



*Review Article*

# From Molecular Diversity to Template-Directed Self-Assembly – New Trends in Metallo-Supramolecular Chemistry

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(Received: 13 October 1998; in final form: 18 January 1999)

**Abstract.** Molecular diversity can easily be generated in metallo-supramolecular systems by simple mixing of oligodentate ligands and appropriate metal ions. In this reaction either a defined coordination compound is formed in a selective self-assembly process or a mixture is obtained. Depending on the system such a mixture can possess a statistical distribution of components or the formation of some species is thermodynamically favored leading to only a few out of several possible compounds (or in the extreme to only one). Simple well-defined mixtures containing only a few components or pure supramolecular aggregates can be generated from sequential or directional ligands, from mixtures of ligands and/or metals, and by introducing templates which support the formation of defined metallo-supramolecular aggregates. In the latter case it is possible first to generate a mixture of components which are in dynamic equilibrium (dynamic combinatorial library). In a second step, a template can be added, which in a dynamic process transforms such a library into one well-defined species. Thus, the initial generation of molecular diversity allows in a subsequent selection step in an evolutionary process the formation of the most favored receptor/substrate adduct (“dynamic combinatorial chemistry”).

**Key words:** Helicates, dynamic combinatorial chemistry, molecular diversity, templating, metallo-supramolecular chemistry.

## 1. Templating in Supramolecular Chemistry

Since Pedersen’s pioneering discovery of the crown-ethers and of their ability to bind cations it is well known that the synthesis of macrocyclic compounds can be favored in the presence of appropriate templates [1].

For example, the formation of 18-crown-6 in the presence of potassium should be mentioned. The potassium binds the linear polyether chain of the macrocycle precursor and brings its reactive parts into close spatial contact. Thus, the precursor is preorganized to favor the intramolecular ring-closing reaction and not the competing intermolecular reaction. Since this discovery more than 30 years

ago, templating plays an important role in supramolecular chemistry. For example, the formation of Cram's carceplexes by reaction of appropriate cavitands with  $\text{CH}_2\text{ClBr}$  in the presence of  $\text{Cs}_2\text{CO}_3$  depends on the template which is present. It could be shown that carceplex preparation is performed best in the presence of pyrazine, while *N*-methylpyrrolidinone is the poorest template which can be used for this reaction [2].

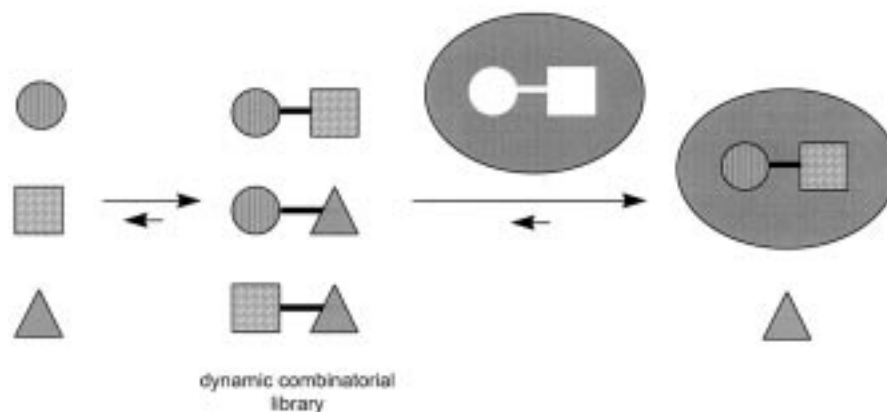
Templating via hydrogen-bonding of substrates can lead to systems in which the template acts as a catalyst for a reaction. If the product of this reaction is identical with the catalyst, an autocatalytic/self-replicating system is present. This principle was demonstrated by several examples which were described by e.g., Orgel, Rebek, or von Kiedrowski [3].

In all the cases which were mentioned above, templating is used to preorganize molecules for the selective formation of covalent bonds and to obtain defined molecules. In this review we will show that the same concept can be transferred to metallo-supramolecular chemistry and that a template or other secondary stabilizing interactions can favor the formation of one specific non-covalently linked supramolecular aggregate [4]. Furthermore, in a dynamic process one defined supermolecule can be removed from a mixture of supramolecular species (= supramolecular library) by addition of a template (dynamic combinatorial chemistry).

## 2. What Is the Meaning of "Dynamic Combinatorial Chemistry"?

In combinatorial chemistry several components undergo a chemical reaction to form a more or less defined mixture ("library") of compounds [5]. Alternatively in an automated preparation process many compounds can be synthesized in parallel. This strategy allows an effective search for lead structures and biologically active molecules through the generation of molecular diversity in the combinatorial library. The combination of the synthesis of such static combinatorial libraries with selection and amplification processes enables the search for highly selective receptors for specific substrates [6].

As an alternative, a mixture of compounds can be generated in a reversible reaction, either by formation of non-covalent or labile covalent bonds [7–9]. In this case all the components of the mixture are in dynamic equilibrium and can be transformed or rearranged into each other (dynamic combinatorial chemistry). The advantage of such a system is, that by addition of a specific receptor it is possible to remove in a dynamic process the most appropriate substrate (the substrate with the highest binding affinity for this receptor) from the equilibrating mixture [10–12]. As a further alternative, a mixture of equilibrating receptors can be formed and one receptor is removed from the equilibrium by addition of a substrate [13]. In such a dynamic system the mixture ("library") might contain several different species which are not well-characterized. However, the addition of an appropriate



*Scheme 1.* Dynamic combinatorial chemistry: A dynamic combinatorial library is obtained from several molecular components by formation of non-covalent or weak covalent bonds. Addition of an appropriate receptor to this equilibrating library leads to the removal of one component and the formation of only one defined receptor/substrate complex.

substrate shows a new possibility for the selection of the most active component of such an equilibrating library.

### 3. Molecular Diversity and Templating in Metallo-Supramolecular Systems

Metal cations are used as templates for the synthesis of topologically interesting organic derivatives such as molecular knots, catenanes or rotaxanes [14]. Here the metal ions are necessary to fix ligands in a defined geometry and thus direct a chemical reaction towards a desired product. On the other hand, templating can play an important role in the self-assembly of metallo-supramolecular aggregates themselves [15].

A field of metallo-supramolecular chemistry where templating is often observed is the chemistry of the helicates [16]. In an early publication on helicate chemistry in 1987 Lehn *et al.* stated that the formation of a double-stranded helicate is supported by  $\pi$ -stacking interactions of the aromatic ligand units [17]. In the following we will present examples in which molecular diversity is generated during the formation of supramolecular coordination compounds and we will show that secondary stabilizing interactions (templating effects) are important as selection steps during the self-assembly processes to obtain well-defined complexes.

#### 3.1. DIRECTIONAL AND SEQUENTIAL LIGAND STRANDS

A simple way to introduce molecular diversity in a supramolecular system is to use directional or sequential ligands in the formation of helicate-type complexes. In double- as well as triple-stranded coordination compounds the directional or sequential ligands can adopt two different relative orientations (presented in Fig-

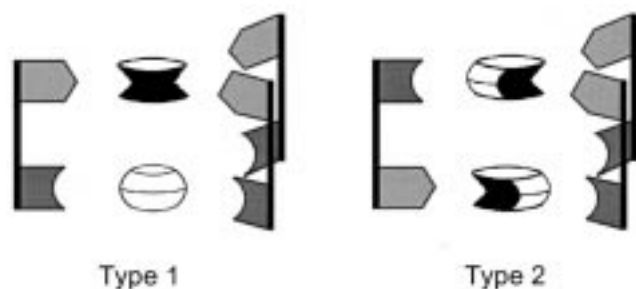


Figure 1. Possible isomers of dinuclear triple-stranded helicates which are formed from directional or sequential ligands.

ure 1 for a triple-stranded dinuclear complex). Either all ligands in the complex are orientated in the same direction (type 1) or one of the ligand strands is orientated in the opposite direction to the other strand or strands, respectively (type 2).

*Directional ligands.* The first investigations with directional ligands were performed by Constable *et al.* using oligopyridines like **1a,b** or **2**. Ligand **1a** with a methyl substituent in the 4-position of one of the terminal pyridine units forms in the presence of copper(I) ions the statistical mixture (1:1) of the two possible isomeric double-stranded complexes. If a *t*-butyl group is introduced instead of the methyl group (ligand **1b**) only the head-to-head isomer (type 1) is observed. Here the influence of the bulky substituent is crucial for the control of the regioselectivity of the self-assembly process [18]. On the other hand, ligand **2**, bearing a chiral bulky group in the 2 position, leads to the exclusive formation of the head-to-tail isomer (type 2) as a single stereoisomer [19].

The directional ligand **3-H<sub>4</sub>** yields upon deprotonation and reaction with titanium(IV) ions the two isomers in a close to statistical ratio (type 1: type 2 = 1: 4) [20]. Similar results were obtained for related dicatechol ligands bearing unsymmetrical amide groups with gallium(III) ions [21].

*Sequential ligands.* A sequential ligand strand can contain two or more binding sites with different denticity. For example, ligand **4** or **5** possesses a bi- as well as a tridentate chelating unit. Upon reaction of **4** with zinc(II) ions a double-stranded dinuclear type 1 complex is formed which contains one hexa- and one tetracoordinated metal center. With lanthanum(III) ions a triple-stranded type 2 complex is observed [22].

Ligand **5** produces with europium(III) and zinc(II) [23] or lanthanum(III) and iron(II) ions triple-stranded type 1 helicates [24]. Similar heterodinuclear coordination compounds are obtained from **4** [25].

On the other hand, the ligands **6a,b** in their deprotonated form possess two binding sites with similar denticity but different electronic features (charge of (1-) or (2-) respectively). Metal-directed self-assembly of three equivalents of **6a,b** in the presence of two equivalents of gallium(III) *or* titanium(IV) ions leads to the exclusive formation of triple-stranded type 2 complexes. If the ligands **6a,b**

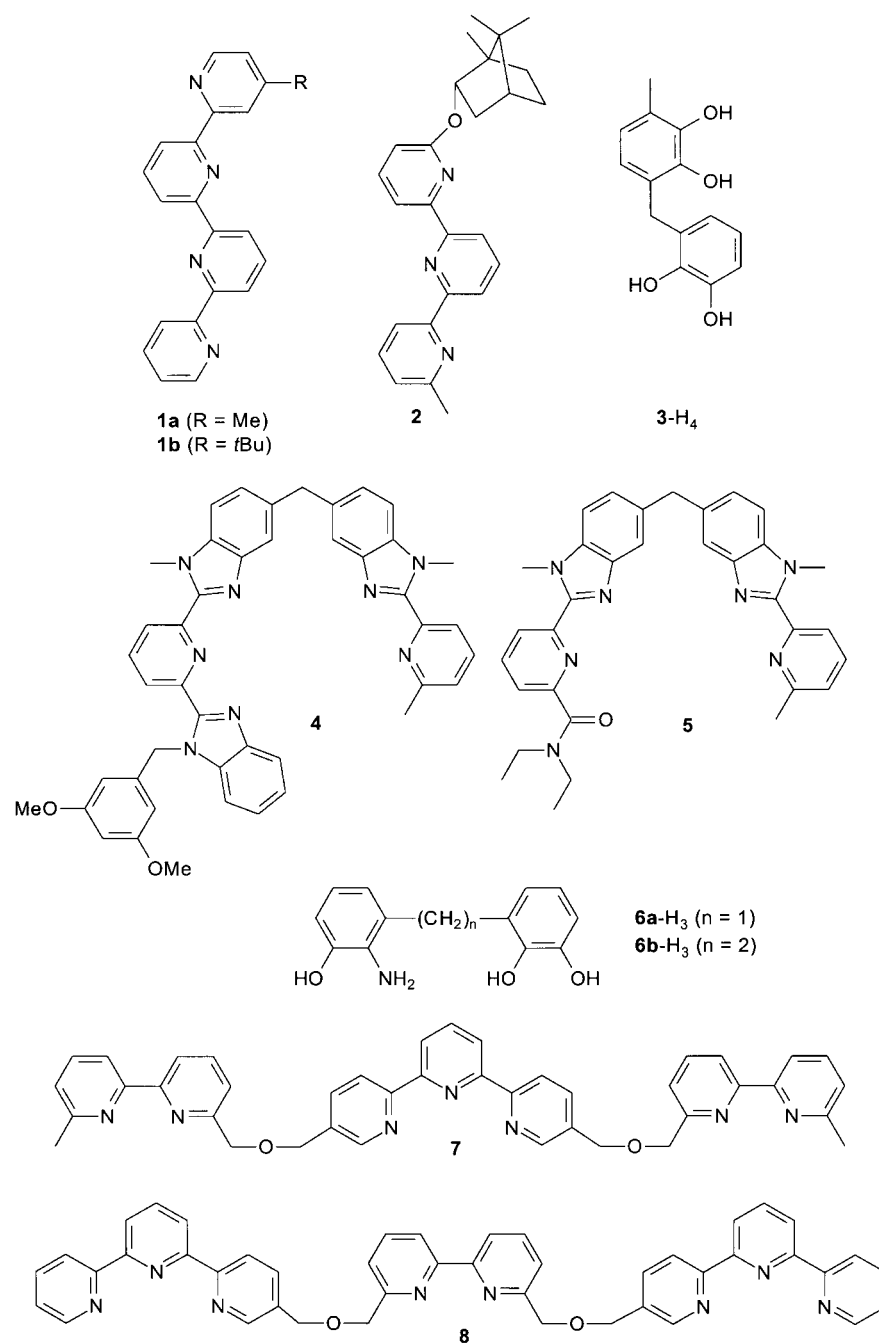


Figure 2. Examples for directional (1–3) and sequential ligands (4–8).

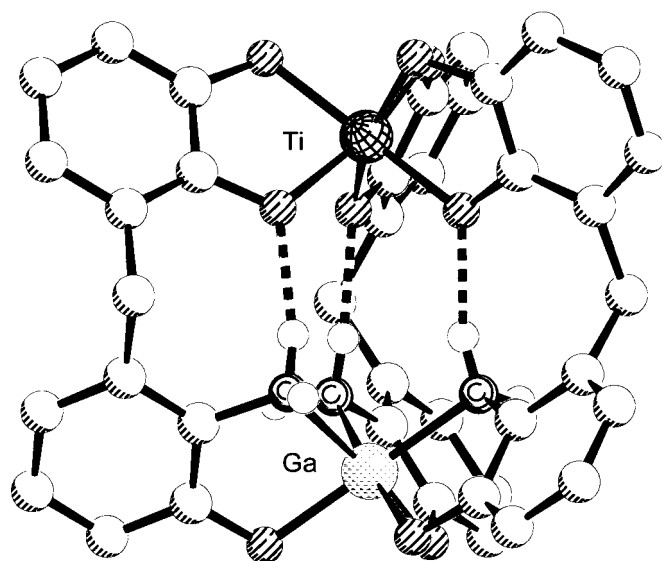


Figure 3. The dianion  $[(6a)_3GaTi]^{2-}$  as found in the crystal.

react with a mixture of gallium(III) and titanium(IV) the heterobinuclear type 1 complexes exclusively are formed in a cooperative self-assembly process. The X-ray structural analysis of  $K_2[(6a)_3GaTi]$  (Figure 3) shows that the complex is stabilized by intramolecular hydrogen-bonding interactions [26].

The symmetrical sequential oligopyridine ligands with three chelating units **7** and **8** can lead to different structures of complexes depending on the metal ions or combinations of metal ions which are used for the assembly of the helicates [27].

Ligand **7** reacts with a mixture of copper(I) and iron(II) ions (2 : 1) and forms double-stranded  $[(7)_2Cu_2Fe]^{4+}$  with an octahedrally coordinated iron and two tetrahedrally coordinated copper centers. On the other hand, a 1 : 1 mixture of **7** and **8** by reaction with copper(II) ions leads to a double-stranded complex  $[(7)(8)Cu_3]^{6+}$  with three pentacoordinated metal centers [27]. Here a self-recognition process between either the metal ions or the ligands takes place and leads to the formation of one defined coordination compound out of various possibilities. This self-recognition is driven by the preferred coordination geometry of the metal centers in combination with the different binding sites of the sequential ligands.

### 3.2. RECOGNITION AND SELF-RECOGNITION IN METAL-DIRECTED SELF-ASSEMBLY PROCESSES

Noyori *et al.* showed that upon mixing of dialkylzinc reagents and racemic 3-exo-dimethylamino isborneol **9-H** only the dimeric achiral zinc complex  $[(2R)\text{-}9][(2S)\text{-}9]Zn_2R_2$  is formed as the thermodynamically favored species. The homochiral complexes are not observed [28]. The high stability of the meso-

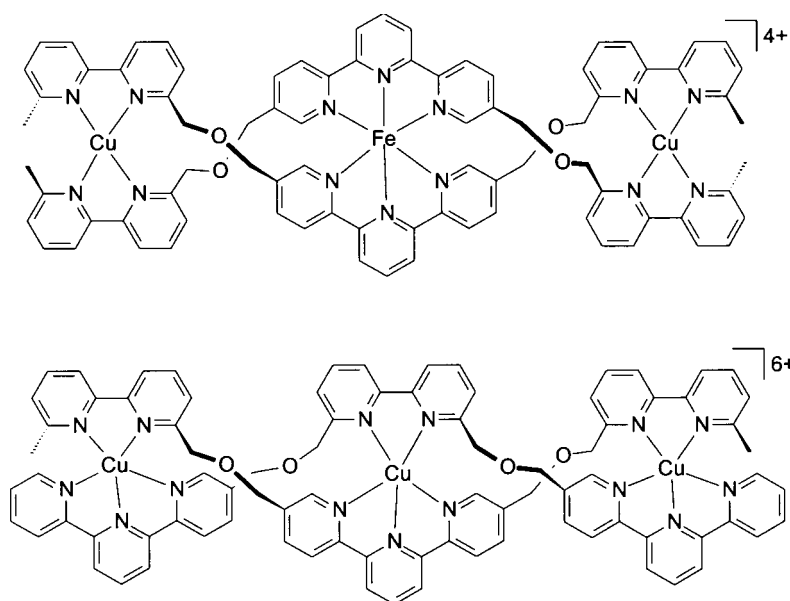


Figure 4.

form leads in the addition reaction of dialkylzinc species with benzaldehyde to a product with a very high enantiomeric excess by use of only slightly enantiomerically enriched **9-H** as catalyst. In the initial step of the reaction a maximum amount of the meso-complex  $[(2R)\text{-}\mathbf{9}]\{(2S)\text{-}\mathbf{9}\}\text{Zn}_2\text{R}_2$  is formed and only the remaining enantiomerically pure ligand acts as a catalyst [28].

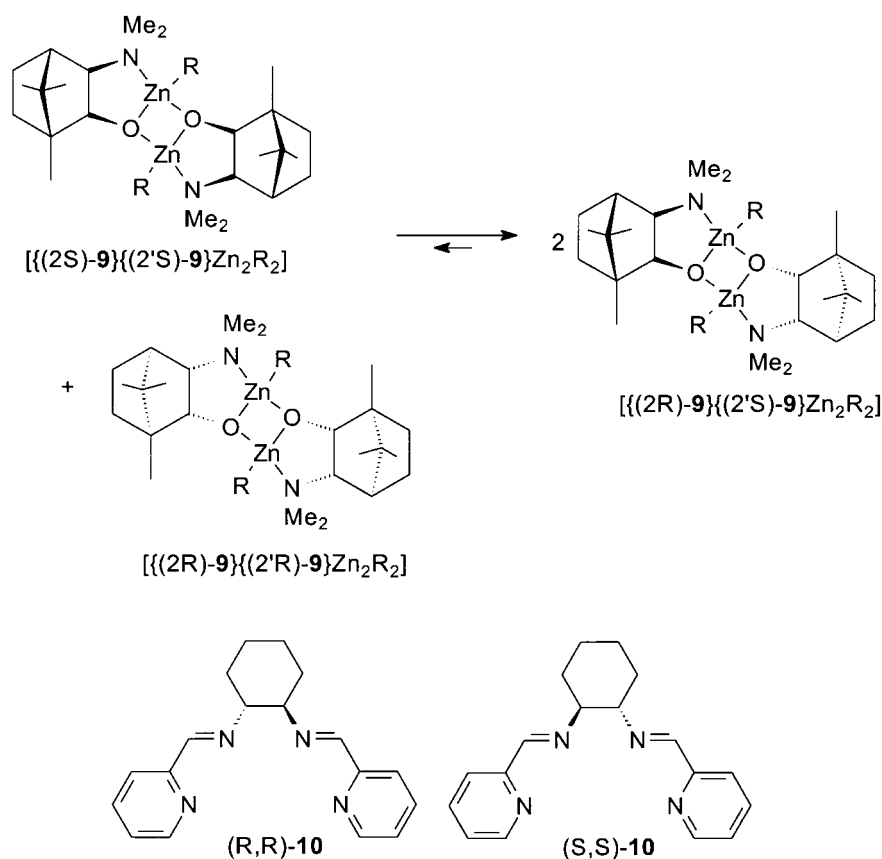
Just recently a contrary example was described by Stack *et al.* Racemic ligand **10** leads with copper(I) ions to a mixture of the two homochiral complexes while the heterochiral complex  $[(R,R)\text{-}\mathbf{10}]\{(S,S)\text{-}\mathbf{10}\}\text{Cu}_2\}^{2+}$  is not observed [29].

In the case of the derivatives **9** or **10** the recognition is controlled by the complementarity or non-complementarity of the antipodes of a ligand when it binds to a metal ion. However, other mechanisms also can control recognition and self-recognition processes.

An example which is related to the reaction discussed for the ligands **7** and **8** with copper(II) ions (Section 3.1, Figure 4) [27] is the formation of a double-stranded helicate in which two different ligand strands recognize each other via copper(II) centers to form a trinuclear helix [30].

Self-recognition in the formation of helicates also can be observed if mixtures of ligands with different numbers of binding sites are used. In the presence of copper(I) ions the ligands **11a-d** lead to the selective formation of the di- to pentanuclear complexes, with identical ligands in each complex. Mixing of ligand strands in the complexes or Vernier-type structures are not observed [31].

Furthermore, reaction of a mixture of **11b** and **12** with a mixture of copper(I) and nickel(II) ions leads only to the formation of the double-stranded helicate



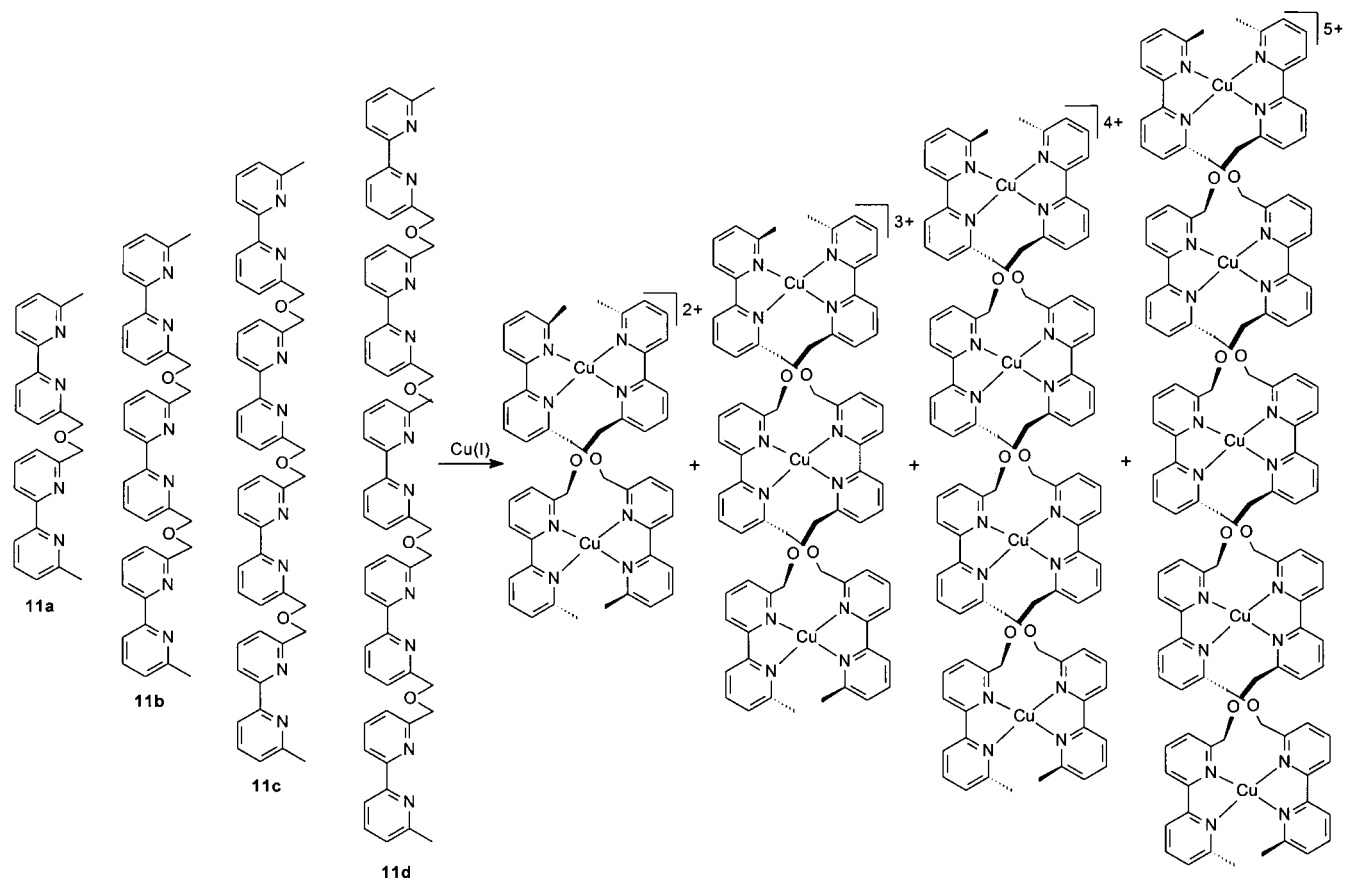
Scheme 2. Systems which upon formation of dimeric metal complexes undergo homo- (9) or hetero-recognition (10).

$[(11b)_2\text{Cu}_3]^{3+}$  and the triple-stranded helicate  $[(12)_3\text{Ni}_3]^{6+}$ . Again no mixing of ligands or metals is observed [31].

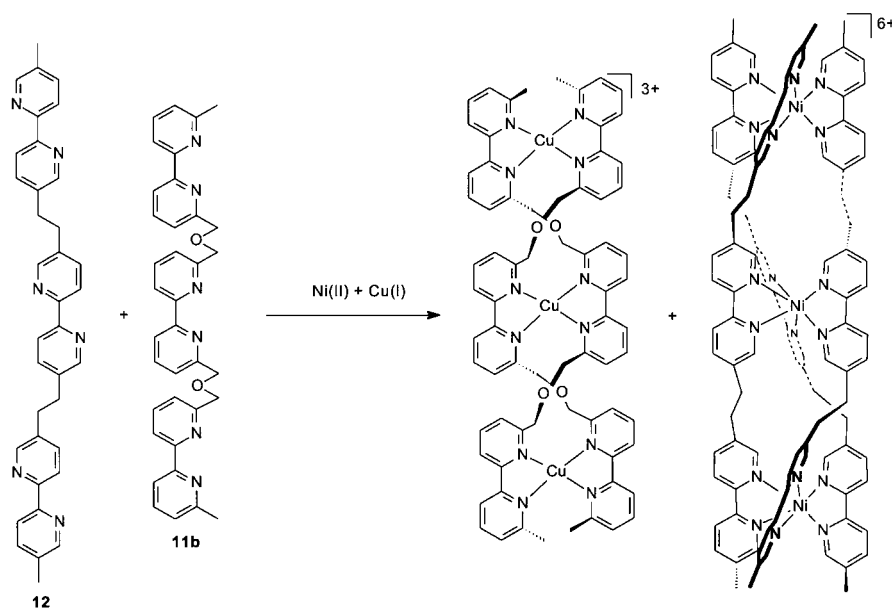
In addition to the (self)-recognition due to (i) the number of binding sites at the ligand, (ii) the coordination geometry at the metal, or to (iii) chirality, discrimination also can occur depending on the size of the ligand. Raymond *et al.* showed that a mixture of the three di(catechol) ligands with different spacers **13–15** with gallium(III) ions yields only the helicates with one ligand type in each dinuclear complex [32].

A mixture (1 : 1) of the alkyl-bridged di(catechol) ligands **16-H<sub>4</sub>** and **17-H<sub>4</sub>** leads with titanium(IV) ions to simple mixtures of coordination compounds. Thus, the structure of the supramolecular complexes highly depends on the counter cations which are present and which act as templates in the formation of the complexes. In the presence of potassium cations a mixture of the homoleptic dinuclear complex **A2** and the unspecified, probably oligomeric material **C** is formed. Sodium as a template leads to the two dinuclear homoleptic compounds **A1** and **A2**.





Scheme 3. Self-recognition in the formation of double-stranded helicates from ligands **11** with different numbers of metal coordination sites.



Scheme 4. Self-recognition due to different coordination geometries at metal centers.

In the presence of lithium cations the heteroleptic coordination compound **B** is found besides **A1** and **A2** [33].

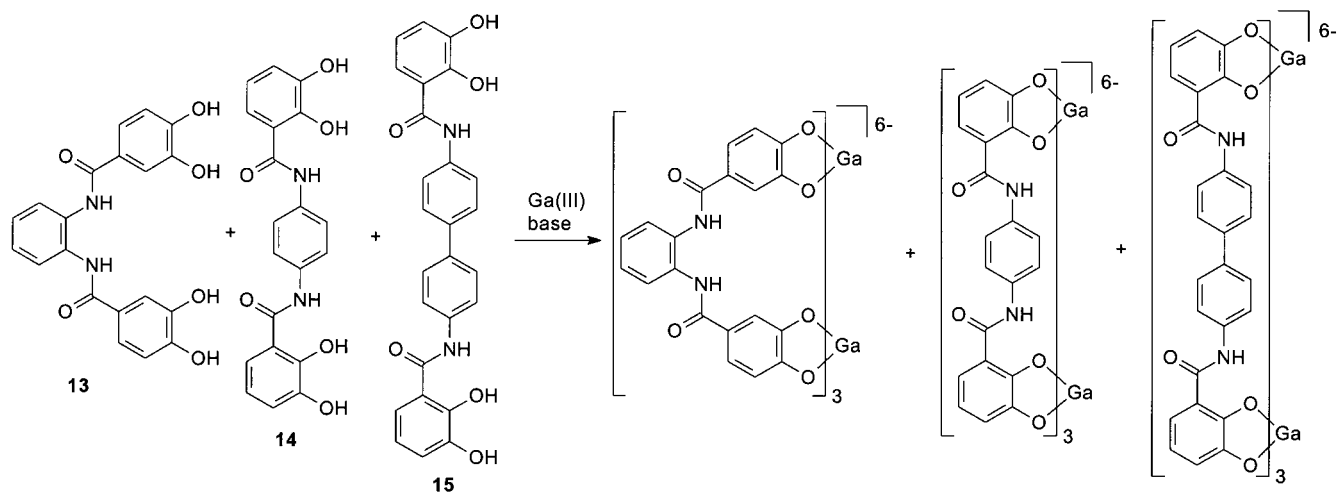
The examples presented show that (self)-recognition in the self-assembly of helicate-type coordination compounds can be controlled by different factors depending on the ligand, the metal, or a template. In such a process a mixture of only a few of the possible supramolecular aggregates are formed from a complex mixture of starting material.

### 3.3. CIRCULAR HELICATES

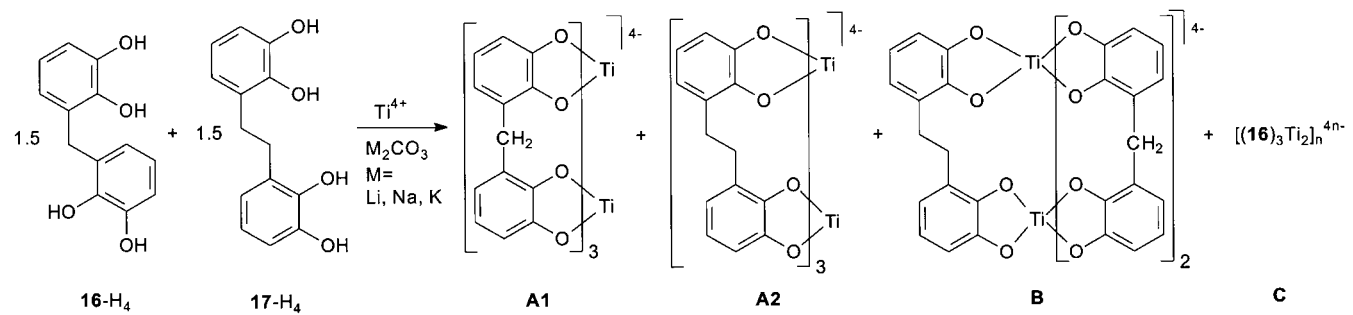
Circular oligonuclear coordination compounds can be formed by metal-directed self-assembly of ligands which possess a geometry that represents a subunit of the curvature of the circular structure [34].

In contrast, circular helicates are formed by self-assembly of linear oligodonor ligands in the presence of metal ions and possess a helical structure arranged in a circular fashion. Mixing of the ligand **18** with copper(I) ions leads to the formation of a mixture of macrocyclic di-, tri- and tetranuclear coordination compounds which is characterized by electrospray mass spectrometry. Upon crystallization this dynamic mixture is transformed into a dinuclear, extremely insoluble copper complex [35].

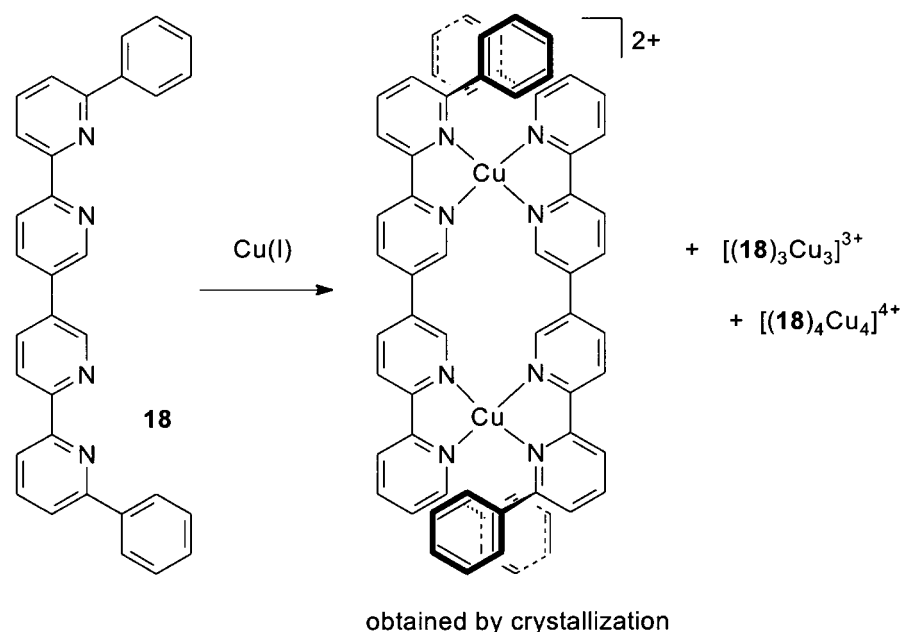
The bis(ethylene) bridged tris(2,2'-bipyridine) ligand **12** forms with nickel(II) ions in the presence of  $\text{ClO}_4^-$  ions a linear trinuclear triple-stranded helicate  $[(\mathbf{12})_3\text{Ni}_3][\text{ClO}_4]_6$  [36]. On the other hand, the same ligand **12** produces with



Scheme 5. Control of self-recognition by the length of rigid spacers.



Scheme 6. Template-directed self-recognition in the self-assembly of helicate-type complexes.



Scheme 7. Formation of a mixture of coordination compounds and crystallization of one defined species.

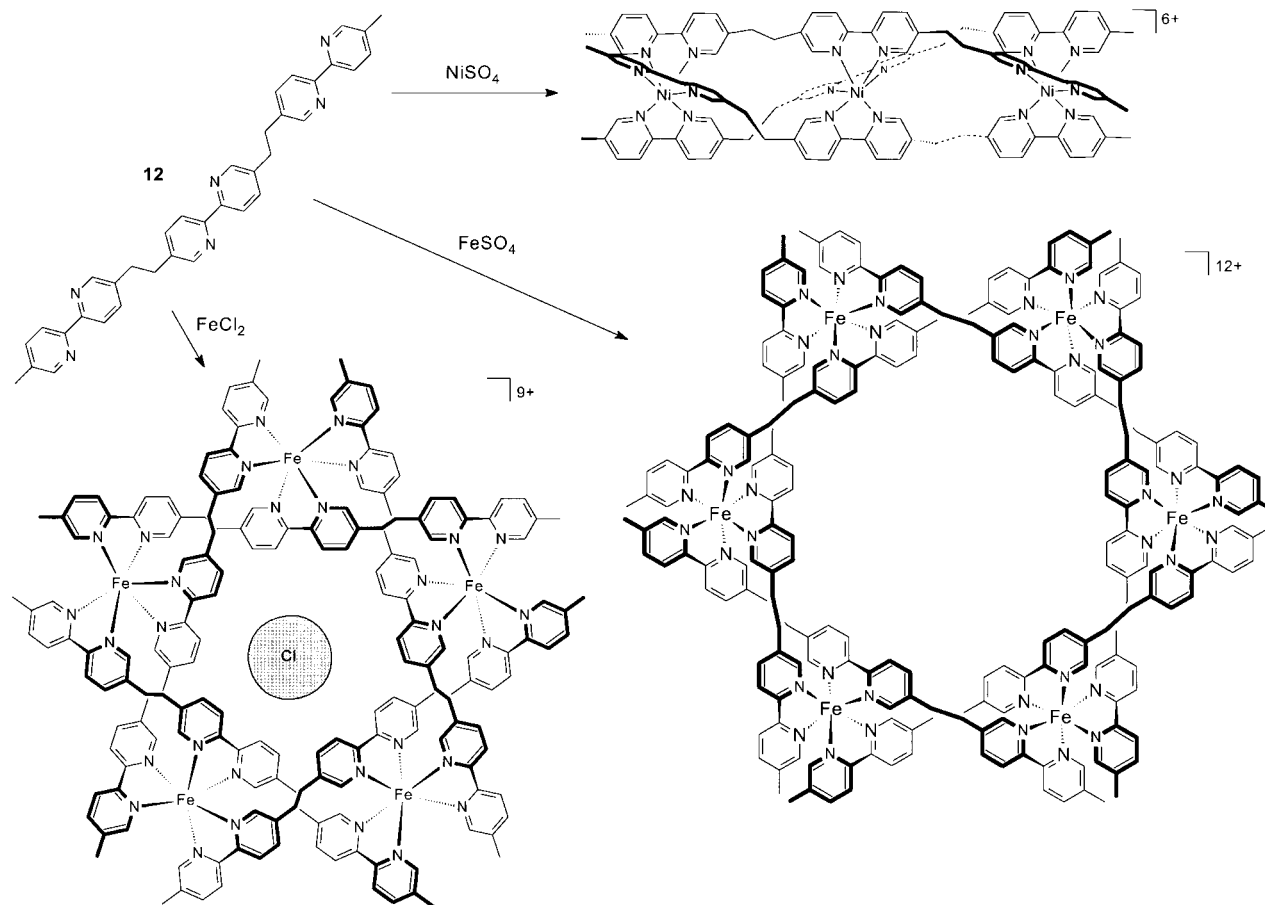
iron(II) ions circular helicates. The size of the circular helicate is dictated, therefore, by the anion which acts as a template during complex formation (Scheme 8) [37].

In the presence of the relatively small chloride anion a pentanuclear circular helicate  $[\text{Cl} \subset \{(\mathbf{12})_5\text{Fe}_5\}]^{9+}$  is formed while the presence of bigger anions like  $\text{BF}_4^-$ ,  $\text{SO}_4^{2-}$ , or  $\text{SiF}_6^{2-}$  leads to the corresponding hexanuclear complex  $[(\mathbf{12})_6\text{Fe}_6]^{12+}$ . The bromide anion possesses an intermediate size and the penta- as well as the hexanuclear iron(II) complexes are obtained [37].

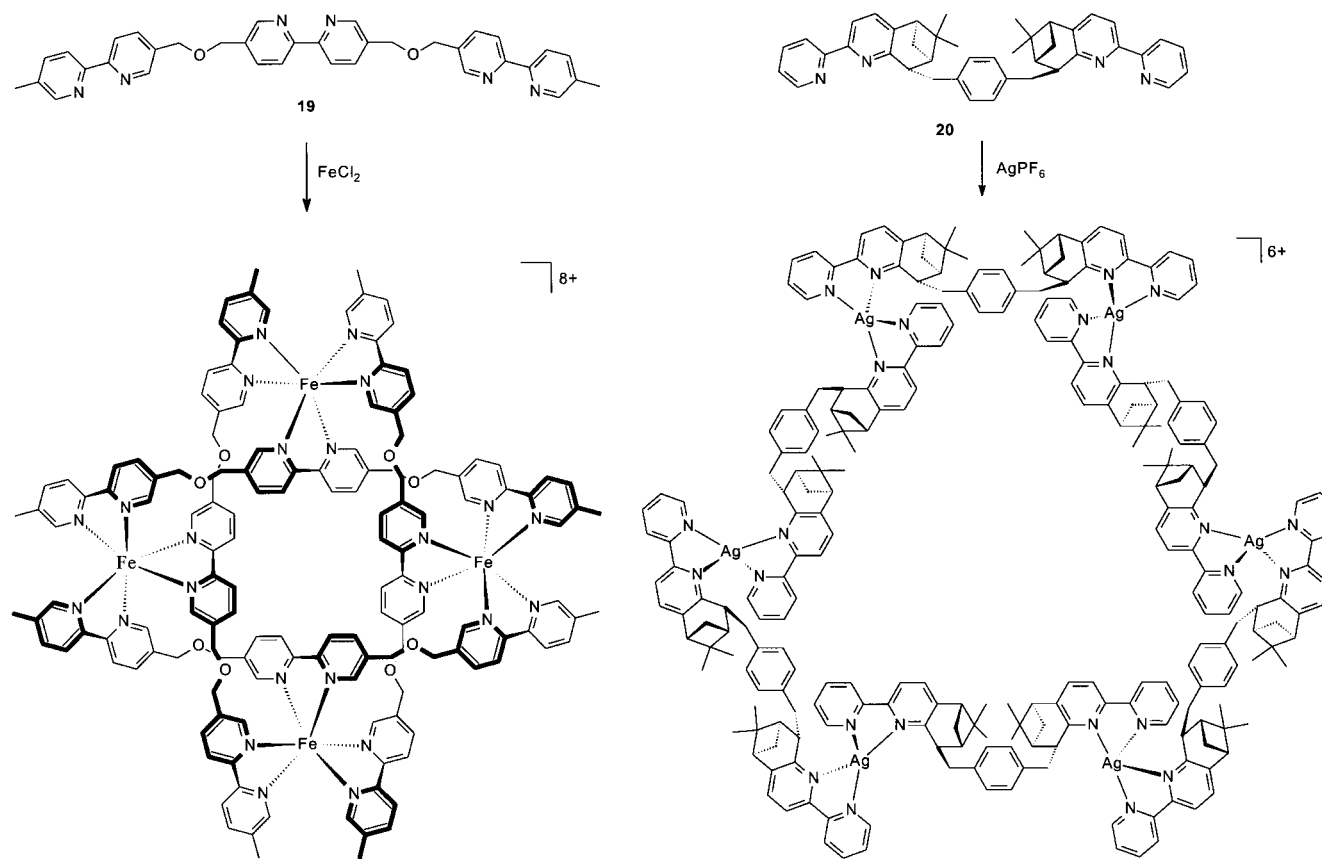
Some other circular helicates are also discussed in the literature. For example, the ether linked tris(2,2'-bipyridine) ligand **19** forms with iron(II) chloride a tetranuclear circular helicate  $[(\mathbf{19})_4\text{Fe}_4]^{8+}$  [37] and an enantiomerically pure hexanuclear circular helicate  $[(\mathbf{20})_6\text{Ag}_6]^{6+}$  is obtained from ligand **20** and silver(I) hexafluorophosphate (Scheme 10) [38].

A circular coordination compound  $[(\mathbf{21})_{12}\text{Co}_8]^{4+}$  which is related to the circular helicates is obtained from ligand **21** and cobalt(II) ions in the presence of  $\text{PF}_6^-$  or  $\text{ClO}_4^-$  ions. Mass spectrometric and X-ray crystallographic results indicate that the anion is fixed in the interior of the torus of the complex. This ion might be important for templating the formation of the octanuclear coordination compound [39].

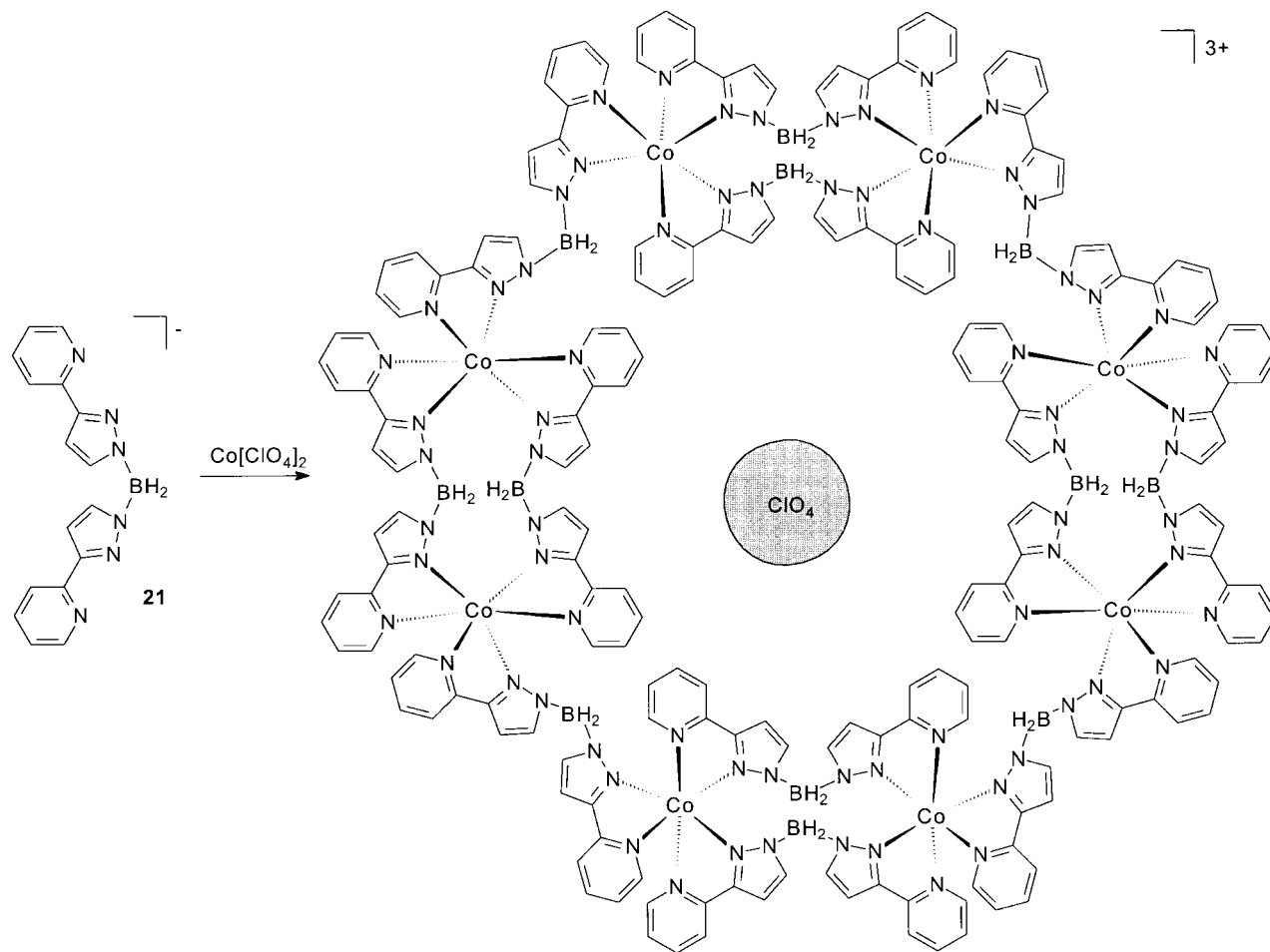
The observation of counterions in the interior of circular helicates and the dependence of the structure of the formed complexes on the nature of the anion which is present during the complex formation shows that here the self-assembly



Scheme 8. Assembly of linear and circular helicates from ligand **12**.

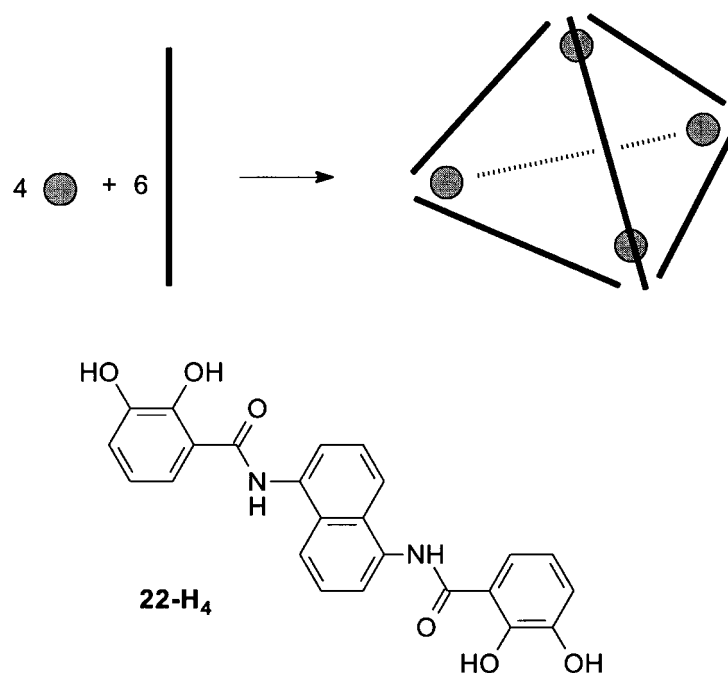


Scheme 9. Two examples of circular helicates.



Scheme 10. A self-assembled molecular wheel.



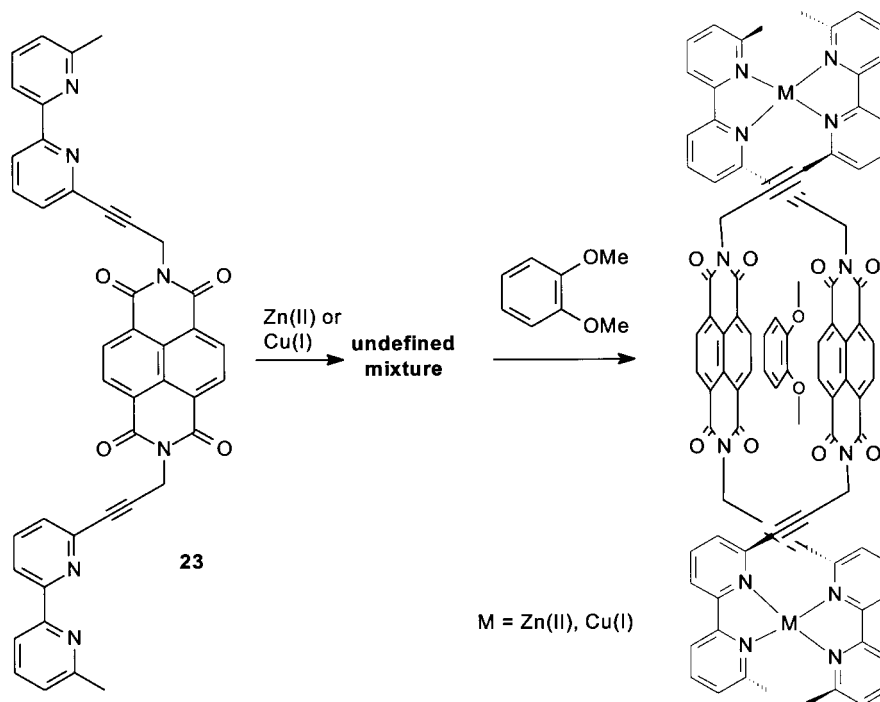


Scheme 11. Self-assembly of tetrahedral complexes from six ligands and four metal ions. Reaction of **22** with gallium(III) ions leads to a tetranuclear complex as indicated schematically.

process not only depends on the geometry of the ligand and of the metal cation. The anions act as templates and thus favor the formation of one defined species. In the case of ligand **12** linear as well as different circular helicates can be obtained. In principle the anions hereby are substrates which during the self-assembly remove in a dynamic process the most appropriate receptor from a dynamic mixture of receptors. Therefore the formation of the circular helicates can be discussed as a dynamic combinatorial process in which an unspecific library of compounds is formed and in a thermodynamically controlled reaction is transformed into one specific complex.

#### 3.4. FROM TEMPLATED SELF-ASSEMBLY TO DYNAMIC COMBINATORIAL CHEMISTRY

In recent years a number of tetrahedral supramolecular coordination compounds were obtained which encapsulate counterions in their interior [40]. The pioneering work of Saalfrank on tetrahedral tetranuclear coordination compounds showed that inclusion of counterions might be important for the formation of the complexes [41]. Raymond *et al.* described an example  $[(R_4N)(\mathbf{22})_6Ga_4]^{11+}$  in which the encapsulated ion could be exchanged. Tetraethylammonium is the most appropriate



Scheme 12. Template-directed formation of a helicate from an unspecified dynamic combinatorial library.

guest for the cavity, although the tetranuclear complex also is stable in the presence of other ammonium cations (R: nPr < Me < Et) [42].

This shows that a tight binding of guests in metallo-supramolecular aggregates can occur in solution. However, very often weak binding of a guest already can stabilize the “super”-structure.

For example, CH=CH-bridged 4,4'-bipyridine derivatives form with the Pd(en)<sup>2+</sup> fragment a mixture of a tetranuclear molecular square and a trinuclear molecular triangle. Both species are in a dynamic equilibrium with their ratio depending on the concentration of the solution. From this solution mixture (library !) the tetranuclear complex can be removed by crystallization. If appropriate guest molecules are added, the equilibrium ratio is shifted favoring the trimer (*p*-dimethoxybenzene as guest) or the tetramer (1,3-adamantanedicarboxylic acid as guest). The binding of the guest molecules to the different coordination compounds depends on the complementarity of substrate and receptor. Addition of an appropriate substrate (template) leads to the preferred formation of only one complex [43].

Similar effects were observed in the formation of double-stranded helicates from linear di(bipyridine) ligand strands with aromatic spacers **23** and zinc(II) or copper(I) ions [44].

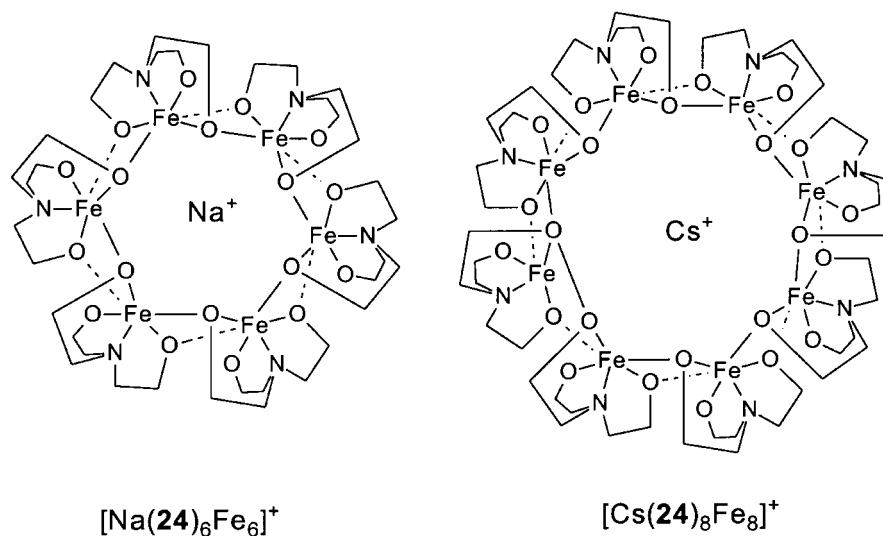


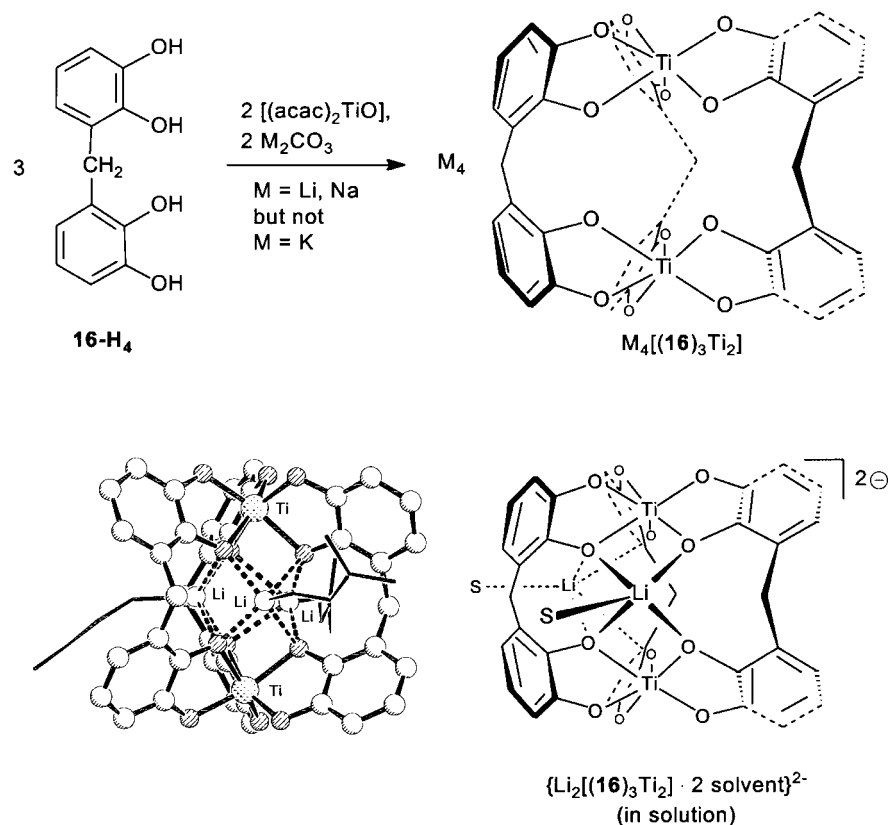
Figure 5.

Reaction of ligand **23** with either copper(I) or zinc(II) ions leads to a mixture of coordination compounds with the general formula  $[(\mathbf{23})\text{M}]^{n+}$  ( $\text{M} = \text{Cu}$ ,  $n = 1$ ;  $\text{M} = \text{Zn}$ ,  $n = 2$ ). This “library” of uncharacterized coordination compounds probably contains cyclic di-, tri- or tetranuclear and noncyclic polymeric species. Addition of *o*-dimethoxybenzene removes from the equilibrium the dinuclear helicate  $[(\mathbf{23})_2\text{M}_2]^{n+}$  by inclusion of the benzene derivative. In this example the electron rich template stabilizes the dinuclear complex by  $\pi$ -stacking interaction with the two electron deficient aromatic systems of the spacer. Similar templating effects were used earlier for the preparation of catenanes and rotaxanes [45].

As observed during the formation of crown-ethers, alkaline metal cations also can act as templates in the formation of metallo-supramolecular aggregates [46].

Ligand **24-H<sub>3</sub>** forms with iron(III) ions neutral coordination compounds  $[(\mathbf{24})\text{Fe}]_n$  with an undefined structure in solution. However, upon addition of NaCl a circular hexanuclear complex  $[\text{Na} \subset (\mathbf{24})_6\text{Fe}_6]\text{Cl}$  is obtained after crystallization. On the other hand, in the presence of CsCl the corresponding octanuclear species  $[\text{Cs} \subset (\mathbf{24})_8\text{Fe}_8]\text{Cl}$  is isolated. As discussed for the circular helicates the template directs the formation of specific complexes starting from an unspecified combinatorial library which is present in solution [46].

Triple-stranded helicate or meso-helicate type titanium(IV) complexes can be obtained from alkyl-bridged dicatechol ligands. Due to internal oxygen donor atoms, countercations are bound in the interior or in the periphery of the self-assembled cryptand-type complexes. In the case of the methylene-bridged ligand **16-H<sub>4</sub>** the triple-stranded meso-helicate  $[(\mathbf{16})_3\text{Ti}_2]^{4-}$  should be formed. If the reaction is performed with  $\text{K}_2\text{CO}_3$  as base, a soluble red solid is obtained which shows a correct elemental analysis for “ $\text{K}_4[(\mathbf{16})_3\text{Ti}_2] \cdot 8 \text{H}_2\text{O}$ ”. However, NMR

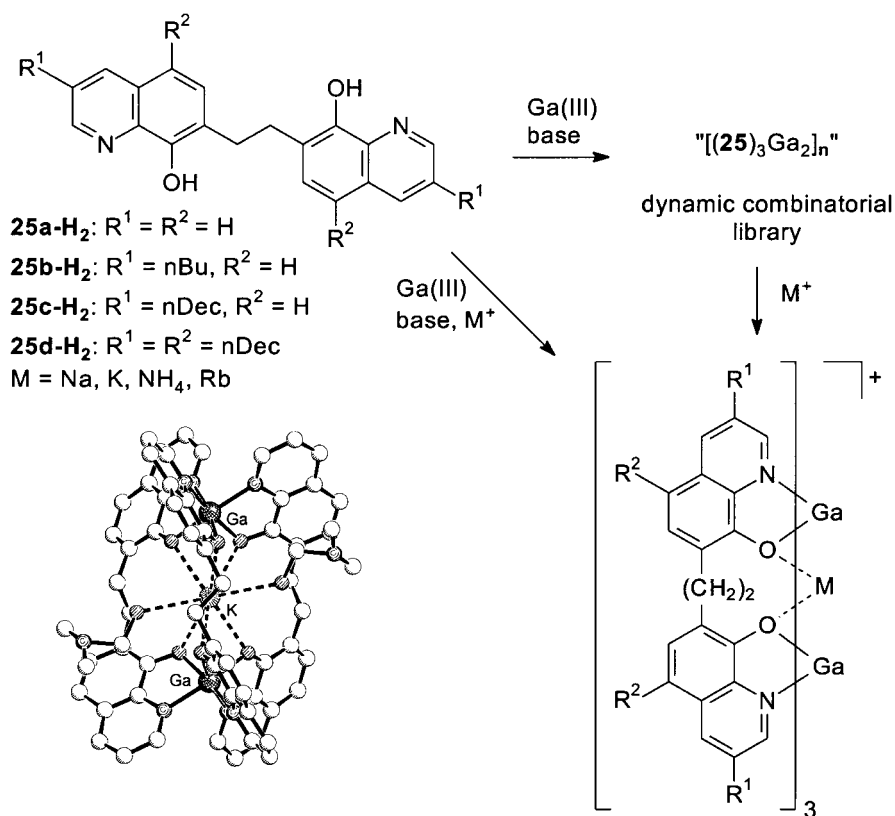


*Scheme 13.* Template-directed self-assembly of a meso-helicate and the structure of the lithium adduct in the crystal and in solution.

spectroscopy reveals that not a defined product but a mixture of isomers and/or oligomers is formed [20, 47].

On the other hand, the use of Na<sub>2</sub>CO<sub>3</sub> or Li<sub>2</sub>CO<sub>3</sub> quantitatively leads to the meso-helicate Na<sub>4</sub>[(**16**)<sub>3</sub>Ti<sub>2</sub>] or Li<sub>4</sub>[(**16**)<sub>3</sub>Ti<sub>2</sub>]. Furthermore, addition of LiClO<sub>4</sub> or NaClO<sub>4</sub> to a solution of preformed “K<sub>4</sub>[(**16**)<sub>3</sub>Ti<sub>2</sub>]” in methanol transforms the mixture within a couple of hours into the well-defined dinuclear complexes. In the presence of potassium cations an unspecified dynamic combinatorial library of titanium complexes is formed. If lithium or sodium cations are added as a substrate (template) the mixture is transformed into the meso-helicate [(**16**)<sub>3</sub>Ti<sub>2</sub>]<sup>4-</sup>. If Na- or Li-cations are present during the formation of the titanium complexes a template-directed self-assembly process takes place [20].

The X-ray structural analysis of Li<sub>4</sub>[(**16**)<sub>3</sub>Ti<sub>2</sub>] shows that the templating does not occur by inclusion of only one cation but three cations bind to the tetraanion in the solid state. NMR spectroscopic investigations (<sup>1</sup>H, <sup>6</sup>Li) on the other hand reveal that in solution only two cations are bound to the meso-helicate [20, 47].



Scheme 14. Formation of an unspecified dynamic combinatorial library of gallium complexes and its transformation into a well defined metalla-cryptate. The X-ray structure of  $[\text{K(dmf)}_2] \cdot [(\text{25a})_3\text{Ga}_2]^+$ .

Here the counterions act as templates/substrates in the formation of the coordination compounds which act as receptors. Thus the self-assembly process depends on the cation which is present leading either to a mixture (library) or a defined complex. Additionally, in a dynamic process the mixture can be transformed into a defined species by addition of appropriate templates. For the design of related systems, in which a library of neutral metallo-receptors is formed and which is able to bind not only counterions but externally added substrates, ligands have to be chosen which in contrast to the catecholato(2-) unit possess a lower negative charge. Therefore, ethylene-bridged di(8-hydroxyquinoline) derivatives **25-H<sub>2</sub>** were synthesized and used in metal-directed self-assembly processes [48].

Reaction of the ligands **25a,b** with gallium(III) nitrate resulted in the formation of an insoluble yellow material which by elemental analysis showed the composition " $[(\text{25a,b})_3\text{Ga}_2] \cdot 8 \text{H}_2\text{O}$ ". Heating of the precipitate with sodium or potassium chloride yields the metalla-cryptates  $[\text{Na} \subset (\text{25a,b})_3\text{Ga}_2]^+$  or  $[\text{K} \subset (\text{25a,b})_3\text{Ga}_2]^+$ . The complexes are soluble in DMSO and can be investigated by

NMR spectroscopy, MS or X-ray structure analysis.  $[\text{Na} \subset (\mathbf{25a,b})_3\text{Ga}_2]^+$  or  $[\text{K} \subset (\mathbf{25a,b})_3\text{Ga}_2]^+$  also can be obtained in a template-directed self-assembly process if a large excess of sodium or potassium cations is present during the formation of the gallium complexes [49].

The X-ray structures of the potassium as well as of the sodium compound show very similar features. The only remarkable difference is observed for the gallium-gallium separation leading for the sodium cryptate to a smaller cavity than for the corresponding potassium complex. Thus the neutral metalla-cryptand  $[(\mathbf{25a,b})_3\text{Ga}_2]$  is able to adjust to the size of different guest species using the gallium complex units as molecular hinges [49].

In order to investigate the material “ $[(\mathbf{25})_3\text{Ga}_2]$ ”, ligands were introduced, which bear *n*-decyl substituents. With  $\mathbf{25c,d-H}_2$  neutral gallium complexes “ $[(\mathbf{25c,d})_3\text{Ga}_2]$ ” are obtained which are soluble in halogenated solvents or in hydrocarbons. However, NMR spectroscopy shows that not a defined complex but a mixture of oligomers or polymers is present. Mass spectrometry (MALDI-TOF as well as FAB) of “ $[(\mathbf{25c})_3\text{Ga}_2]$ ” shows the peaks of the dinuclear  $[(\mathbf{25c})_3\text{Ga}_2]$  as well as the tetranuclear species  $[(\mathbf{25c})_3\text{Ga}_2]_2$ . By addition of appropriate cations this dynamic library can be transformed into well-defined complexes  $[\text{M} \subset (\mathbf{25c})_3\text{Ga}_2]^+$  [48]. Similar results are obtained with other metal-ions like aluminum(III), iron(III), chromium(III) or zinc(II) [50].

The formation of the metalla-cryptates  $[\text{M} \subset (\mathbf{25c})_3\text{Ga}_2]^+$  via a library of neutral coordination compounds represents a nice example for a dynamic combinatorial process in which an unspecified mixture of complexes by binding to a substrate is transformed into one well-defined coordination compound.

#### 4. Conclusion

In this paper several examples were presented in which molecular diversity is generated in metallo-supramolecular systems. Different mechanisms were discussed which enable us to control the composition of mixtures by molecular recognition or self-recognition processes or which allow us to obtain only pure and well-defined complexes. In the latter case, the generation of dynamic combinatorial libraries and their transformation into single substrate/receptor complexes showed the potential which is hidden in metallo-supramolecular chemistry and which might lead us to new concepts in the search for new lead structures for receptors or substrates. The future will show if dynamic combinatorial chemistry really is this powerful tool which at the moment it seems to be.

The supramolecular structures which are obtained in metal directed self-assembly processes highly depend on the “shape” and electronic features of the organic (ligands) as well as the inorganic (metal ions) building-blocks. Additionally, intra- as well as intermolecular interactions can favor the formation of a specific structure due to stabilizing effects like hydrogen bonding, charge-transfer interaction, or interaction with templates (small organic molecules, ammonium ions,

or metal cations). All those factors are important in the self-assembly process and their combined action leads to the formation of specific supramolecular aggregates.

The topics which were discussed in this paper show that chemists start to develop some understanding of principles behind recognition and self-assembly processes which are very important in natural systems. To adopt reactivity or structural motifs from nature and to use those to develop artificial systems with defined functions is a major goal for supramolecular as well as metallo-supramolecular chemistry in the future.

### Acknowledgments

This work would not have been possible without the help of my coworkers and collaborators Dr. Cyrill Riether, Oliver Blau, Matthias Schneider, Karen Witt, Dr. Herbert Röttele, Dr. Roland Fröhlich and Dr. Sirpa Kotila. I want to thank those people and I want to thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support.

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