



## Supramolecular one-dimensional objects

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### Abstract

Preparing polymer-like materials through supramolecular chemistry is an area of growing interest, yet full understanding of how non-covalent forces may be used to prepare such materials is lacking and as a result the success of these strategies is often serendipitous. Recent examples of discrete one-dimensional supramolecular fibers employing the most important types of non-covalent interactions (metal coordination, hydrogen bonding,  $\pi$ - $\pi$  stacking, hydrophobic effect) illustrate our current ability to prepare these types of materials and point the way for future designs. © 2001 Published by Elsevier Science Ltd.

### 1. Introduction

Advances in our understanding of molecular organization in living systems have revealed that they are built from small building blocks and assembled into complex hierarchies of functional superstructures. Many of them are constructed by self-assembly, meaning that the component parts spontaneously aggregate into a well-defined object based purely on the chemical structure and geometry of the subunits and do not require external guidance to yield the desired product. Lehn was one of the first to realize that these types of self-assembled structures could be mimicked by chemists [1] and potentially have properties and applications unique to this new class of materials [2,3]. One important subclass of these supramolecular materials are those that are one-dimensional, yielding a fiber or string-like object. These systems have also been termed supramolecular polymers [4]. Nature utilizes many different one-dimensional supramolecular polymers, for example actin filaments and microtubules. These fibers illustrate some of the chief advantages that supramolecular polymers

have over traditional covalent polymers such as dynamic assembly and disassembly, and are intimately involved in such complex processes as motility, chemical transport, and structural integrity. These materials are therefore useful standards by which to judge the potential scope of the field and the relative success of existing synthetic systems.

Fig. 1a depicts an actin filament (red) coated with tropomyosin (blue) and myosin (yellow) [5–8]. This complex supramolecular fiber has two features which may characterize advanced supramolecular polymers. First, the actin polymer is dynamic in that it can be repeatedly assembled and disassembled in a controlled fashion based on the environment in which it is located (subunit, ion and ATP concentration). Second, the polymeric filament displays a chemically diverse surface allowing it to interact with its environment in a specific and sophisticated way (actin–myosin interactions are responsible for muscle contraction and cell division amongst other things). The ability to prepare this type of advanced polymer that can react and adapt to the environment in which it is placed is clearly desirable. This goal will only be achieved with an understanding of the types of weak interactions normally involved in their synthesis. A stable well-defined nanostructure can only form if it has a significant thermodynamic advantage in comparison with the starting material and all the possible intermediates. In other words, the final supramolecular product should represent the global thermodynamic minimum for a given set of self-assembling subunits. Therefore, the interactions between the structural building blocks should be highly directional and

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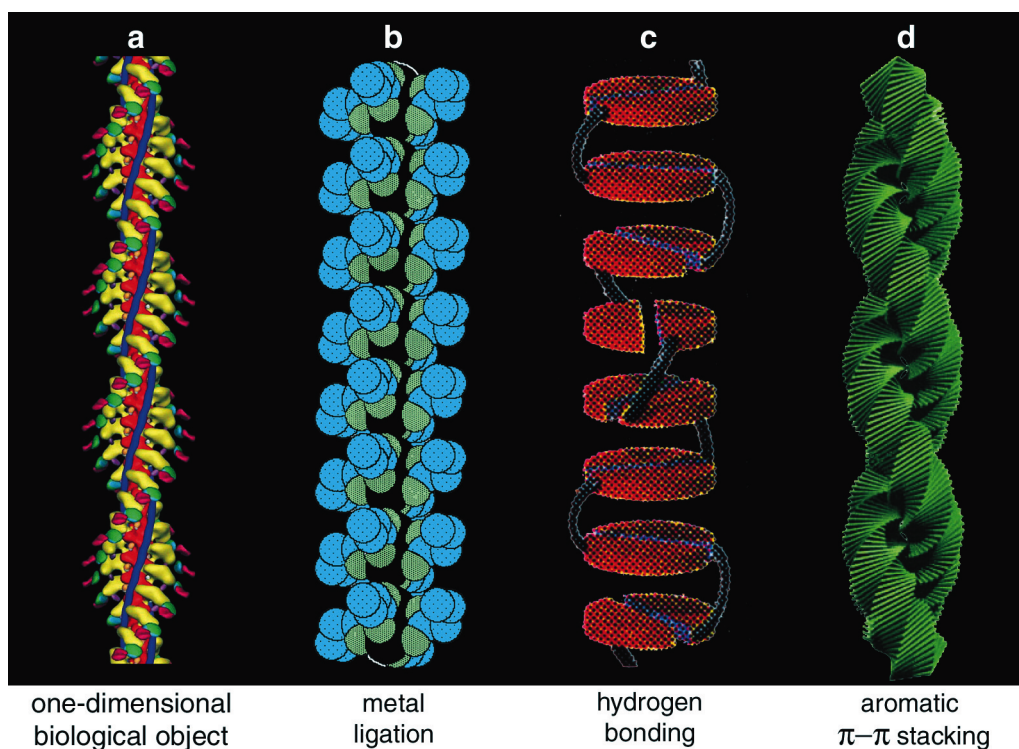


Fig. 1. (a) An actin filament decorated with myosin heads. (b) Terech's monomolecular thread prepared using metal ligation. (c) Meijer's helical fiber formed through hydrogen bonding. (d) Nolte's double helix formed through  $\pi$ - $\pi$  stacking.

cooperative, and should readily occur on a time scale of the self-assembling process. Most studies of molecular recognition are based on a specific type of non-covalent interactions, i.e. hydrogen bonding [9–11], metal–ligand coordination [12–14], or aromatic  $\pi$ - $\pi$  stacking [15–17], since their geometry is often predictable. This review focuses on recent application of these forces to prepare discrete one-dimensional materials.

## 2. Metal coordination

Fig. 1b [18,\*19] is an example of a self-assembling one-dimensional polymer in which the primary force guiding the assembly is metal coordination. Terech uses a simple ligand (ethylhexanoic acid) to bind  $\text{Cu}^{2+}$  ions. This forms a sandwich-like structure composed of two copper ions coordinated by four alkylacid ligands. These sandwiches are able to stack upon one another in such a way that the copper ion from one pair can favorably interact with an oxygen of an adjacent copper–ligand sandwich. Although a given bimetallic tetracarboxylate complex is relatively rigid, inter-complex interactions are more flexible and allow for curvature of the 'monomolecular thread'. Terech's organometallic wires illustrate one of the great attractions of self-assembling systems in that simple subunits of proper chemistry and geometry may

come together to form larger and more complicated objects in a rapid and facile way.

## 3. Hydrogen bonding

Utilization of hydrogen bonding is the most common method of driving molecules into supramolecular structures in both natural and synthetic systems. Recently Meijer and coworkers described a beautiful example which forms a one-dimensional supramolecular polymer [\*20] depicted in Fig. 1c. His system is based on the hydrogen bonding of a functionalized ureidotriazine moiety which can form a homodimer connected by four hydrogen bonds. To the periphery of this pair are attached solubilizing chains which can be modified to allow solubility in both organic solvents and water. The subunits dimerize in hydrogen bonding permissive solvents and these pairs are then able to stack upon one another in non-polar solvents such as dodecane to form columnar aggregates. Meijer takes this system to a higher level of sophistication by linking two of the ureidotriazine units to one another via a flexible spacer and using a chiral solubilizing chain. Together this forces the columnar aggregates to adopt a helical conformation in solvents that promote hydrogen bonding and pair stacking. The helical columns thus formed have a diameter of 1.5 nm and have a con-

centration dependent length ranging from 10 nm at 0.2% by weight and up to 19 nm at 1.0% by weight.

#### 4. $\pi$ - $\pi$ Stacking

Although aromatic  $\pi$ - $\pi$  stacking interactions are much weaker than metal-ligand coordination or hydrogen bonding, their utilization for construction of one-dimensional ensembles can be very successful as well. Nolte and co-workers [\*21] have recently reported on the self-assembly of chiral disk-shaped molecules that spontaneously organize into helical superstructures exclusively via  $\pi$ - $\pi$  stacking interactions. These molecules have a central phthalocyanine ring with four crown ether substituents attached to its periphery. The crown ether moieties, in turn, bear chiral aliphatic tails. When the aggregation occurs in organic solvents the disk-like molecules form one-dimensional stacks with a twisted morphology, so that the plane of each disk is rotated by  $6.5^\circ$  along the stack axis with respect to adjacent neighbors. The self-assembling process then brings the system to the next hierarchical level when two or more right-handed one-dimensional objects wrap around each other to produce left-handed superhelical structures (Fig. 1d). Perhaps, the most interesting finding made by authors is related to blocking of 'helicity transfer' from the peripheral chiral tails to the central aromatic core. This was achieved by adding potassium ions prior to aggregation of disk-like molecules. Strong complexation between the crown ether moieties and  $K^+$  ions prevents staggering orientation of molecules which instead pack exactly one on top of the other in an 'eclipsed' (face-to-face) fashion. As a result, the fibers adopt a cylindrical morphology and the helicity disappears almost completely in spite of the presence of chiral side chains. This example demonstrates that supramolecular chirality of one-dimensional objects can be tuned in a controlled way by simply changing the strength and directionality of non-covalent interactions.

#### 5. Hydrophobic effect

Entropically driven formation of micelles in aqueous solutions [22–24] is one of the simplest and well-known examples of self-organization of amphiphilic molecules. Therefore it offers an easy way for construction of supramolecular and covalent polymers with exceptionally high molecular weights. This was recently demonstrated by Bates and co-workers [\*25], who reported on worm-like micelles formed by diblock copolymer of ethylene oxide and butadiene in water. These flexible cylindrical objects have a well-defined cross-section and lengths on the order of microns. The structures can exist in a fully isolated state in a dilute concentration regime due to their much greater amphiphilicity relative to conventional non-ionic surfac-

tants. In other words, formation of these worm-like micelles does not require any additional stabilization which is normally achieved by packing interactions between cylinders. The most outstanding achievement of this work is the highly controlled covalent fixation of these structures through internal cross-linking of the butadiene core. The authors performed cryo-transmission electron microscopy experiments which clearly demonstrated that the cylindrical morphology remains intact upon the conversion of these supramolecular objects into covalent macromolecules (Fig. 2a). The molecular weight of the resultant polymer can be as high as one billion daltons which is nearly three orders of magnitude higher than that of typical synthetic polymers. This particular system proves yet another time that supramolecular chemistry can be used very effectively for the preparation of structures and materials inaccessible via traditional synthesis.

#### 6. Multiple non-covalent interactions

All the systems described above involve one primary type of non-covalent interaction. This general feature makes the quest for even more sophisticated systems quite obvious. That is the synthesis of self-assemblers that would be driven to aggregate through different types of interactions simultaneously. Recently such a system was reported by Fenniri et al. [\*26]. The authors synthesized a molecule which has complementary hydrogen bonding sites analogous to those existing in natural nucleobases (guanine and cytosine) and attached a chiral amino acid on its periphery. They also introduced a hydrophobic methyl group on the outside of the nucleobase-like moiety in order to reduce the competition of water molecules for the hydrogen bonding and facilitate the formation of six-membered macrocycle referred to as a rosette. It was found that the self-assembling process in water proceeds through two consecutive steps: first the molecules organize into rosettes and then these macrocycles stack into one-dimensional objects or nanotubes (Fig. 2b). The formation of rosettes is primarily driven by hydrogen bonding, whereas their stacking is caused by electrostatic interactions [27,28] and hydrophobic effect [29,30]. This is the first example of both H-bonded macrocycles and nanotubular objects spontaneously forming in water and is a particularly beautiful example of molecular programming.

Our laboratory has also become interested in one-dimensional supramolecular polymers. Two examples have recently been prepared, one to investigate its ability to interface with biological systems and the other to modify traditional synthetic polymers. The first example deals with a system designed to promote the healing of damaged and diseased tissue [31]. Toward this end the one-dimensional fibers are prepared via the self-assembly of biocompatible peptide-amphiphiles (Fig. 2c). These amphiphiles have the geometry such that they will prefer to self-assemble into

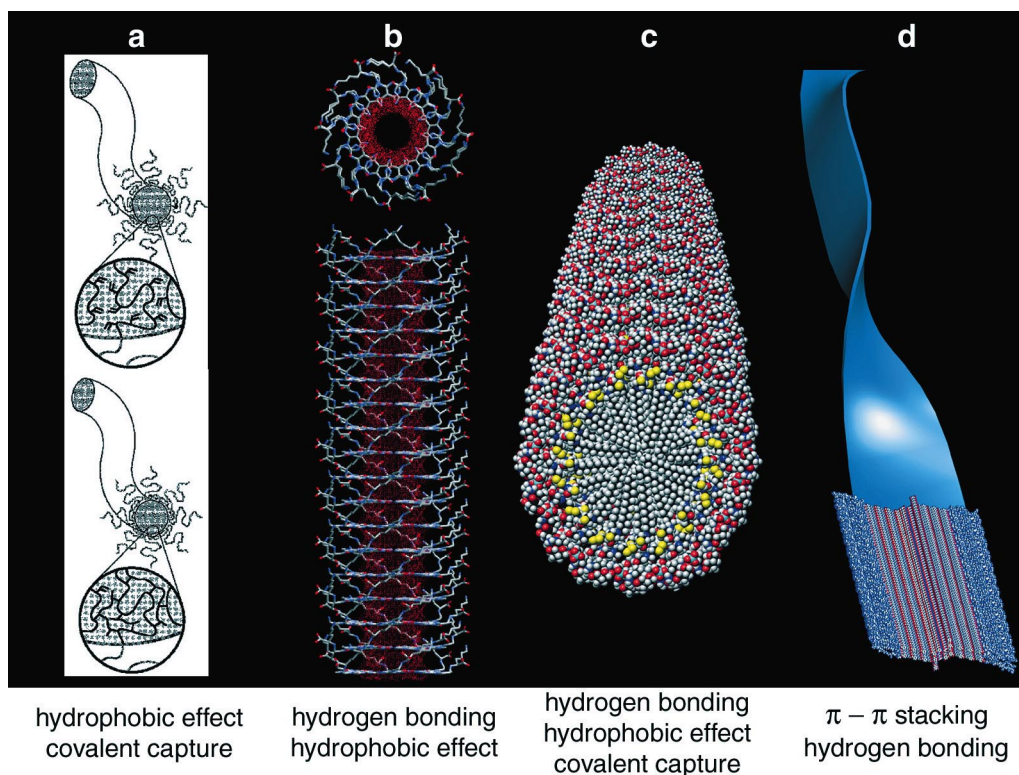
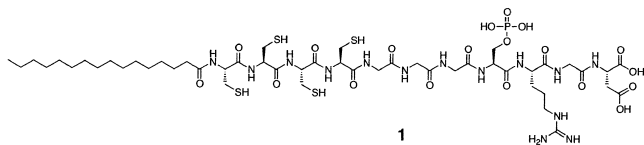


Fig. 2. (a) Bates' giant worm-like micelles showing both the reduced (top) and covalently captured (bottom) forms. (b) Fenniri's nanotube which displays two stages of self-assembly: formation of disks through hydrogen bonding and stacking of these disks to form a tube through the hydrophobic effect. (c) Stupp's peptide-amphiphile nanofibers which can be reversibly self-assembled and covalently captured. (d) Stupp's dendron rodcoil nanoribbon which utilizes  $\pi - \pi$  stacking and hydrogen bonding during self-assembly.

cylindrical micelles as judged by the rules for amphiphile self-assembly described by Israelichvili's theory [32]. The use of a short peptide allows for rapid and facile synthesis using standard solid phase methodology and incorporation of nearly any natural or unnatural amino acid allows for a broad range of chemistries to be displayed on the one-dimensional object's surface. Initial studies have focused on molecule **1** shown below.



The amino acid selection for the peptide-amphiphile **1** provides for several important characteristics of the material. First, the highly charged nature of the peptide allows the material to be readily dissolved in water at neutral pH. However, upon acidification of the solution, the net charge of the molecule changes from  $-3$  to neutral as several of the acidic groups are protonated. When this occurs, the coulombic repulsion between molecules is eliminated and the hydrophobic alkyl tails are able to aggregate to form a cylindrical micelle (Fig. 3). These charges create a pH induced switch for self-assembly allowing the system to assemble and disassemble based on the pH environment.

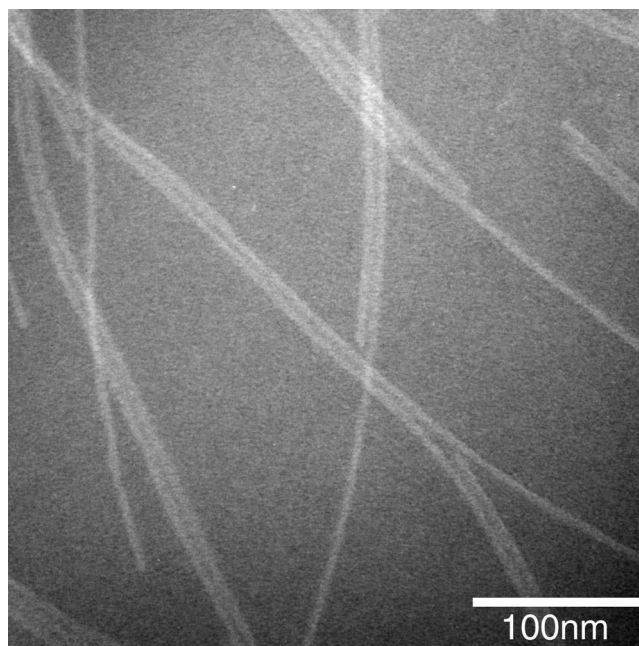
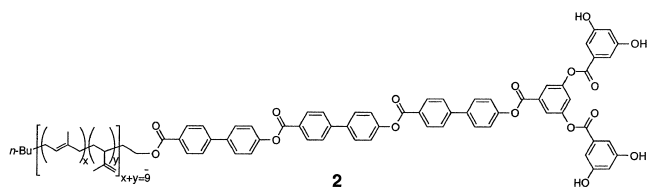


Fig. 3. Negative stain transmission electron microscopy image of molecule **1** after pH induced self-assembly. Average fiber diameter is between 5 and 8 nm while the length can be in excess of a micron.

Second, the tetra-cysteine sequence just before the hydrophobic tail allows the self-assembled material to be covalently captured through the formation of intermolecular disulfide bonds. Covalent capture is an effective tool for stabilization of preorganized self-assembled structures as illustrated in the work of Bates [25] above and other examples in the literature [33–37]. This effectively allows the system to be locked into a covalent material with the same morphology as that of the self-assembled object. This makes the crosslinked product stable at high pH where before crosslinking it would have disassembled. Given the molecular weight of the peptide-amphiphile and the length of the self-assembled fibers as imaged by transmission electron microscopy, the molecular weight of the polymer after crosslinking is  $\sim 2 \times 10^7$  Da. Because the tetra-cysteine region is centered in the peptide-amphiphile the formation of disulfide bonds only occurs within a single fiber and does not link multiple fibers to one another. Like the pH induced self-assembly, the covalent capture is also reversible simply by oxidizing and reducing the material. These two reversible steps allow one to move from dissolved molecule to supramolecular fiber to high molecular weight polymer and back again at will, simply by altering the environment in which the material is placed.

The second system prepared in our laboratory represents a unique example of highly directional self-assembly involving cooperative interplay of both hydrogen bonds and  $\pi$ -stacking of rigid aromatic units (Fig. 2d). We synthesized triblock molecule **2** referred to as dendron rodcoil (DRC) which is composed of the hydroxyl-terminated dendron (generation 1), biphenyl-ester mid-section, and oligoisoprene tail [\*38]



Each block plays its specific role in the self-assembling process. Phenolic and carbonyl groups of the dendron are strongly driven to form hydrogen bonds in non-polar solvents resulting in formation of head-to-head dimers. The biphenyl ester units can then stack the preformed dimers in at least one dimension via aromatic  $\pi$ -stacking interactions. The oligoisoprene segment, on the other hand, is readily solvated by non-polar organic solvents and can remain rotationally free after the aggregation of molecules through the rod-dendron portion takes place. This reduces the loss of conformational entropy upon the aggregation and makes the self-assembling process thermodynamically more favorable. When the DRC is dissolved in aprotic solvents, a spontaneous gelation rapidly occurs and the organic media transforms into birefringent gel at exceedingly small concentrations of DRC ( $\sim 0.2$  wt.%). This

initial observation suggested formation of a network which can immobilize organic solvent in a highly effective way. Specifically, the ratio of solvent to DRC molecules can be as high as 7000:1. Transmission electron microscopy of the samples prepared from the DRC gels diluted in excess dichloromethane revealed the presence of one-dimensional structures with uniform width of 10 nm and length on the order of microns (Fig. 4).

The width of these strands is consistent with bimolecular packing of DRC molecules which are  $\sim 6.5$  nm long in their fully extended conformation. The morphology of these structures was determined by atomic force microscopy experiments which showed that the strands have a uniform thickness of 2 nm. Therefore DRC forms well-defined bimolecular ribbons which lay flat on the substrate used for imaging.

There are several important features of these supramolecular structures which distinguish them from typical organogel fibers [39]. First, the width and the thickness of DRC ribbons is on the size scale of individual molecules, whereas most organogelators form strands with diameters hundreds or even thousands of times greater than the size of the fiber-forming molecules. The cross-section of DRC ribbons is nearly monodisperse throughout their entire length, which is in contrast to typical organogel fibers which display a continuous variation in their diameter. Second, the DRC nanoribbons exist in a fully isolated state (at low concentration) as opposed to uncontrolled spontaneous formation of bundles of fibers observed in most other systems regardless of concentration. We believe that the presence of two wedge-shaped dendritic segments located in the center of the nanoribbon prevents their

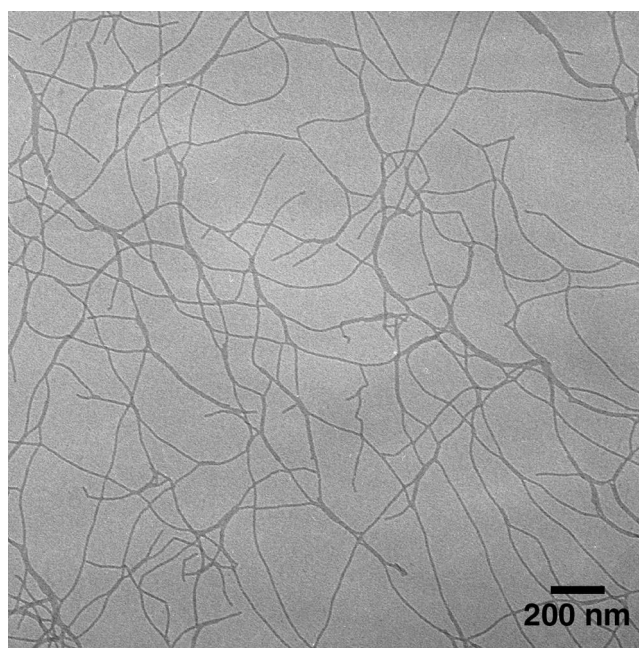


Fig. 4. Transmission electron microscopy image of DRC structures formed in dichloromethane.

aggregation in one direction (perpendicular to the plane of the ribbon), whereas the oligoisoprene coil segments placed on the periphery are highly solvated in organic solvents (as was confirmed by NMR) and thus prevent the edge-to-edge stacking of ribbons. The high structural fidelity of this self-assembling process and nearly precise control of the cross-section of ribbons is therefore encoded in the specific molecular architecture of the DRC and the presence of different functionalities. The observed structures are supramolecular polymers with ‘molecular weight’ approaching  $10^8$  Da. Current work on this system has revealed that these rigid supramolecular objects can profoundly change bulk properties of conventional polymers such as polystyrene and poly(2-ethylhexyl methacrylate). This was observed by measuring the orientation factor of the polymer chains in pure and gel-derived samples which revealed much higher order parameter for DRC-containing materials.

## 7. Conclusion

Collectively these examples are a snapshot of the current state of the art in one-dimensional supramolecular polymers. Although these synthetic systems are not yet to the level of sophistication of their biological predecessors, it is obvious that this gap is decreasing rapidly with the most important advances required in the future in the areas of fiber dynamics and chemical functionality.

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