TUTORIAL REVIEW

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Supramolecular chirality of self-assembled systems in solution

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Self-assembly plays an important role in the formation of many (chiral) biological structures, such as DNA, α-helices or β-sheets of proteins. This process, which is the main tool of Supramolecular Chemistry (*i.e.* the chemistry of the molecular assemblies and of the intermolecular bonds), starts to play a significant role in nanotechnology for the construction of functional synthetic structures of nanometer size. The control of chirality in synthetic self-assembled systems is very important for applications of these systems *e.g.* in molecular recognition or mimicking of the catalytic activity of enzymes. This *tutorial review* deals with the most representative contributions in the field of supramolecular chirality. Specifically, the discussion centers on several examples that represent the control over chirality for self-assembled systems in solution.

Introduction

The *general* term of *self-assembly* has been defined as the autonomous organization of components into patterns or structures without human intervention.[1] Self-assembly is of vital importance in biological processes such as the transfer and storage of genetic information in nucleic acids and the organization of proteins into efficient molecular machines. Therefore, the use of self-assembly is a very powerful tool to mimic biological functions.[2] Self-assembly is also regarded as the most efficient way in the *bottom-up* approach in nanotechnology for the fabrication of complex 'supermolecules' and structures.[3,4] Their spatial disposition is transferred from one or more chiral centers[5] to the molecules that form these supramolecules or macromolecular aggregates, and consequently to the

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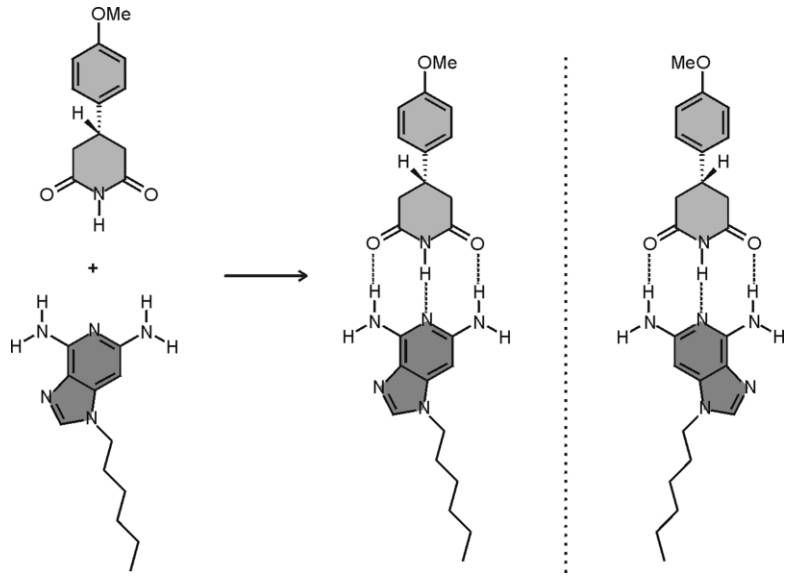

Fig. 1 Assembly process of two achiral molecules leading to a chiral supermolecule due to the perpendicularity of the symmetry planes of the molecular components.

nanoscopic dimension. The control over the spatial disposition of atoms and molecules is very important because it can have dramatic consequences in chemical systems. For example, some enzymes only catalyze the reaction of one enantiomer leaving the other enantiomer unchanged.[6] Also in materials science, chirality has great effects. The use of one enantiomer instead of the racemic mixture (mixture of equal amounts of a pair of enantiomers) increases the second-order nonlinear optical (NLO) susceptibility about 30 times.[7] The initial study and control of the supramolecular chirality in solution should also aim to translate the chirality into two-dimensional structures because any kind of a working device will probably need to be confined to a surface.[3,8] There are already a few examples dealing with the concept of chirality on surfaces ("two-dimensional chirality").[3,9] Nevertheless, they are still concerned with very simple concepts of chirality without much stereocontrol. In contrast, the field of supramolecular chirality in solution starts nowadays to master the control over almost all aspects of chirality.

In this contribution, we describe mainly the general principles governing supramolecular chirality of finite self-assembled structures in solution. Chirality in the process of molecular recognition (host–guest interactions), which is the basis in supramolecular chemistry, will be also discussed briefly. The very recent supramolecular examples of chirality on surfaces,[3,9] gels,[10] and self-assembled polymers and other macroscopic structures[11–13] will not be covered. The field of liquid crystals, even though they are not strictly well-defined (finite) structures, will be briefly discussed at the end of this contribution due to the importance of supramolecular chirality in this field for the fabrication of materials with interesting properties for practical applications. Self-assembly has also been used in the synthesis of dynamic supramolecules such as catenanes and rotaxanes. These structures are not self-assembled systems in a strict sense (they are not under thermodynamic equilibrium), so they are not enclosed here. Nevertheless, they display an interesting case of supramolecular chirality, *i.e.* topological or dynamic chirality.[14,15]

Supramolecular chirality: concepts

It is well know that chirality at the *molecular level* is displayed when the atoms of a molecule are arranged in one unique manner in space. This different arrangement is due to the presence of a chiral centre or the absence of planes of symmetry. Isomers that contain chiral centres are called stereoisomers and they are divided in two categories: enantiomers (stereoisomers whose molecules are non superposable mirror images of each other) and diastereomers (stereoisomers whose molecules are not mirror images of each other). Similarly, chirality is also expressed at the *supramolecular level*. Supramolecular chirality involves the nonsymmetric arrangement of molecules in a noncovalent assembly. This can be initiated by the properties of the components, *i.e.* one or more of the components are asymmetric or the achiral components associate in such a way that the assembly has no elements of symmetry (Fig. 1).[16] Therefore, noncovalent synthesis allows the preparation of supramolecules in a diastereomeric or enantiomeric form.

1 Supramolecular chirality in molecular recognition

Molecular recognition is defined by the selective recognition of substrate molecules (guests) by synthetic receptors (hosts).[17] This binding process can lead to the formation of chiral supermolecules if the substrate and/or the receptor are chiral or the binding process occurs in an asymmetric fashion.[18] The field of supramolecular chemistry in the area of molecular recognition has reached such a level of control that the complexation of biologically interesting chiral molecules such as carnitine,[19] cytochrome c,[20] and many others has been achieved. Even though there are some examples of selective chiral molecular recognition, the control over this process remains elusive. A beautiful example has been reported by Morán and coworkers.[21] They studied the recognition of a (*S*)-lactic acid derivative with a chromenone-benzoxazole derivative receptor (Fig. 2). The chiral recognition in these systems arises from strong steric hindrance, so that the association constant for the two enantiomeric hosts differs by a factor of 9. The chiral molecular recognition process has also been named induction of supramo-

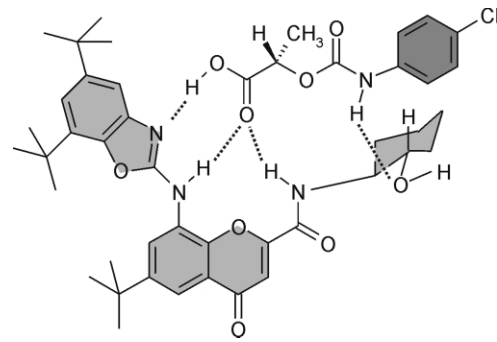

Fig. 2 Proposed structure for the complex of chromenone-benzoxazole receptor and (*S*)-lactic acid derivative.

lecular chirality.[22] This type of chiral recognition has been reviewed.[23–25]

2 Self-assembly of finite chiral superstructures

The term *molecular self-assembly* can be defined as the spontaneous association of two or more molecules under thermodynamic equilibrium resulting in the generation of well-defined aggregates (strict self-assembly) or of extended polymolecular assemblies (self-organization) by means of noncovalent interactions such as hydrogen bonds, metal-coordination or π–π interactions.[4,16] The use of noncovalent bonds has the advantage that they are formed spontaneously and reversibly under thermodynamic equilibrium, with the possibility of error correction and without undesired side products. For these reasons, self-assembly is a valuable tool for the noncovalent synthesis of nanostructures such as helicates, grids,[26] capsules,[27] *etc*. To achieve this, kinetically labile reactants capable of suitable exchange reactions in solution are required, but this allows rapid racemization to occur. Consequently, the majority of the supramolecular architectures are formed of a racemic mixture, but for functional supramolecules[14,28] it is important to control the stereoselectivity in the self-assembly process.

2.1 Diastereoselective noncovalent synthesis. As it has been pointed out above, all the assemblies that have an asymmetric arrangement of their building blocks are chiral. The general method to control the supramolecular chirality is the introduction of chiral

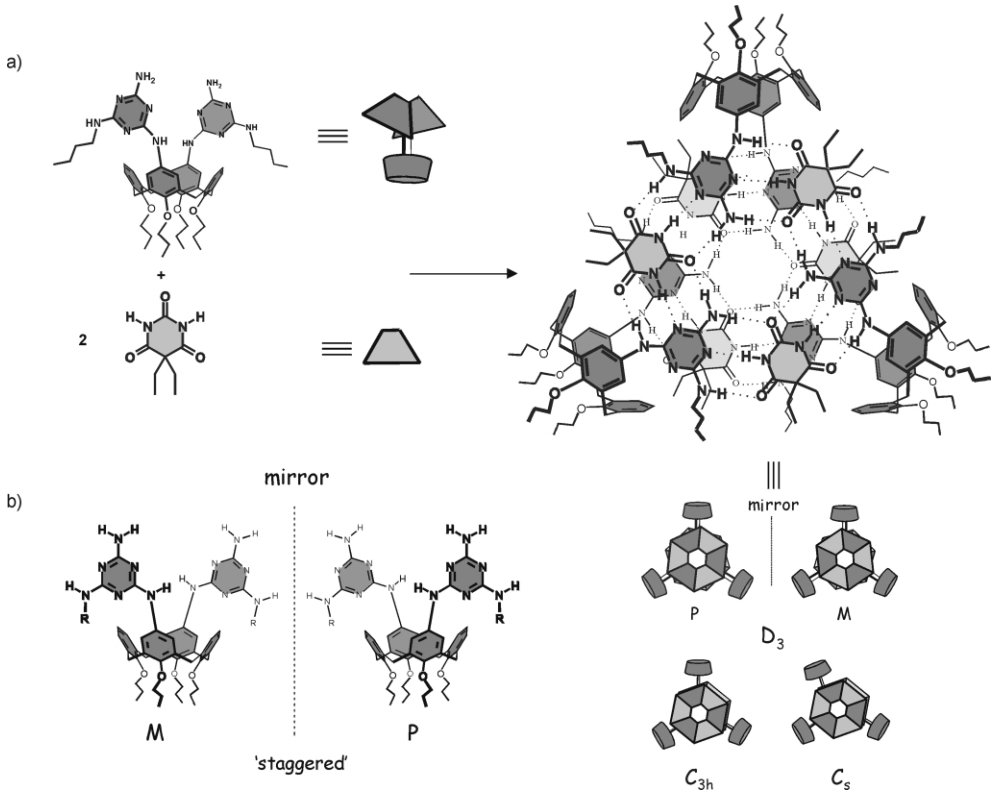

Fig. 3 a) Formation of the double rosette assemblies and schematic representation of the building blocks and the different possible constitutional isomers with D_3-, C_{3h}-, and C_s-symmetry. b) Representation of the two staggered conformations of the dimelamine fragments of the calix[4]arene components.

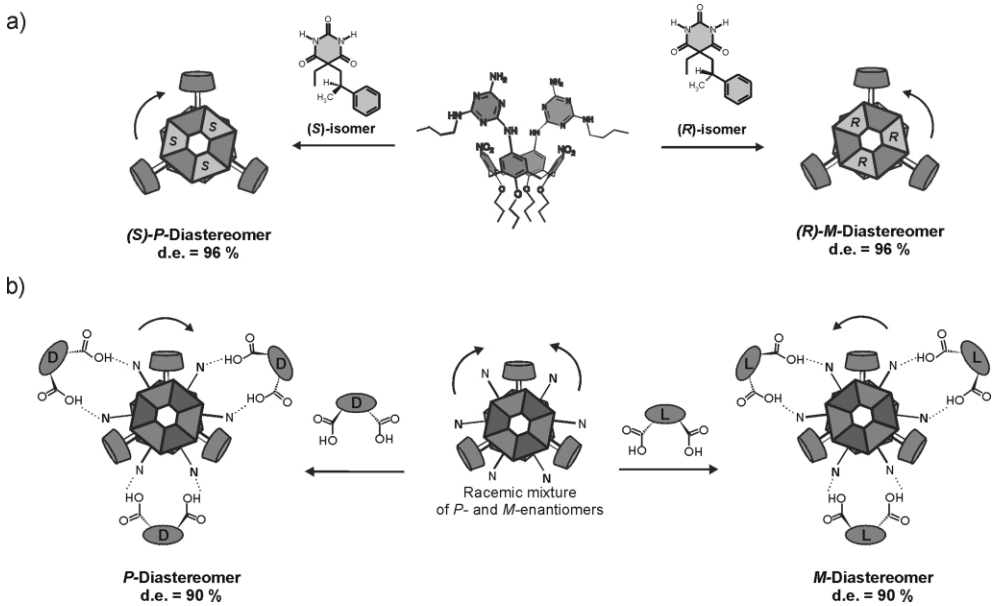

Fig. 4 Diastereoselective synthesis of double rosette assemblies *via* a) introduction of chiral centers in the assembly using a chiral barbiturate and b) complexation of chiral carboxylic diacids.

centers in the building blocks (asymmetric induction). In this way, the resulting chiral assemblies exist as two different species that have a diastereomeric relationship. This approach is called induction of chirality or diastereoselective noncovalent synthesis.

Using noncovalent synthesis, diastereomeric relations can be induced in self-assembled aggregates, ranging from hydrogen-bonded rosette assemblies[29] to hydrogen-bonded[30] or metal-coordinated capsules.[27]

Nice examples of diastereoselective noncovalent synthesis of double rosette assemblies have been described by Reinhoudt *et al*. Double rosettes are formed upon mixing calix[4]arene dimelamines and barbituric or cyanuric acid derivatives in a ratio of 3 : 6 in

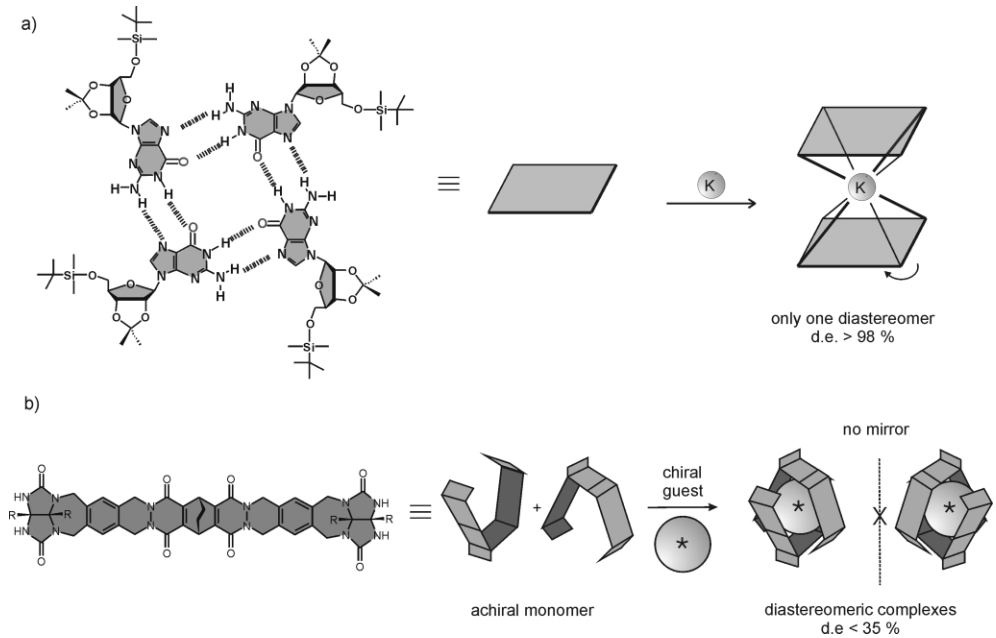

Fig. 5 Diastereoselective noncovalent synthesis of a) guanosine octamers templated by K^+ ions and b) molecular capsule upon guest complexation.

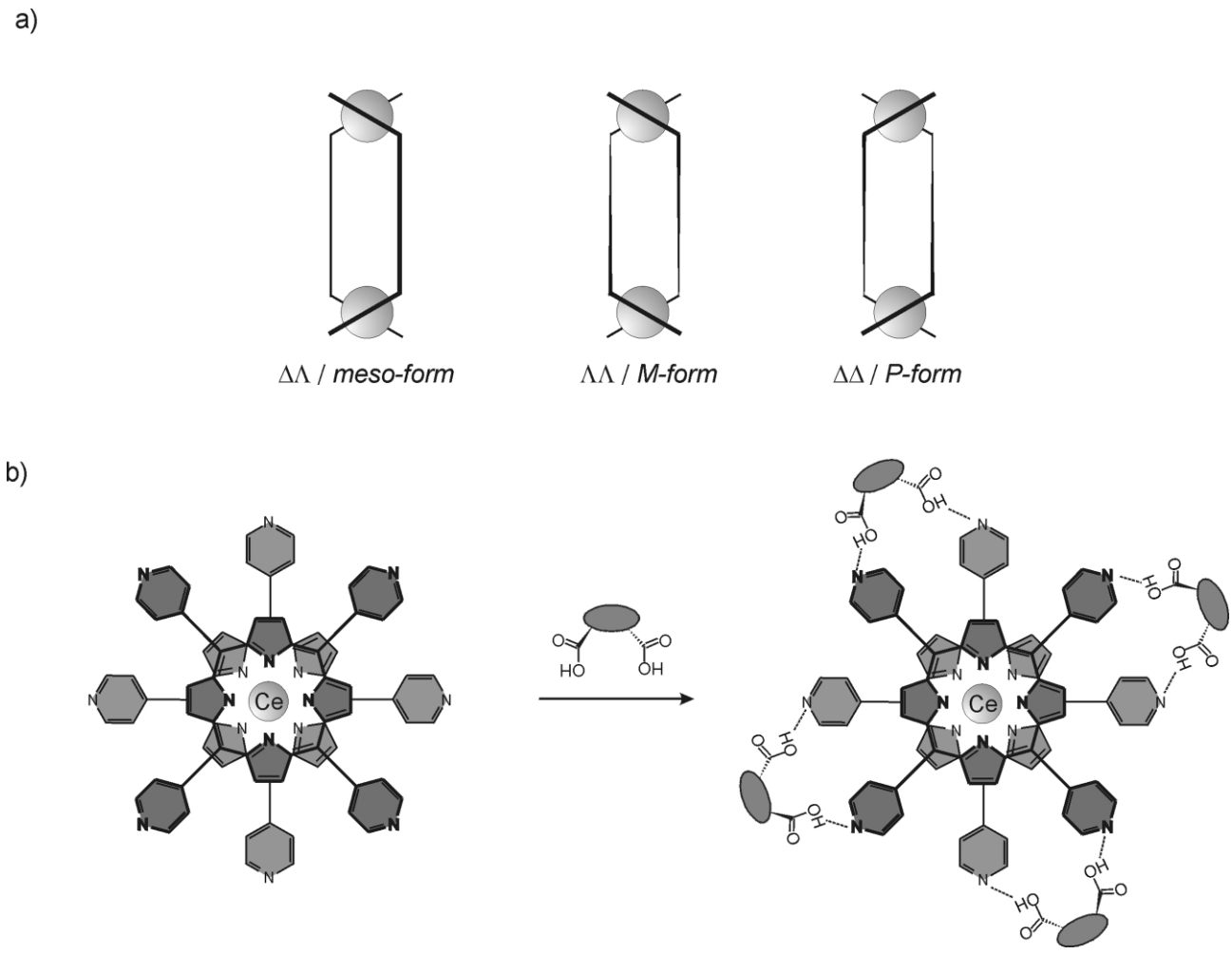

Fig. 6 Schematic illustration of chirality for metal helicates and b) diastereoselective synthesis of porphyrinate double-deckers.

apolar solvents such as chloroform, toluene, or benzene.[31] These hydrogen-bonded assemblies can exist in three different conformations with D_3-, C_{3h}-, or C_s-symmetry (Fig. 3a). In the D_3-conformer the two melamine fragments of the calix[4]arene component adopt an antiparallel (staggered) orientation (Fig. 3b), which renders the assembly chiral. The chirality of these assemblies arises from the fact that the two melamines can adopt either a clockwise (*P*) or counterclockwise (*M*) configuration.

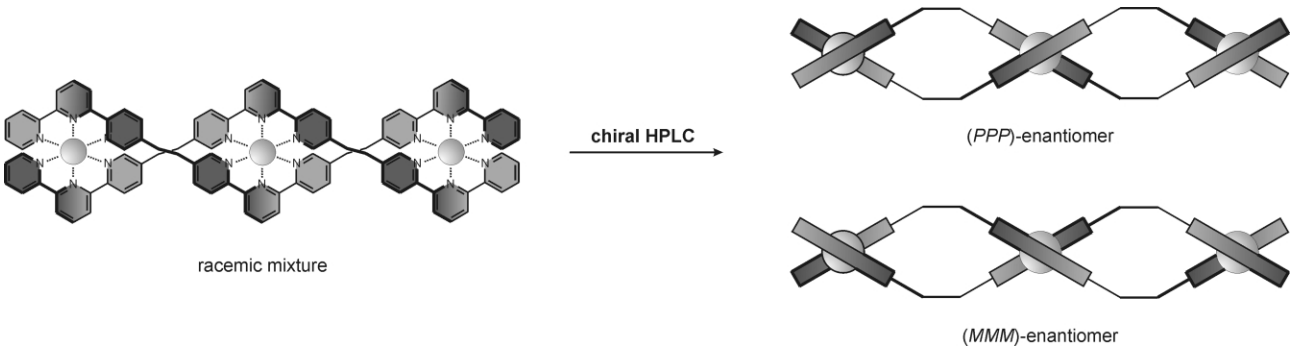

Fig. 7 Chromatographic resolution of metal helicates.

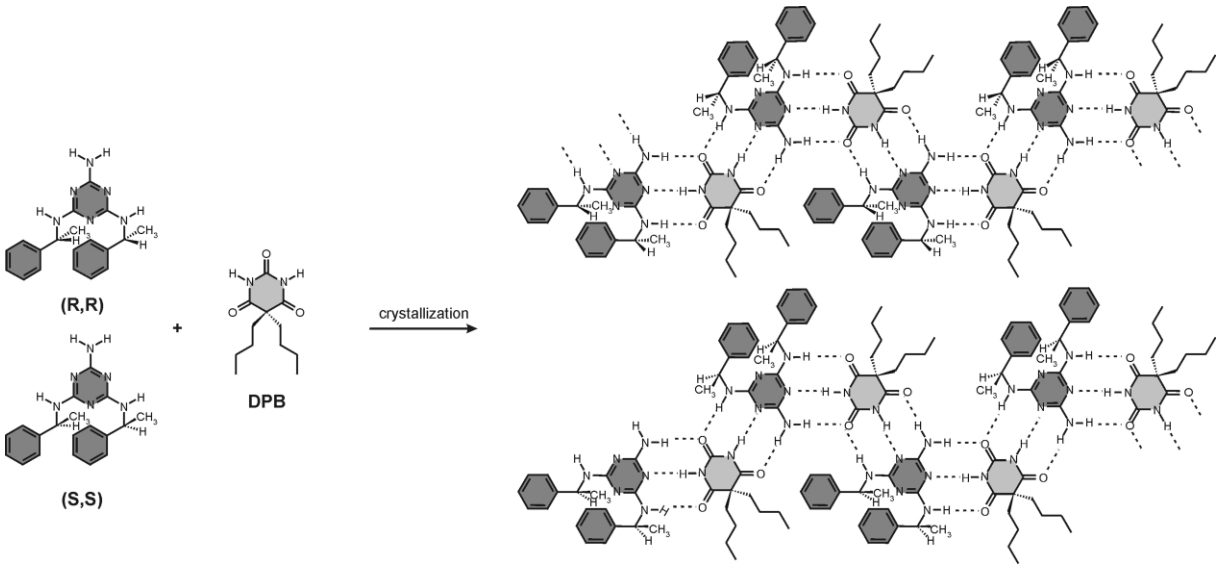

Fig. 8 Stereoselective self-assembly of chiral dimelamines and DPB (5,5-dipropyl-barbiturate) giving the two homochiral 'crinkled' tapes.

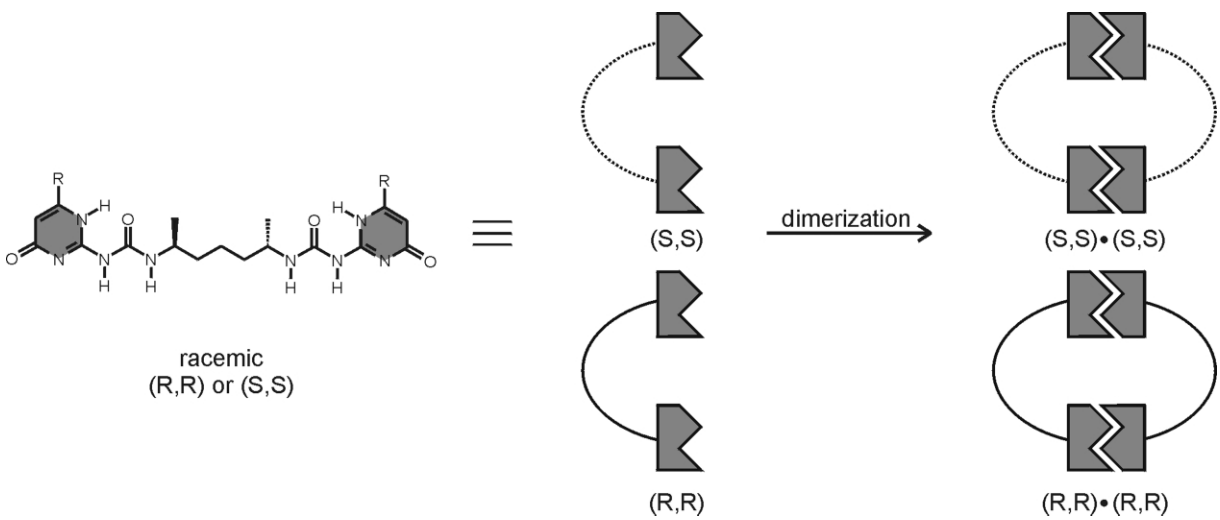

Fig. 9 Schematic representation of the dimerization process of the racemic Upy units.

The complete noncovalent diastereomeric synthesis (formation of only one handness of the possible two (*P*) or (*M*), see Fig. 3b) has been achieved in two different ways. Firstly, *via* the introduction of chiral centers in one of the components (Fig. 4a), either the calix[4]arene dimelamine or barbituric/cyanuric acid derivative. This results in the presence of 6 chiral centers in close proximity to the core of the assembly.[32] Secondly, *via* complexation of chiral acids or diacids by a racemic mixture of amino-substituted double rosette assemblies (Fig. 4b).[33,34] The first methodology leads to assemblies with a diastereomeric excess (d.e.) of 96%. The second case gives assemblies in which the d.e. is ~90%.

Complete diastereoselectivity, *i.e.* formation of only one diastereomer, has been achieved by Gottarelli and Davis with guanosine octamers, templated by K^+ ion, due to the presence of eight sugar moieties (Fig. 5a).[35] Rebek *et al*. demonstrated that certain symmetric molecules, possessing groups able to form and accept hydrogen bonds, dimerize to form molecular capsules with dissymmetrical cavities in the presence of a chiral template. These capsules preferentially form one of the two possible diastereomeric complexes (Fig. 5b). This leads to a diastereomeric excess up to ~35%.[36]

The two different approaches used for the diastereomeric noncovalent synthesis in hydrogen-bonded assemblies have been also used for the diastereoselective formation of self-assembled structures based on metal coordination, *e.g.* metal helicates,[37,38] and porphyrinate double deckers (Fig. 6).[39] However, when chiral ligands are introduced in metal helicates (discrete linear polynuclear oligomer formed by one or more organic ligands coordinating a series of metal ions) three forms of chirality must be distinguished. Firstly, the chirality given by the optically active carbon (*R*/*S*), secondly, the coordination environment around the metal centers (*Δ*/*Λ*), and thirdly the overall *P* or *M* sense of the helix (Fig. 6a).[40]

In general, for metal-coordinated assemblies the control over the chirality is somewhat different due to their higher kinetic stability when compared to the hydrogen-bonded assemblies. In this regard, chiral metal-coordinated assemblies resemble more their analogous synthesized by reversible covalent bonds.

2.2 Enantioselective noncovalent synthesis. By definition, enantiomers have equal thermodynamic stabilities. Therefore, the formation or isolation of pure enantiomers is a challenging task. In general, in covalent synthesis there are two ways to obtain pure enantiomers, either *via* resolution of racemic mixtures by crystallization (self-resolution) or chiral chromatography, or by means of enantioselective synthesis. In principle, these strategies are also applicable in noncovalent synthesis. Enantiomerically pure metal–ligand complexes (Fig. 7) and porphirinate double-deckers have been obtained *via* chiral column chromatography.[41–43] In general, the enantioselective noncovalent synthesis of self-assembled structures is more challenging, due to the inherently low kinetic stability of these assemblies.

2.2.1 Self-resolution. Self-resolution or enantioselective self-assembly has been defined as the spontaneous selection of components with the same chirality from an enantiomeric mixture that leads to the formation of homochiral assemblies. This is a characteristic phenomenon in the solid state (Fig. 8),[44,45] but it still is a rare event in solution, in liquid crystals or self-assembled monolayers.[9,46]

Nevertheless, some examples of self-resolution have been reported in solution. The cyclization of racemic 2-ureido-4[1*H*]-pyrimidinone (Upy) derivatives in chloroform solutions leads to the selective formation of the homochiral cyclic dimmers of Upy derivatives (Fig. 9).[47]

Also double rosette assemblies display complete enantioselective self-resolution. Mixing of building blocks with opposite handedness or chirality does not lead to the formation of heterochiral assemblies (Fig. 10).[32] Surprisingly, for assemblies comprising nonchiral calix[4]arene dimelamine components the formation of heteromeric or heterotopic (*i.e.* assemblies comprising

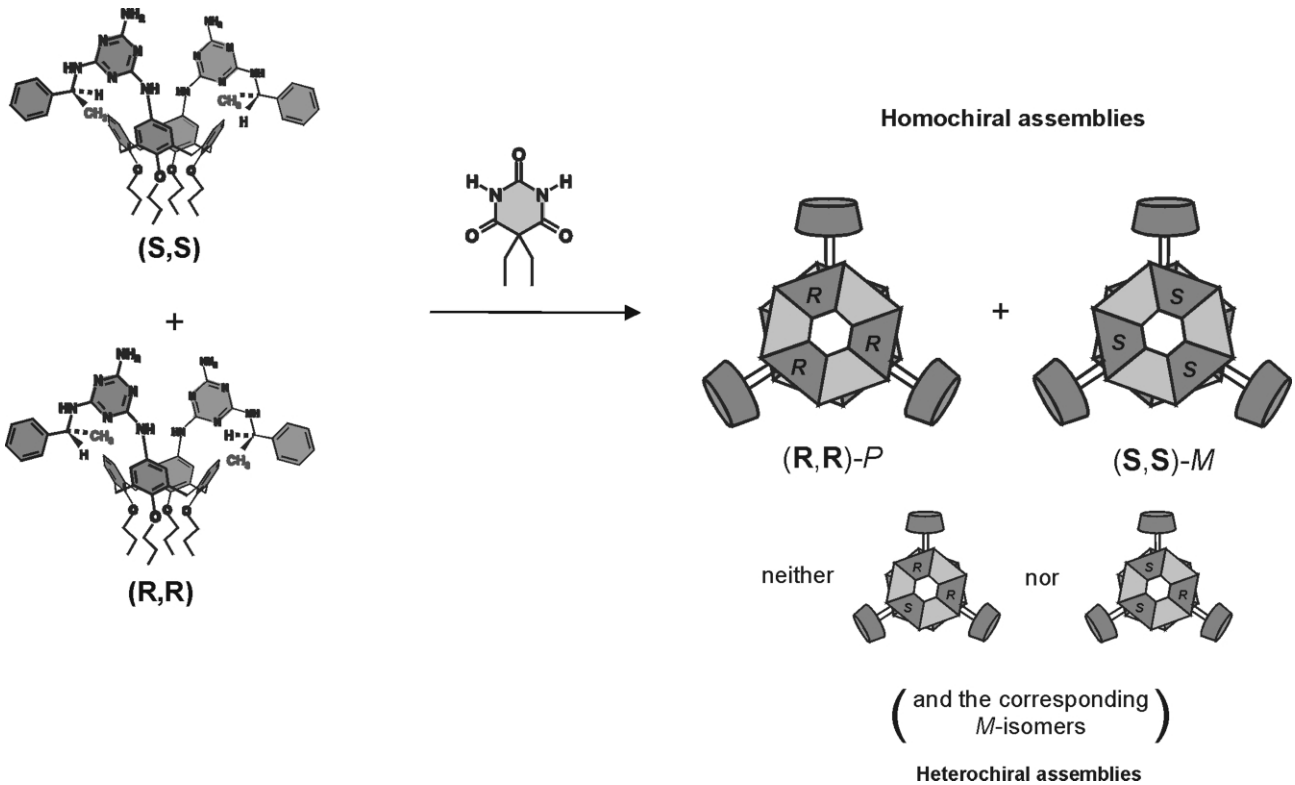

Fig. 10 Enantioselective self-resolution in double rosette assemblies from a mixture of enantiomeric building blocks.

structurally different building blocks) double rosette assemblies is possible.[48,49]

2.2.2 Chiral memory. The synthesis of enantiopure self-assembled aggregates from achiral components has been achieved using the "chiral memory" concept previously reported by the group of Yashima for the enantioselective synthesis of covalent *P*- or *M*-helical polymers.[50] The *chiral memory* concept implies the use of a chiral auxiliary that interacts stereoselectively in a noncovalent manner to give preferentially one of the two possible enantiomeric forms. Subsequently, the additive is removed or replaced by an achiral analogue while the induced chirality is preserved. This replacement of the chiral "additive" is the crucial step in this strategy. The resulting structure is still optically active, although none of its components are chiral. This strategy has been used to synthesize enantiomerically enriched self-assembled double rosette assemblies with an enantiomeric excess (e.e.) of 90 to 96%.[34,51] This enantioselective noncovalent synthesis of the double rosette assemblies (Fig. 11a,b) has been accomplished in two different ways. Formation of a diastereomeric assembly using chiral building blocks that are later replaced by achiral ones leading to an enantiopure system, or complexation of chiral diacids by amino-substituted double rosette assemblies and subsequent removal of the acids. In the first case, the use of a chiral barbiturate compound leads to the formation of a diastereomeric assembly with a d.e. of 96%. The subsequent exchange of the chiral barbiturate for an achiral cyanurate gave an enantiopure assembly with a e.e. of 96% (Fig. 11a). This exchange of the barbiturate for a cyanurate is possible because of the formation of stronger hydrogen bonds between the melamine–cyanurate pair than between melamine–barbiturate pair due to the higher acidity of the cyanurate. In the second way, the formation of only one diastereomer with a d.e. up to 90% is induced by complexation with chiral dicarboxylic acids. The removal of the diacids by precipitation of the salt upon the addition of amine leads also to the formation of the enantiopure assemblies (Fig. 11b). Similarly, noncovalent H-bonded capsules have been synthesized with 50% e.e. (Fig. 11c) by Rebek *et al*.[52] The crucial step is the exchange of the guest without racemization of the assembly. This step proceeds through windows of the capsule that form without disrupting the entire hydrogen-bonded seam of the capsule.

The memory of chirality has been also reported for the enantioselective synthesis of the more kinetically stable metal complexes and porphyrinate double deckers. Raymond *et al*. reported the enantioselective formation of tetrahedral metal complexes of tris(catecholate)gallium(III). These complexes encapsulate ammonium cations. In the presence of an achiral guest, they exist as a mixture of enantiomers ($\Lambda\Lambda\Lambda\Lambda$ or $\Delta\Delta\Delta\Delta$). The encapsulation of a chiral ammonium cation leads to the formation

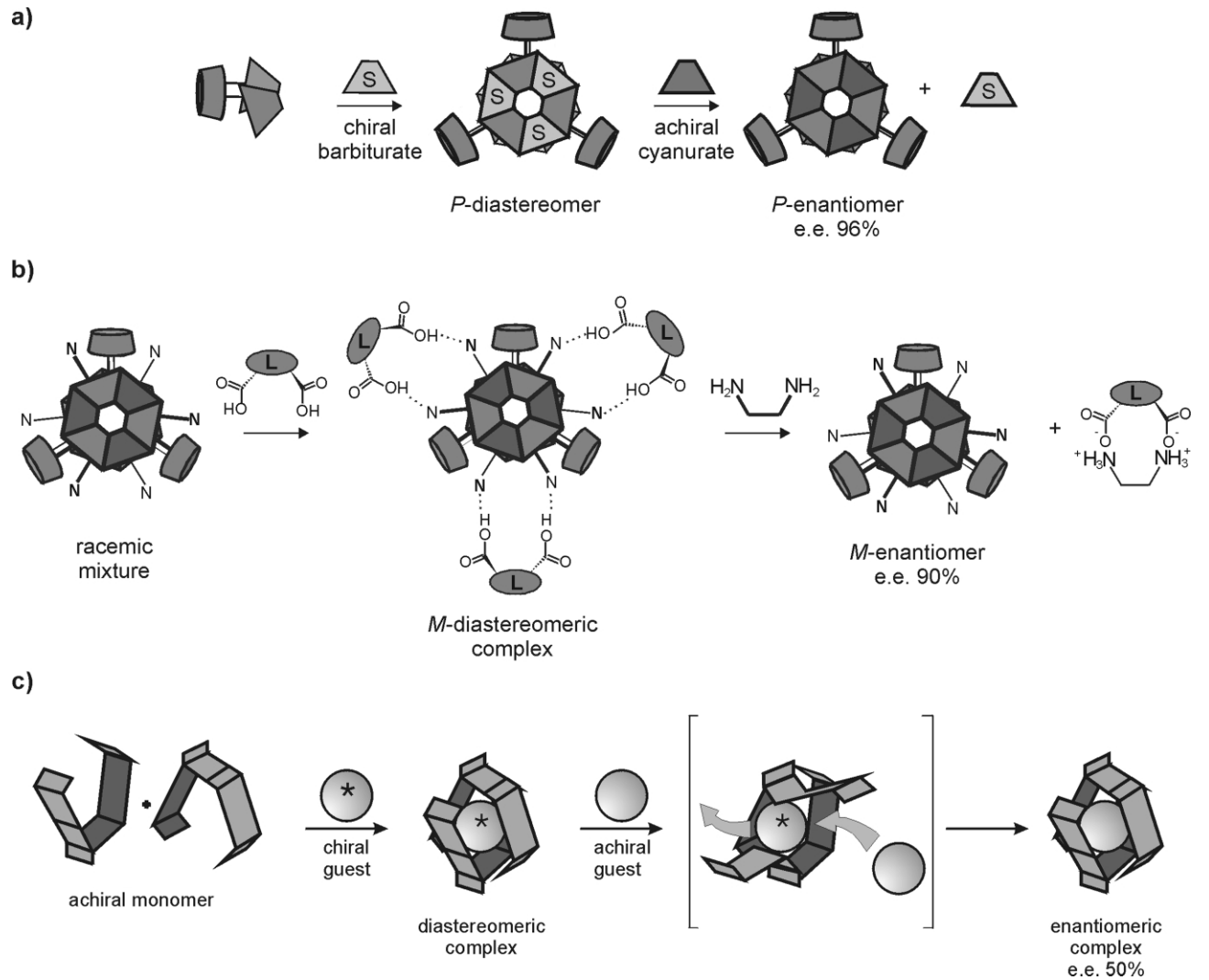

Fig. 11 Schematic representation of the noncovalent enantioselective synthesis of double rosette assemblies *via* introduction of chiral barbiturate and posterior exchange by achiral cyanurate (a) or *via* complexation of chiral dicarboxylic acids (b) and of H-bonded capsules using the concept of chiral memory showing the nondissociative exchange of the guest (c).

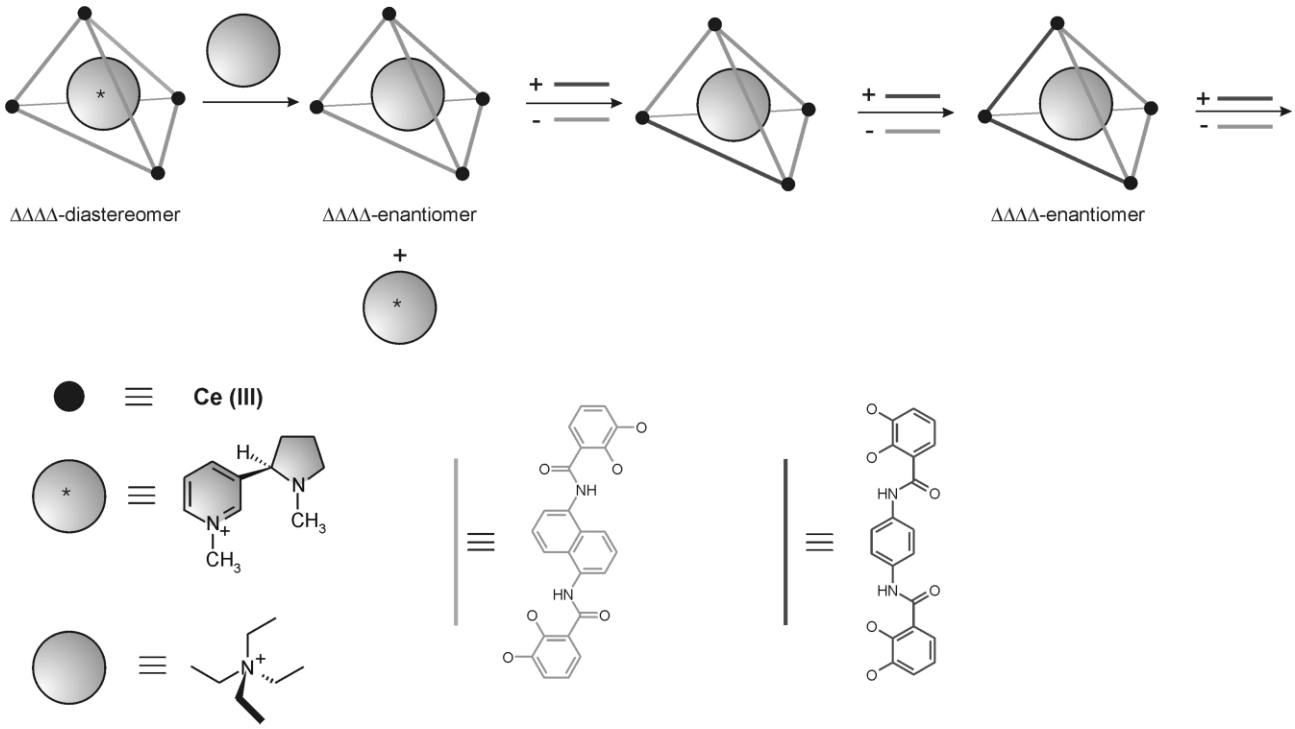

Fig. 12 Schematic representation of the replacement of the chiral ammonium cation for an achiral one and posterior exchange of the ligand substitution. In both steps the chirality of the complex is preserved.

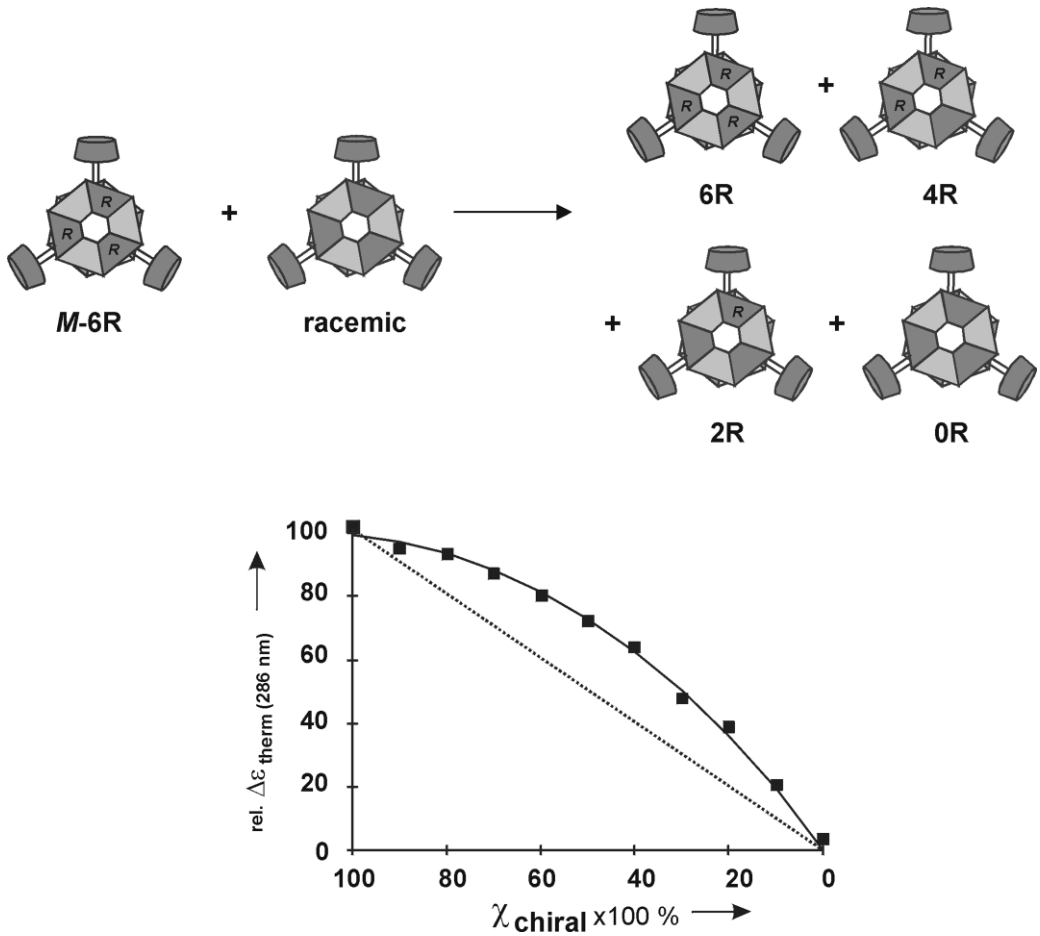

Fig. 13 Schematic representation of the formation of the heteromeric assemblies (top). Plot of the relative CD-intensities at the thermodynamic equilibrium for different mole fractions of the chiral component. The dotted line represents the values in absence of chiral amplification (bottom).

of only one of the two possible diastereomers. Subsequent exchange of the chiral ammonium for an achiral one results in a formation of an enantiopure complex that retains its enantiopurity for at least eight months.[53] Moreover, the complex retains its chirality even after exchange of the ligands that form the complex (Fig. 12).[54]

3 Amplification of chirality: the 'sergeants and soldiers' principle. Amplification of chirality occurs in systems in which a small initial amount of chiral bias induces a high diastereomeric or enantiomeric excess.[28] Green and coworkers reported few years ago for the first time the amplification of chirality in polyisocyanates having a stiff helical backbone.[55] They found that polymers containing small percentage of the chiral monomers still expressed a strong chiroptical activity. The reason for this amplification is that the achiral units are forced to follow the helicity induced for the chiral units. This is commonly referred to as the 'sergeants and soldiers' principle. This phenomenon has been also studied in noncovalent polymeric structures by Meijer *et al*.[56]

The amplification of chirality in well-defined systems has been investigated in double rosette assemblies using the 'sergeants and soldiers' principle.[57] For this purpose, solutions of chiral and achiral assemblies in benzene were mixed in ratios varying between 90 : 10 and 10 : 90 at room temperature. Interestingly, the CD-intensities increase in time as a result of the formation of the heteromeric assemblies (Fig. 13).[48] A plot of the thermodynamic value against the ratio of chiral rosette used shows the typical nonlinear behavior of the 'sergeants and soldiers' experiments (Fig. 13).

4 Chirality in liquid crystals. Liquid crystals may be defined as an ordered fluid that is intermediate between the three dimensionally ordered crystal phase and the disordered liquid phase.[58] This is referred as a mesophase and its components as mesogens. These mesophases are classified according to their symmetry, distinguishing three major classes: nematic, cholesteric (also denominated chiral nematic[59]) and smectic. Due to their symmetries, the three mesophasic structures can be chiral, leading to materials with interesting properties for practical applications such as materials for processing and displaying color information, and optical filters and reflectors.[59,60] Chirality in these systems can be introduced *via* the chiral centers of the mesogens molecules and *via* the use of achiral bent-core molecules ('bow' or 'banana' shape molecules[61]). This kind of molecules can form chiral liquid crystal phases due to the spontaneous chiral supramolecular organization of the achiral molecules. Furthermore, the use of self-assembled systems based on metal coordination and H-bonding interactions has been found to be a versatile tool to obtain liquid crystals with controlled supramolecular chirality.[62–64] In this context has been reported the formation of diastereomeric species,[65] the observation of self-resolution[66] and the amplification of chirality ('sergeants-and-soldiers' principle).[61,63,64]

5 Conclusions and outlook. For more than a century, chemists have been concerned with the synthesis of new molecules *via* disruption and construction of covalent bonds. In covalent synthesis, the preparation of pure chiral molecules is still a major topic of interest especially because of its implication in the development of new drugs and catalysts. However, in noncovalent synthesis the formation of chiral self-assembled aggregates is still in its infancy, due to the highly dynamic character of noncovalent interactions. Nevertheless, in this review it has been shown that there are examples of noncovalent systems in which the process of self-assembly can be fully controlled, resulting in the stereoselective synthesis of diastereomeric and enantiomeric assemblies. Control over the processes of chiral memory and chiral amplification has very promising consequences. It is clear that control over supramolecular chirality of synthetic increasingly complex assemblies will be of crucial importance to their application in the field of molecular recognition, catalysis, material sciences, and especially nanotechnology.

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