Hierarchical self-assembly of columnar aggregates

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Biology often uses hierarchical self-assembly to produce complex functional structures from smaller components. At each level of this stepwise process, non-covalent interactions bring together the subunits of a lower level of complexity, using the information encoded in their structures. Applying this approach to synthetic systems represents a formidable challenge, because it requires a high degree of command of non-covalent interactions. In this *tutorial review*, recent developments in the hierarchical self-assembly of discrete columnar aggregates are discussed.

Introduction

Fibrils, tubules and columns are one-dimensional architectures with essential functions in natural systems. They are used for their defined internal structure in transmembrane ion channels. They also form closed reaction chambers that together with the functionalized internal surface provides a sophisticated system for selective catalysis. Another important role in natural systems is played by one-dimensional structures with mechanical functions, *e.g.* collagen fibrils in connective tissue, or actin filaments in muscle. In the last few decades, it has become increasingly clear that nature often builds up complex structures by hierarchical self-assembly of smaller components. As the term suggests, hierarchical self-assembly is a stepwise process in which components are brought together in a precisely defined way by non-covalent interactions. The units produced at each level, form the building blocks for self-assembly at the next higher level of complexity. The information needed for the formation of large objects is encoded within the covalent structure of the subunits, and is expressed by the "instruction set" of non-covalent interactions.[1–3] In such a modular approach only relatively small components have to be produced *via* covalent synthesis, minimizing the risk of translation errors or misfolding. Furthermore, the use of small non-covalently bound components permits the rapid assembly and disassembly according to local need and allows easier transportation. In strict self-assembly, the components spontaneously aggregate without external guidance into ordered structures. A well-studied example of hierarchical self-assembly is the assembly of the tobacco mosaic virus (TMV).[4] It is well established that in the assembly of the coat protein of this virus into a helical column, the viral RNA acts as a template and provides additional stability to the helical columnar aggregate after formation. Assembly of a virus particle is initiated by the binding of the RNA to a short 'two turn' helical aggregate consisting of coat protein molecules. Remarkably, the coat protein is able to self-assemble into a helical structure without the presence of the viral RNA. In other words, the structure of the coat protein by itself already contains enough information to self-assemble into a helical structure. An important difference between TMV coat protein and other globular proteins is the presence of large

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hydrophobic patches on its surface. The external layer of the TMV coat protein is enriched in hydrophobic residues like tryptophan and tyrosine as shown in Fig. 1.[5] Extensive studies have shown that self-assembly of the coat protein is a complicated, not yet fully understood process. Depending on pH, ionic strength and concentration, different assemblies have been found, ranging from monomers to double layered disks (17 units), small stacks of disks, and helices, which are not necessarily interconvertible.

The intriguing self-assembly process of the TMV coat protein shows that well-defined structures can be obtained by hierarchical self-assembly, but that the self-assembly is a subtle process, the outcome of which depends on the environmental conditions.

Inspired by biological examples of self-assembled columnar aggregates such as those formed by TMV, many synthetic systems are currently being investigated. For the synthesis of large structures self-assembly offers a number of advantages above covalent synthesis.[2] Among those advantages are the possibility for error correction, facile formation of the end product, and synthetic economy. A hierarchy of orthogonal sets of assembly instructions helps to simplify the design process of a specific aggregate. In that respect the role of hierarchy may be expected to be even more important in designed systems than in naturally evolved systems, where an almost unlimited amount of trial and error can be used to optimize functionality. On the other hand, unlike nature, synthetic systems are not restricted to a limited set of components, allowing other approaches with radical new designs. This review will focus on stable well-defined columnar aggregates formed through hierarchical self-assembly of molecules *via* specific interactions. The requirements for a system to be formed in a hierarchical fashion and the study of the hierarchical assembly process by means of chirality will be discussed. Recently, a review of hierarchical self-assembly in synthetic systems in general by Nolte and co-workers[6] was published, while one-dimensional aggregates were reviewed by Stupp and co-workers.[7] Self-assembled tubular aggregates such as peptide nanotubes, foldamers, and phenyl acetylene macrocycles have recently been discussed in a review by Ghadiri *et al.*[8] Because essential aspects of hierarchical self-assembly such as reversibility and dynamics are lacking in the solid state[9] or in gels,[10] studies concerning these states of matter will not be discussed. Although a combination of different non-covalent interactions is involved in the formation of wormlike micelles, a clear hierarchy is usually not discernible in the self-assembly process. Therefore wormlike micelles formed by block copolymers,[11] amphiphiles, or peptide amphiphiles[12] are beyond the scope of this review.

Hierarchical aggregation through disk shaped aggregates

Large functional columnar aggregates can be obtained by hierarchical self-assembly when first a closed oligomeric disk-shaped aggregate is formed, followed by aggregation of multiple disks into rods, cylinders or wormlike objects. For the second step the disks must have relatively large planar surfaces that can interact through non-covalent interactions such as solvophobic and π–π interactions. Several groups[13–20] have shown that hydrogen bonds can be used to form stable macrocycles in solution. They found that the preferential formation of cyclic structures by non-covalent synthesis above their linear counterparts is a complex process governed by subtle interactions like pre-organization of the covalent structure, peripheral crowding, solvent type and binding strength. Hydrogen bonds are often used to form macrocyclic systems because they are directional, specific, and have a relatively high binding strength, all properties being important requirements for the selective formation of cycles.

The application of this strategy to form columnar aggregates *via* hierarchical self-assembly in water has recently been reported by Fenniri *et al.*[21–23] These researchers designed a unit **1** containing two different multiple hydrogen bonding

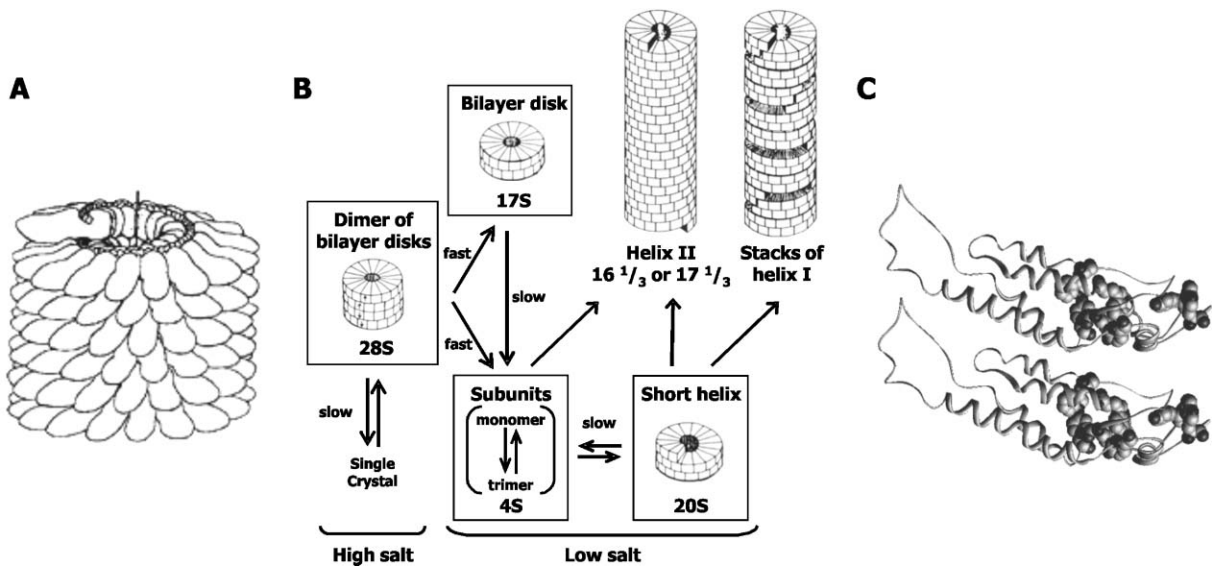

Fig. 1 A. Tobacco mosaic virus (TMV); B. Relationship between structures of the coat protein of the TMV; C. Side-view of the structure of two TMV coat protein subunits in the virus. The virus axis is situated on the left. Tyrosine and tryptophan residues are highlighted.[1]

sites, one containing an array of donor–donor–acceptor (DDA) sites like those found in guanine and the complementary ADD array like in cytosine (Fig. 2). A molecule based on this design had been reported before to form cyclic hexamers.[18] To enhance the tendency of the molecules to form a rosette-like structure in water, the hydrogen bonding arrays were shielded from the solvent by methylation of the amino group in the DDA array. Furthermore, chiral centers were introduced on the periphery of the rosette by attaching an amino acid moiety *via* an ethylene spacer. The large hydrophobic surface created by the self-assembly of a rosette in combination with the electrostatic interactions between the amino acid side chains provides a strong driving force for stacking in water. The remarkable temperature dependence of the aggregation of the rosettes—the length of the stacks increases when the temperature is raised—indicates that the self-assembly of the rosettes is an entropy driven process.

Gottarelli, Spada and co-workers reported the hierarchical self-assembly of the sodium or potassium salts of oligomeric deoxyguanosines **2** into chiral columns in water.[24,25] The system is of interest because of its strong similarities to DNA and the possible role of guanosine aggregation in replication. Guanosine units **2** form cyclic tetramers (G-quartets) through hydrogen bonding. These G-quartets then stack *via* hydrophobic interactions and phosphodiester bridges into well-defined "barrels". Subsequently more extended columns are formed by the stacking of these "barrels" (Fig. 3). Even without the phosphodiester bridge G-quartets show hierarchical self-assembly into columns, as was shown for a mono-functional guanosine derivative. Above a certain concentration, aqueous solutions of **2** form lyotropic liquid crystalline mesophases with hexagonal order, while at even higher concentrations a cholesteric phase was observed. The onset of cholesteric order increased with the length of the oligomers and reflects the balance between hydrophobic and hydrophilic groups. Alkali metal ions which bind to the inner carbonyl groups of the G-tetramer stabilize the columnar aggregates. In the presence of potassium ions the degree of polymerization and the stability of the columnar aggregate are increased.

Gottarelli and Davis *et al.* prepared apolar lipophilic deoxyguanosine bases **3** and demonstrated their hierarchical self-assembly into columnar structures in apolar solvents.[26] Unlike their polar counterparts in water the apolar lipophilic deoxyguanosine bases **3** do not form a G-quartet in apolar solvents by hydrogen bonding only. The lipophilic deoxyguanosine bases are molecularly dissolved in chloroform, but upon contact of the organic layer with an aqueous layer containing potassium salts the potassium ions are extracted from the aqueous layer. The potassium ion templates the

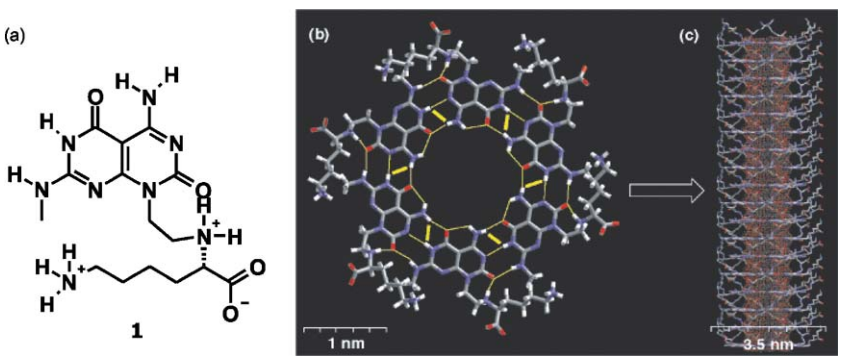

Fig. 2 Hierarchical self-assembly of rosette nanotubes: (a) the hydrogen bonding unit **1**; (b) model of the rosette; (c) molecular model of the nanotube. Reprinted with permission from ref. 22. Copyright 2001, American Chemical Society.

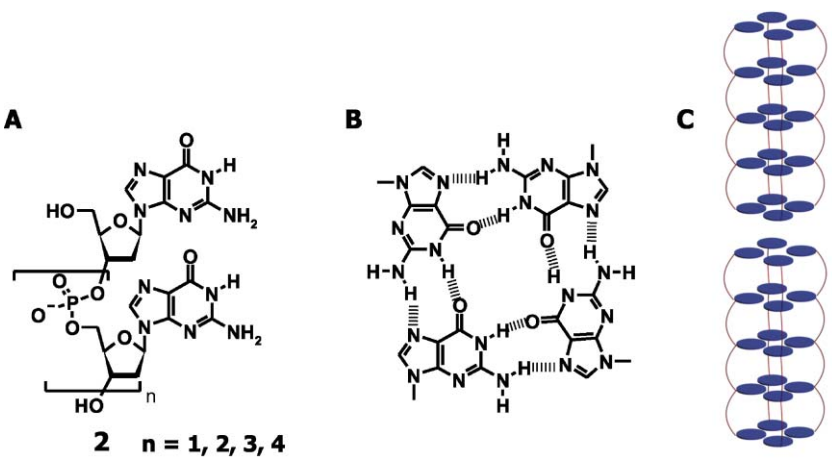

Fig. 3 A. Deoxyguanosine oligomers **2**; B. G-quartet; C. Hierarchical self-assembly of 'barrels' into columns.

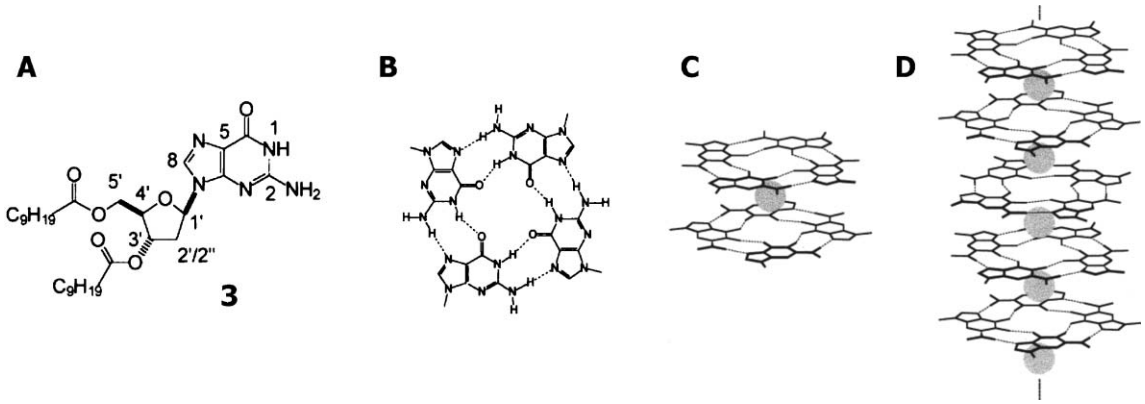

Fig. 4 A. Apolar lipophilic deoxyguanosine base **3**, B. G-quartet, C. Octamer, D. Columnar aggregate.

formation of an octamer in which the potassium ion is sandwiched between two G-quartet disks and is coordinated to the carbonyl groups of the guanosine bases. Depending on the potassium concentration, these G-quartets form either an octamer or longer columnar aggregates in the case of a higher potassium concentration (Fig. 4). Thus, the potassium ions have a two-fold function: they induce the formation of closed G quartets over the linear tape-like structure and provide together with solvophobic interactions the driving force for further assembly into columnar aggregates.

The groups of Reinhoudt[27] and of Whitesides[28] have reported independently on the formation of supramolecular "nanorods" based on the well-known cyanuric acid-melamine motif. The hydrogen-bonded polymeric rods are composed of stacked cyanuric acid–melamine rosettes (Fig. 5). Mismatching dimelamine **4** and dicyanurate **5** were prepared, in which the spatial distance between the two cyanurate units is different from the distance between the two melamine units. It was anticipated that this mismatch would prevent the formation of a closed disk-like assembly and induce the formation of polymeric entities. A 1 : 1 mixture of dimelamine **4** and dicyanurate **5** leads to a high viscosity in aprotic solvents resulting from the formation of high molecular weight columnar aggregates. The aggregation behavior was studied by NMR spectroscopy and showed broadening of the hydrogen-bonded protons in chloroform. Microscopy techniques such as transmission electron microscopy (TEM) and tapping mode scanning force microscopy (TM-SFM) showed a large influence of the solvent on the morphology of the aggregates in the solid state.

Hirschberg *et al.*[29] and Brunsveld *et al.*[30] have developed mono-functional ureidotriazine units that dimerize *via* quadruple hydrogen bonds with an association constant (K_{ass}) of 2×10^{-4} M^{-1} in chloroform into disc shaped dimers **6–9** (see Fig. 6). The aromatic surface of the dimers is enlarged by a phenyl substituent on the triazine rings to which solubilizing chains are attached. The hydrogen-bonded dimers form a large planar aromatic core, surrounded by six flexible alkyl tails, thus providing an ideal environment for stacking the dimers by π–π and solvophobic interactions.

Not only polar solvents like water and butanol induce aggregation of the core, but also a highly apolar solvent such as dodecane is able to induce stacking of the ureidotriazine dimers. In contrast to this, no stacking is observed in chloroform. By connecting two ureidotriazine units *via* a hexamethylene linker, bifunctionalized molecules are obtained, forming aggregates that switch from a random-coil hydrogen-bonded supramolecular polymer to a columnar polymeric architecture when the solvent is changed from chloroform to dodecane. An increased stability and length of the columnar architectures was observed for the bifunctionalized ureidotriazine units, which was ascribed to the higher local concentration of the ureidotriazine units.

Chirality as a probe

A fundamental and intriguing issue in the formation of columnar aggregates *via* hierarchical self-assembly concerns the internal structure of the aggregate: do the columns consist of a stack of disks, or is it a helically folded polymer? When columnar structures are formed by a combination of hydrogen bonding and stacking interactions, the answer to this question depends on whether polymers or closed aggregates (dimers or rings) are formed by hydrogen bonding. Columns are then formed by intramolecular stacking interactions in the polymer or by intermolecular stacking of the closed aggregates. Once these aggregates are formed, however, their interconversion is a process that can take place with minimal structural reorganization. When cyclic structures open up and the hydrogen bonding ends of the resulting oligomer are connected with corresponding ends of the neighboring layers, a helical structure is obtained. Chirality is often used to probe the mode of aggregation and can be determined with circular dichroism (CD) spectroscopy. Gottarelli and co-workers performed an extensive study of the aggregation behavior of the oligomeric deoxyguanosines **2** (Fig. 3) using CD spectroscopy. They showed that upon increasing the concentration above a critical concentration the CD spectrum showed an intensive negative band, which they ascribed to the formation of a cholesteric phase. In this phase the chiral columns aggregate in a similar fashion as in the cholesteric phase of double stranded DNA. They were able to determine the handedness of these superhelices and showed that the handedness is determined by a delicate interplay of the non-covalent interactions and the phosphodiester bridges.

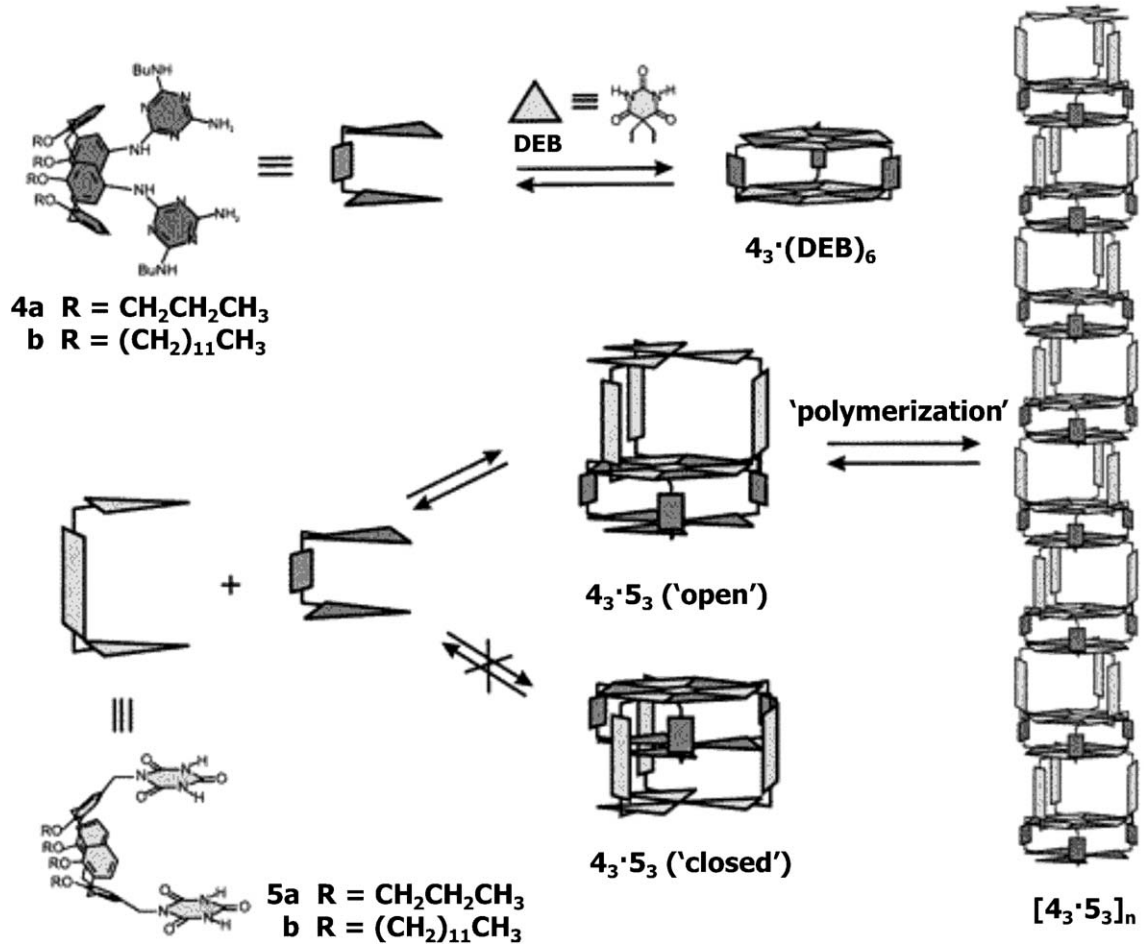

Fig. 5 Schematic representation of molecular components **4** and **5** and the polymerization to rod-like nanostructures.

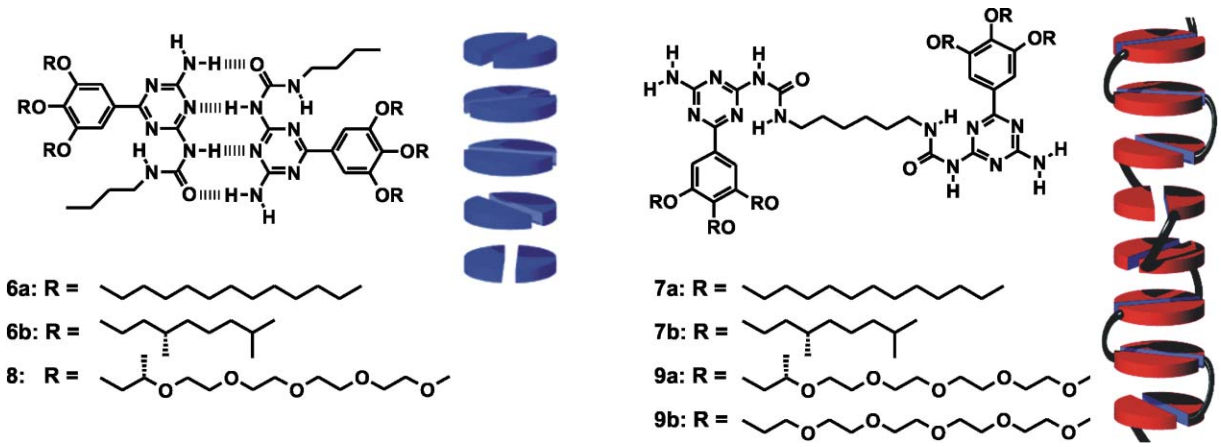

Fig. 6 Mono- and bifunctionalized ureidotriazines **6–9**; to the right molecular models of the respective structures in apolar solvents.

Supramolecular chirality can sometimes be induced by placing stereo centers in the periphery of the assembly, which introduces only a small perturbation in the molecular structure. Even though the chiral centers are far removed from the core of the disk-shaped structure, in the columnar aggregate the peripheral side chains transfer their chirality to the core of the column. By introducing chiral alkyl chains in bifunctionalized triazines **7** and **9**, it was shown with CD spectroscopy that the dimeric disks aggregate into helical columns (Fig. 6). A Cotton effect typical for a helical arrangement in the absorption bands of the aromatic core was found. Even at concentrations as low as 10^{-6} M the Cotton effect was only reduced by a factor of 2 showing that even at these low concentrations the molecules are still

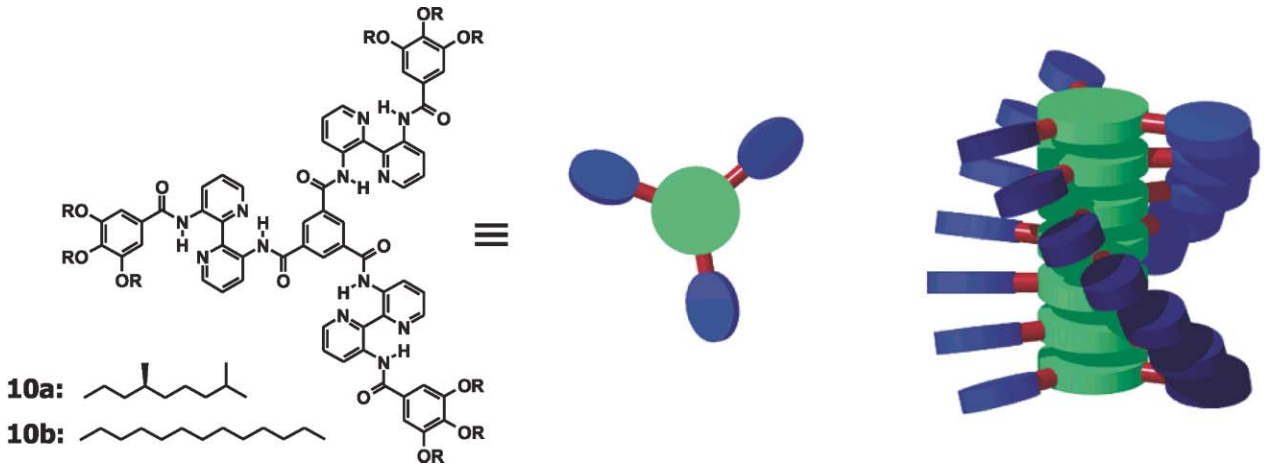

Fig. 7 Bipyridine based C_3-symmetrical disks **10a, b** and a cartoon representing their helical supramolecular stacking.

assembled into helical columns. In contrast to the bifunctionalized triazine dimers, the dimers of mono-functional triazines containing chiral side chains do not show a Cotton effect because the relative orientation of the dimers is not locked by a hexamethylene linker.

Small amounts of chiral monomers can completely bias the helicity of polymers with conformational chirality. This 'sergeants and soldiers' effect has also been used to study cooperativity of aggregation in non-covalent columnar assemblies.[31] The effect results in amplification of the chirality of a sergeant in a mixed aggregate with achiral soldiers. The degree of cooperativity of the 'sergeants and soldiers' effect as well as the total number of monomers in a column determines the number of achiral soldiers to which the sergeant is able to transfer its chirality. Bipyridine C_3-symmetrical disks **10** aggregate in a hierarchical fashion, with intramolecular hydrogen bonds preorganizing the propeller shaped molecules to aggregate into columns *via* intermolecular hydrogen bonds and stacking interactions (Fig. 7). In mixed solutions in dodecane, chiral sergeants **10a** are able to transfer their chirality to up to 200 achiral C_3-symmetrical disks **10b**.[32]

A different way to induce chirality in hierarchical self-assembled columnar structures is by using a chiral auxiliary or promoter. Chirality is transferred to the columnar assembly through molecular recognition of chiral promoters by the

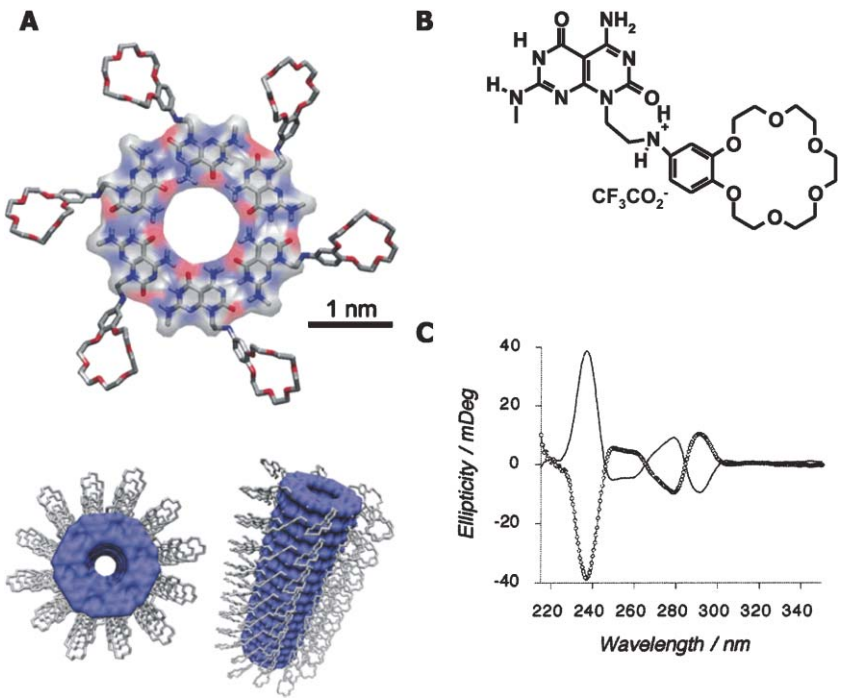

Fig. 8 A. Hierarchical self-assembly of compound **11** into a six-membered supermacrocycle (rosette upper) and resulting nanotube, top (lower left) and side (lower right) views; B. Heterobicyclic base **G**$\wedge$**C 11**; C. CD spectra of **11** (0.04 mM) + L-Ala (0.4 mM) (○) and **11** (0.04 mM) + D-Ala (0.4 mM) (–) recorded continuously until the induced circular dichroism (ICD) stabilized (<24 h after mixing). Reprinted with permission from ref. 21. Copyright 2003, American Chemical Society.

columnar structure. Fenniri and co-workers[21] recently reported such a kind of chirality induction in rosette nanotubes, by chiral amino acid promoters, which bind to crown ether groups at the periphery of the columnar structure (Fig. 8). The chiral amino acid promoters D-Alanine and L-Alanine are able to transfer their chirality resulting in the opposite handedness of the helical columnar aggregate P or M, respectively (Fig. 8C).

The induced circular dichroism (ICD) effect was shown to be promoter-specific and to depend on minor structural variations, which influence the binding to the prochiral crown ether substituted guest. Unlike the 'sergeants and soldiers' mode of chirality induction, the amino acid promoters induce chirality in an 'all-or-nothing' fashion. Only when all the crown ether sites are occupied they are able to transfer their chirality. The chiral promoters were shown not only to induce chirality, but also to enhance the stability of the columnar aggregates in a pathway that the authors proposed to be autocatalytic (see Fig. 9).

Functional aggregates

In recent years, numerous possible applications for hierarchical self-assembled columnar or tubular aggregates have been proposed. An important reason for the interest in these systems is the typical size of the aggregates. With a diameter of 1–10 nm and lengths up to micrometers these structures bridge the gap between conventional molecular objects and top-down structures created by lithographic techniques. The process of hierarchical self-assembly leads to well-defined structures with built-in error correction and to architectures that can be controlled by subunit design. These properties are of special interest for the development of electro-optical devices such as solar cells, light emitting diodes (LEDs) and field effect transistors (FETs) in which control of the mesoscopic structure in the π-conjugated systems is a subject of great importance. Recently, formation of functional helical columnar aggregates in dodecane was reported by the hierarchical self-assembly of mono-functional ureidotriazine units **12**.[33] Chiral π-conjugated

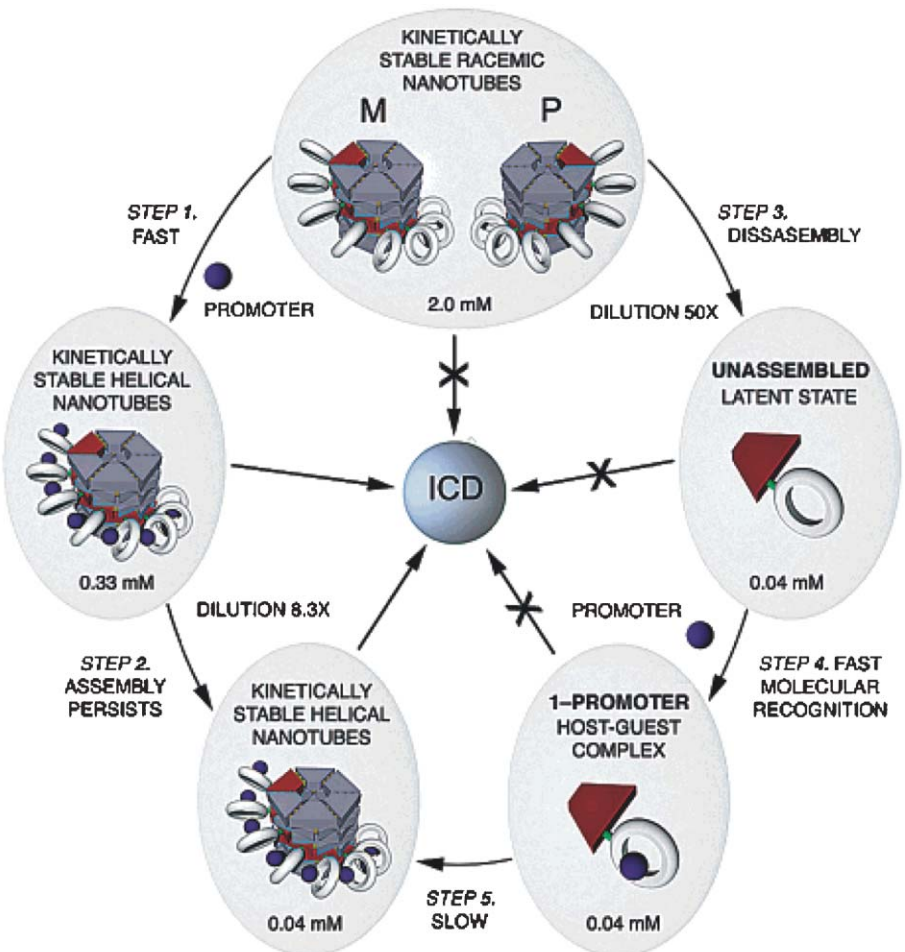

Fig. 9 Schematic representation of the supramolecular pathways leading to the self-assembly of helical rosette nanotubes with tunable chiroptical properties. The fast pathway (steps 1 and 2) involves premixing concentrated solutions of **11** (2.0 mM) and L-Ala (4.0 mM) prior to dilution to the desired concentration. The slow pathway (steps 3–5) involves prediluting the stock solution of **11** (to 0.04 mM) prior to adding L-Ala (10 equiv.). Steps 1 and 2 show that the nanotubes are kinetically stable in the presence of a promoter, and steps 3–5 show that the formation of the nanotubes can be triggered with a promoter. Both pathways lead to the helical rosette nanotubes. Reprinted with permission from ref. 21. Copyright 2003, American Chemical Society.

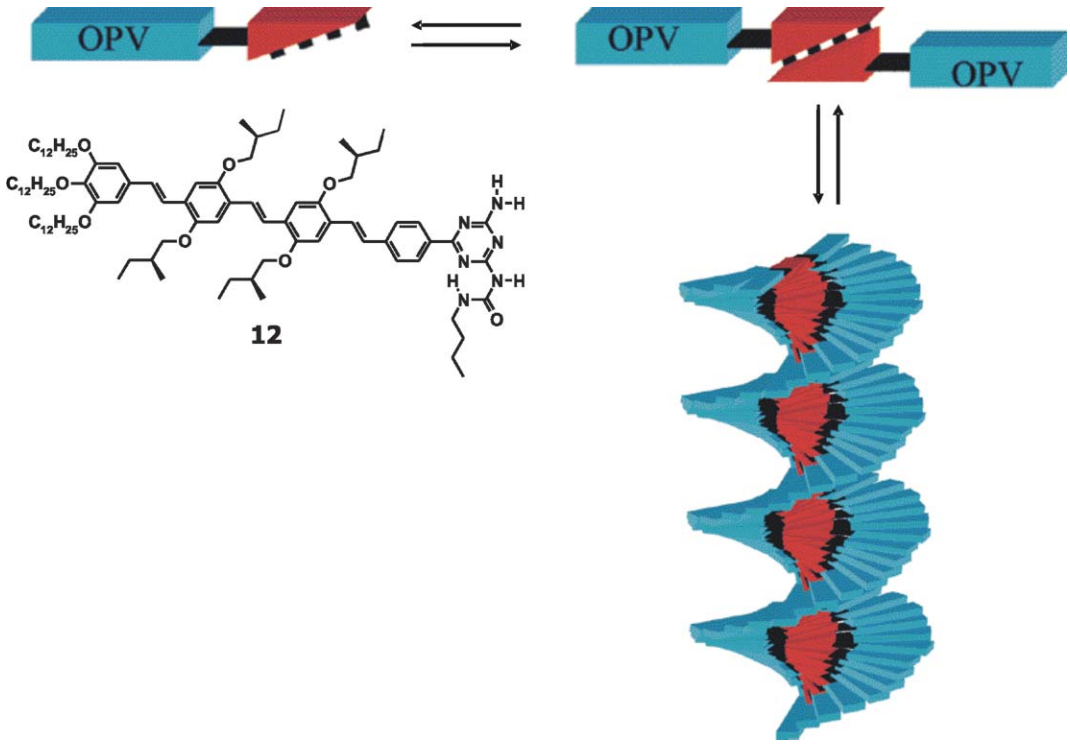

Fig. 10 Schematic representation of the hierarchical organization of MOPV **12** in dodecane.

oligo(*p*-phenylene vinylene) (OPV) units are attached to the triazine (Fig. 10). Similar to the mono-functional ureidotriazine molecules **6–9** with chiral side chains (Fig. 6) the chiral side chains on the OPV unit at the periphery of the molecule are able to induce the formation of a helical stack of hydrogen-bonded ureidotriazine dimers.

Whereas ureidotriazines without OPV units require a hexamethylene linker between the hydrogen-bonded triazines to induce helical order, the π–π interactions in OPV triazines are sufficiently strong to give helical columns of monofunctional derivatives. The well-defined structure of the mono-functionalized oligo(*p*-phenylene vinylene) (MOPV) columnar aggregates provides an attractive scaffold for studying energy transfer in these columns.[34] Indeed, when a small number of ureidotriazine units with a longer conjugation length (MOPV4) are incorporated within a columnar stack of MOPV3 a highly efficient energy transfer from the MOPV3 molecules to the MOPV4 molecules is observed (Fig. 11). The energy is transferred to the MOPV4 because the absorption maximum of the MOPV4 is red shifted compared to the MOPV3.

Another interesting application of the defined architecture of hierarchical self-assembled columnar structures is the

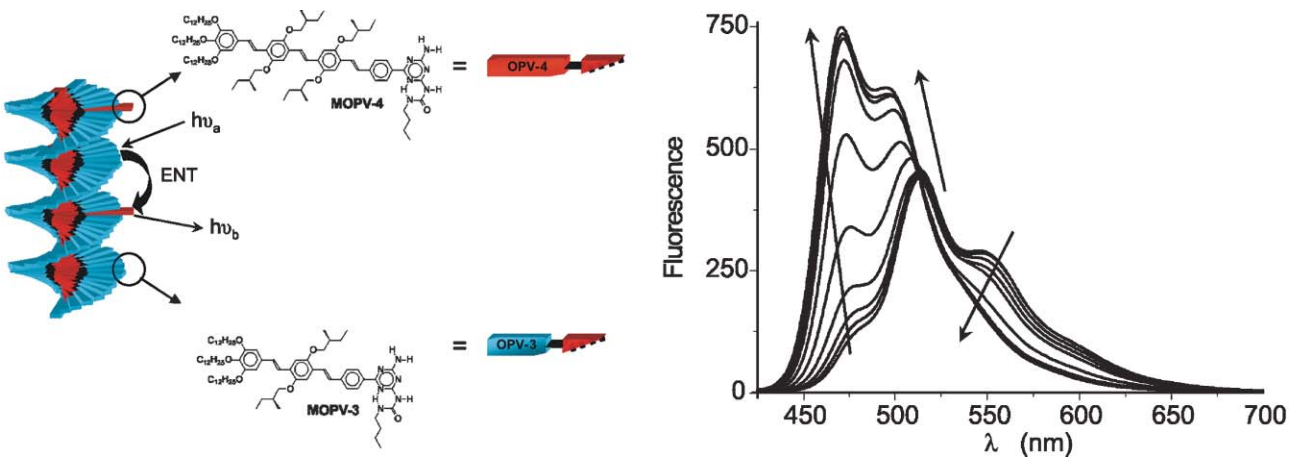

Fig. 11 Temperature-dependent fluorescence spectra of a MOPV3 (blue) solution in dodecane with 1.2 mol% trap molecules MOPV4 (red). The arrows indicate a temperature rise from 0–90 °C. At high temperatures, when the oligomers are molecularly dissolved, the presence of MOPV4 cannot be distinguished. At low temperatures, when mixed stacks are present, the spectrum resembles a molecularly dissolved MOPV4 spectrum. This is a consequence of very efficient energy transfer from MOPV3 to the isolated trap molecules in the ordered assembly.

selective binding or transport of ions. Gottarelli and Spada, reported[35,36] the enantioselective extraction of chiral potassium salts from water into the organic phase by lipophilic deoxyguanosine derivatives. The anionic enantiomers show preferential binding, due to the homochiral helical architecture of the columnar aggregate. The helical columnar aggregate is even capable of inducing a Cotton effect in the achiral potassium *N*-(2,4-dinitrophenyl)glycinate. Intriguingly, for some of the anions the octamer and polymer show opposite selectivity, illustrating the difference in supramolecular chirality of the two. The use of these polymers as artificial ion channels is currently under investigation, as the apolar sidechains would allow incorporation into a membrane.

Conclusion

Nature is using a modular approach to produce large functional aggregates from building blocks, which are orders of magnitude smaller. Hierarchical self-assembly is nature's solution to make this process as reliable and versatile as possible. Chemists have recently begun to mimic some of the aspects of hierarchical self-assembly of columnar aggregates. In these systems, multiple hydrogen bonds provide the strength and specificity needed for the formation of aggregates with large solvophobic surfaces. One level higher in the hierarchical process, stacking of these surfaces brings about specific folding and/or aggregation, resulting in columnar aggregates. Detailed characterization of such aggregates in solution is by no means trivial, but probing supramolecular chirality with CD spectroscopy has proven itself as a valuable tool for studying the details of aggregation. Several challenges remain, among which are the precise control over the length of the aggregates and the formation of a controlled tertiary architecture. Although the typical length-scale of the aggregates described in this review makes them of interest to bridge the gap between conventional molecular objects and top-down structures created by lithographic techniques, research in that area has hardly started.

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