chem Int Ed* 43:6662–6666
- Albrecht M, Triyanti, de Groot M, Bahr M, Weinhold E (2005a) A fluorescent quinoline derivative as selective receptor for fluoride anions. *Synlett* 2095–2097
- Albrecht M, Mirtschin S, de Groot M, Janser I, Runsink J, Raabe G, Kogej M, Schalley CA, Fröhlich R (2005b) Hierarchical assembly of helicate-type dinuclear titanium(IV) complexes. *J Am Chem Soc* 127:10371–10387
- Albrecht M, Nolting R, Weis P (2005c) Preparation of amino acid-bridged dicatechol ligands for dinuclear titanium(IV) complexes. *Synthesis* 1125–1135
- Albrecht M, Baumert M, Klankermayer J, Kogej M, Schalley CA, Fröhlich R (2006a) Dicatechol *cis*-dioxomolybdenum(VI): a building block for a lithium cation templated monomer-dimer equilibrium. *Dalton Trans* 4395–4400
- Albrecht M, Janser I, Burk S, Weis P (2006b) Self-assembly and host-guest chemistry of big metallosupramolecular  $M_4L_4$  tetrahedra. *Dalton Trans* 2875–2880
- Albrecht M, Triyanti, Schifffers S, Ossetka O, Raabe G, Wieland T, Russo T, Rissanen K (2007a) Anion receptors based on a quinoline backbone. *Eur J Org Chem* 2850–2858
- Albrecht M, Fiege M, Baumert M, de Groot M, Fröhlich R, Russo L, Rissanen K (2007b) Hierarchical lithium-templated assembly of helicate-type complexes: how versatile is this reaction? *Eur J Inorg Chem* 609–616
- Albrecht M, Burk S, Stoffel R, Lüchow A, Fröhlich R, Kogej M, Schalley CA (2007c) Protonation of *tris*(iminocatecholate) complexes of gallium(III) and titanium(IV). *Eur J Inorg Chem* 1361–1372
- Amabilino DB, Stoddart JF (1995) Interlocked and intertwined structures and superstructures. *Chem Rev* 95:2725–2828
- Ariga K, Kunitake T (1998) Molecular recognition at air–water and related interfaces: Complementary hydrogen bonding and multi-site interaction. *Acc Chem Res* 31:371–378
- Ariga K, Kunitake T (2006) *Supramolecular chemistry. Fundamentals and applications*. Springer, Berlin Heidelberg New York
- Badjić JD, Cantrill SJ, Grubbs RH, Guidry EN, Orenes R, Stoddart RF (2004) The exclusivity of multivalency in dynamic covalent processes. *Angew Chem Int Ed* 43:3273–3278
- Beer PD, Gale PA, Smith DK (1999) *Supramolecular chemistry*. Oxford University Press, Oxford
- Bianchi A, Bowman-James K, Garcia-Espana E (1997) *Supramolecular chemistry of anions*. Wiley, New York, NY
- Carrano CJ, Raymond KN (1978) Coordination chemistry of microbial iron transport. 10. Characterization of the complexes of Rhodotorulic acid, a dihydroxamate siderophore. *J Am Chem Soc* 100:5371–5374
- Caulder D, Raymond KN (1999) The rational design of high symmetry coordination clusters. *J Chem Soc Dalton Trans* 1185–1200
- Clapham G, Shipman M (1999) Selective complexation of 2-hydroxyethyl esters using Lewis acids. *Tetrahedron Lett* 40:5639–5642
- Constable EC (1991) Helices, supramolecular chemistry, and metal-directed self-assembly. *Angew Chem Int Ed Engl* 30:1450–1451
- Corbett PT, Leclair J, Vial L, West KR, Wietor J-L, Sanders JKM, Otto S (2006) Dynamic combinatorial chemistry. *Chem Rev* 106:3652–3711
- Dutzler R, Campbell EB, Cadene M, Chait BT, MacKinnon R (2002) X-ray structure of a CIC chloride channel at 3.0 Å reveals the molecular basis of anion selectivity. *Nature* 415:287–294
- Ehrlich P (1906) *Studies on immunity*. Wiley, New York, NY
- Fiedler D, Leung DH, Bergman RG, Raymond KN (2005) Selective molecular recognition, C–H bond activation, and catalysis in nanoscale reaction vessels. *Acc Chem Res* 38:349–358
- Fischer E (1894) Einfluss der Configuration auf die Wirkung der Enzyme. *Ber Deutsch Chem Ges* 28:2985–2993
- Fujita M, Tominaga M, Hori A, Therrien B (2005) Coordination assemblies from a Pd(II)-cornered square complex. *Acc Chem Res* 38:369–378
- Goshe AJ, Steele IM, Ceccarelli C, Rheingold AL, Bosnich B (2002) Supramolecular recognition: on the kinetic lability of thermodynamically stable host–guest association complexes. *Proc Natl Acad Sci U S A* 99:4823–4829
- Greig LM, Philp D (2001) Applying biological principles to the assembly and selection of synthetic superstructures. *Chem Soc Rev* 30:287–302
- Grote Z, Scopelliti R, Severin K (2003) Adaptive behavior of dynamic combinatorial libraries generated by assembly of different building blocks. *Angew Chem Int Ed* 42:3821–3825
- Hamacek J, Borkovec M, Piguet C (2005a) A simple thermodynamic model for quantitatively addressing cooperativity in multicomponent self-assembly processes—part 1: theoretical concepts and application to monometallic coordination complexes and bimetallic helicates possessing identical binding sites. *Chem Eur J* 11:5217–5226
- Hamacek J, Borkovec M, Piguet C (2005b) A simple thermodynamic model for quantitatively addressing cooperativity in multicomponent self-assembly processes—part 2: extension to multimetallic helicates possessing different binding sites. *Chem Eur J* 11:5227–5237

- Hider RC, Liu ZD (2004) Siderophores. In: Atwood JL, Steed JW (eds) Encyclopedia of supramolecular chemistry. Marcel Dekker, New York, NY, pp 1278–1290
- Klug A (1983) From macromolecules to biological assemblies. *Angew Chem Int Ed Engl* 22:565–582
- König B (1995) Molecular recognition. The principle and recent chemical examples. *J Prakt Chem* 337:339–346
- Lawrence DS, Jiang T, Levett M (1995) Self-assembling supramolecular complexes. *Chem Rev* 95:2229
- Lehn J-M (1988) Supramolecular chemistry—scope and perspectives molecules, supermolecules, and molecular devices. *Angew Chem Int Ed Engl* 27:89–112
- Lehn J-M (1990) Perspectives in supramolecular chemistry—from molecular recognition towards molecular information processing and self-organization. *Angew Chem Int Ed Engl* 29:1304–1319
- Lehn J-M (1994) Perspectives in supramolecular chemistry: from molecular recognition towards self-organization. *Pure Appl Chem* 66:1961–1966
- Lehn J-M (1995) Supramolecular chemistry—concepts and perspectives. VCH, Weinheim
- Lehn J-M (1999) Dynamic combinatorial chemistry and virtual combinatorial libraries. *Chem Eur J* 5:2455–2463
- Lehn J-M (2000) Programmed chemical systems: multiple subprogrammes and multiple processing/expression of molecular information. *Chem Eur J* 6:2097–2102
- Lehn J-M, Rigault A, Siegel J, Harrowfield J, Chevrier B, Moras D (1987) Spontaneous assembly of double-stranded helicates from oligobipyridine ligands and copper(I) cations: structure of an inorganic double helix. *Proc Natl Acad Sci U S A* 84:2565–2569
- Lindsey JS (1991) Self-assembly in synthetic routes to molecular devices. Biological principles and chemical perspectives: a review. *New J Chem* 15:153–180
- Lippard SJ, Berg JM (1994) Principles of bioinorganic chemistry. University Science Books, Mill Valley, CA
- Lützen A (2005) Self-assembled molecular capsules—even more than nano-sized reaction vessels. *Angew Chem Int Ed* 44:1000–1002
- MacGillivray LR, Atwood JL (1999) Structural classification and general principles for the design of spherical molecular hosts. *Angew Chem Int Ed* 38:1018–1033
- Park CH, Simmons HE (1968) Macrobicyclic amines. III. Encapsulation of halide ions by in,in-1,(k + 2)-diazabicyclo[k.l.m.]alkane ammonium ions. *J Am Chem Soc* 90:2431–2432
- Pedersen C (1988) The discovery of crown ethers. *Angew Chem Int Ed* 27:1021–1027
- Percec V, Cho W-D, Ungar G, Yeardley DJP (2000) From molecular flat tapers, discs, and cones to supramolecular cylinders and spheres using Fréchet-type monodendrons modified on their periphery. *Angew Chem Int Ed* 39:1597–1602
- Philp D, Stoddart F (1996) Self-assembly in natural and unnatural systems. *Angew Chem Int Ed* 35:1154–1196
- Piguet C, Bernardinelli G, Bünzli J-CG (1997) Helicates as versatile supramolecular complexes. *Chem Rev* 97:2005–2062
- Rebek J, Wattlely RV Jr, Costello T, Gadwood R, Marshall L (1981) Allosteric effects: binding cooperativity in a subunit model. *Angew Chem Int Ed* 20:605–606
- Safarowsky O, Windisch B, Mohry A, Vögtle F (2000) Nomenclature for catenanes, rotaxanes, molecular knots and assemblies derived from these structural elements. *J Prakt Chem* 342:437–444
- Schalley CA, Lützen A, Albrecht M (2004) Approaching supramolecular functionality. *Chem Eur J* 10:1072–1080
- Scherer M, Caulder D, Johnson DW, Raymond KN (1999) Coordination number incommensurate cluster formation. Part 11. Triple helicate–tetrahedral cluster interconversion controlled by host–guest interactions. *Angew Chem Int Ed* 38:1588–1592
- Schneider HJ (1991) Mechanisms of molecular recognition: investigations of organic host–guest complexes. *Angew Chem Int Ed Engl* 30:1417–1436
- Steed JW, Atwood JL (2000) Supramolecular chemistry. Wiley, New York
- Sun X, Johnson DW, Caulder D, Raymond KN, Wong EH (2001) Rational design and assembly of  $M_2M'_3L_6$  supramolecular clusters with  $C_{3h}$  symmetry by exploiting incommensurate symmetry numbers. *J Am Chem Soc* 123:2752–2763
- Urich T, Gomes CM, Kletzin A, Frazao C (2006) X-ray structure of a self-compartmentalizing sulfur cycle metalloenzyme. *Science* 311:996–1000
- Vögtle F (1992) Supramolekulare Chemie. Teubner, Stuttgart
- Watson JD, Crick FCH (1953) Molecular structure of nucleic acids: a structure for deoxyribose nucleic acid. *Nature* 171:737–738
- Werner A (1893) Beitrag zur Konstitution anorganischer Verbindungen. *Z Anorg Chem* 3:267–330
- Whitesides GM, Boncheva M (2002) Beyond molecules: self assembly of mesoscopic and macroscopic components. *Proc Natl Acad Sci U S A* 99:4769–4774
- Whitesides GM, Mathias JP, Seto CT (1991) Molecular self-assembly and nanochemistry: a chemical strategy for the synthesis of nanostructures. *Science* 254:1312–1319
- Williams DH, Stephens E, O'Brien DP, Zhou M (2004) Understanding noncovalent interactions: ligand binding energy and catalytic efficiency from ligand-induced reductions in motion within receptors and enzymes. *Angew Chem Int Ed* 63:6596–6616
- Würthner F, Yao S, Beginn U (2003) Highly ordered merocyanine dye assemblies by supramolecular polymerization and hierarchical self-organization. *Angew Chem Int Ed* 42:3247–3250