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Peptide–Polymer Hybrids

Learning from Nature: β-Sheet-Mimicking Copolymers Get Organized

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β sheets · block copolymers · hydrogen bonds · peptides · supramolecular chemistry

The solution structures formed by coil–coil copolymers arise from the selective solvation of one of the two blocks and have been well described. In most cases in such relatively simple synthetic structures there are no specific attractive forces that can aid the aggregation process. Nature, however, provides plenty of inspiring polymeric architectures that are shaped and ordered hierarchically by noncovalent forces. The high level of structural definition displayed by proteins, for example, is unmatched by synthetic polymers. An emerging area of interest in polymer science tries to combine the best of both worlds, the natural and the synthetic, by conjugating synthetic polymers and β-sheet-forming peptides. Understanding the supramolecular organization of the block copolymers driven exclusively by the intermolecular attractive forces of the peptide sequence is of particular interest. Not only do these peptide–polymer hybrid structures present an interesting new class of materials, they can also provide important insights into self-organization processes prevalent in nature.

1. Introduction

Bioinspired block copolymers have recently received significant attention. The motivation behind these research efforts extends from medical applications to understanding the basic rules of nanoscale self-assembly. Of the many natural polymers and oligomers that have been conjugated with synthetic macromolecules, proteins and peptides have been investigated the most thoroughly.[1–4] Among the first reports on polymer–peptide conjugates were those Gallot et al.,[5–7] in which polydisperse peptides were typically used. In this review we will focus exclusively on β-sheet-forming peptides and their analogues for which the molecular weight and amino acid sequence is precisely defined. Synthetic routes to block copolymers consisting of polydisperse polypeptide blocks and polymer–protein conjugates have been reviewed elsewhere.[1,8,9] Here, only those hybrid materials will be addressed in which the supramolecular structure of the polymer–peptide conjugate arises exclusively from the self-organizing features of the peptide block.

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2. Linear Oligopeptide Copolymers

The first example of a β-sheet-forming peptide attached to poly(ethylene glycol) (PEG) was reported by Lynn and coworkers.[10] A sequence of 26 central core amino acids of the β-amyloid peptide was synthesized on a solid support using a PAP Tentagel resin. Cleavage from the resin gave the PEG–peptide conjugate. Individual fibrils were formed with widths (ca. 8 nm) corresponding to the molecular dimensions of the peptide. Fibril formation of the copolymer depended on concentration, ionic strength, and pH. It could be shown that the hybrid material adopts a structure consisting of up to six laminated parallel β sheets propagating along the fibril axis surrounded by the PEG block.[11–13] The data further suggested that the peptide strands within the sheet were fully extended. Each individual sheet deviated slightly from planarity, leading to a helically twisted fibril. In essence, the observed fibrils were formed by a twisted stack of six β-sheet tapes. It was suggested that this twist might be the factor

limiting the number of sheets within a stack. While the peptide sequence alone formed bundles of fibrils irreversibly, these could rarely be observed in the copolymer or even copolymer/peptide mixtures. It was suggested that the PEG block coats the surface of the fibrils, thereby preventing or retarding lateral aggregation.

Inspired by the structure of *Bombyx mori* silk fibroin, Sogah's group synthesized segmented block copolymers in which a tetrapeptide sequence (Gly-Ala-Gly-Ala) alternated with oligo- or poly(ethylene glycol) chains.[14,15] Phase separation as a result of β-sheet formation could be observed in thin films of the copolymers.

The groups of Klok and Hamley prepared AB diblock and ABA triblock copolymers consisting of an amphiphilic β-strand peptide sequence (B) and PEG (A). The diblock copolymers were synthesized on a PAP Tentagel resin; the triblock copolymers were prepared by conjugating the resin-bound diblock with a PEG-monocarboxylic acid. FTIR and SAXS/WAXS (small- and wide-angle X-ray scattering) investigations revealed that the block copolymers formed lamellar superstructures of PEG alternating with antiparallel β sheets in the solid state.[16] The same groups investigated a range of similar diblock and triblock copolymers in aqueous solution. They found that the pH sensitivity of the peptide strand was less pronounced in the PEG conjugate than in the native peptide.[17] Larger fibrils, formed by a hierarchical self-assembly of β-sheet tapes, were observed for a PEG–peptide diblock copolymer. It was proposed that these could be similar in shape to those modeled by Aggeli et al. for native β-sheet peptides, that is, consisting of twisted stacks of β sheets.[18]

A comparison of native β-sheet peptides with their PEG conjugates was also carried out by Collier and Messersmith.[19] Diblock and ABA triblock copolymers of a β-sheet peptide (A) and monodisperse undeca(ethylene glycol) (B) chains were synthesized. As noted in the previous reports, PEG conjugation strongly prevented lateral aggregation of the fibril-forming peptides. Individual fibrils of uniform width (8 nm) were observed that extended over several hundred nanometers.

Kelly et al. could show that preorganized threonine–valine diads $(Thr\text{-}Val)_2$ attached to the 2- and 8-positions of a dibenzofuran template form fibers composed of β sheets.[20] In contrast, linear analogues, $(Thr\text{-}Val)_x$ repeats of less than $x = 5$, do not associate intermolecularly.[21] Using a carbazole instead of a dibenzofuran, the Börner group demonstrated that the same holds for a PEG conjugate (Figure 1).[22] Linear fibers up to several micrometers in length and a few nanometers in width (4 ± 3 nm) and height could be shown by atomic force microscopy (AFM) and transmission electron microscopy (TEM).

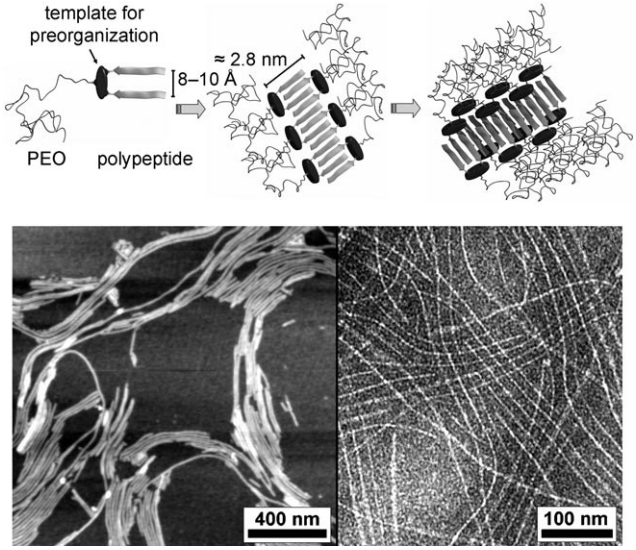

Figure 1. Fork-like preorganization of short peptide strands results in the formation of extended fibers. Top: Arrows represent β sheets consisting of $(Thr\text{-}Val)_2$. Bottom left: AFM micrograph; bottom right: TEM image.[22]

Recently, Hayashi and Kiso et al. described a synthetic strategy that allows the preparation of strongly aggregating β-sheet peptides.[23] During the solid-supported synthesis, aggregation was prevented by O-acylation of threonine residues, thereby disrupting the amide backbone structure. After cleavage from the resin, an intramolecular O-N acyl migration was induced by pH change. Börner et al. exploited this synthetic strategy in the synthesis of H_2N-Gly-Trp-$(Thr\text{-}Val)_5$-Gly-PEG[24] as well as poly(butyl acrylate) (PBA)-$(Thr\text{-}Val)_5$-Phe-Gly-OH[25] conjugates. The resulting hybrid polymers formed micrometer-sized fiberlike aggregates in water (PEG conjugate)[24] as well as in diethyl ether/methanol mixture

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(PBA conjugate).[25] The PEG–peptide hybrid forms fibers 2 μm in width and several millimeters in length. Such large dimensions, which can not be directly correlated to the molecular structure of the polymer, must therefore be the result of a hierarchical self-organization. Owing to the large difference between the size of the aggregated molecules and the dimensions of the fibers, several stages of self-assembly are conceivable. The authors proposed that the fibers arise from flat stacks of antiparallel β sheets, with the sheets extending parallel to the fiber axis. Furthermore, the width of the fibers is limited owing to the overall dipole moment of the (nontwisted) fibers. In contrast, the PBA–peptide conjugate forms helically twisted tapes of β sheets. The authors propose that this occurs in order to cancel out any residual dipole moments of the β sheet in organic media with low dielectric constants. It could be shown by AFM that the helical β sheets formed macroscopic gels by formation of double- and triple-helical strands.

A recent elegant report by the Frauenrath group highlights the potential of peptide block copolymers consisting of β sheets for the organization of functional groups in solution.[26] A tetra(L-alanine) segment was constructed in a stepwise fashion at the end of a hydrogenated short poly(isoprene) chain. The N terminus of the tetrapeptide was further functionalized with a diacetylene moiety. They found that depending on whether the diacetylene moiety was terminally functionalized with an acetamido group, the block copolymer formed parallel or antiparallel β sheets in dichloromethane solution. Only in the parallel β sheets were the diacetylene moieties perfectly arranged for a topochemical UV-induced solution polymerization. A molecular model was proposed by the authors, in which two parallel β-sheet tapes form a tubular double-helical aggregate. This thesis was supported by AFM studies in which double-helical fibers were observed that extended over several micrometers in length and with a uniform width of approximately 5 nm (Figure 2).

A completely different synthetic approach towards peptide–polymer conjugates was described by van Hest et al.[27] Monodisperse polypeptides $([Ala\text{-}Gly]_3\text{-}Glu\text{-}Gly)_n$ with $n = 10$ or $n = 20$ were prepared by protein engineering. The polypeptide carried cysteines at the C and N termini which allowed conjugation with a monomaleimide-functionalized PEG. TEM revealed the formation of fibrils in water. It was proposed that a true antiparallel β-sheet copolymer was formed which then stacked orthogonal to the direction of hydrogen bonds (Figure 3). AFM images obtained by spin-coating the material from water revealed individual β-sheet fibrils 2 nm in height and several micrometers in length. An accurate width could not be determined owing to resolution limitations of the AMF tip.

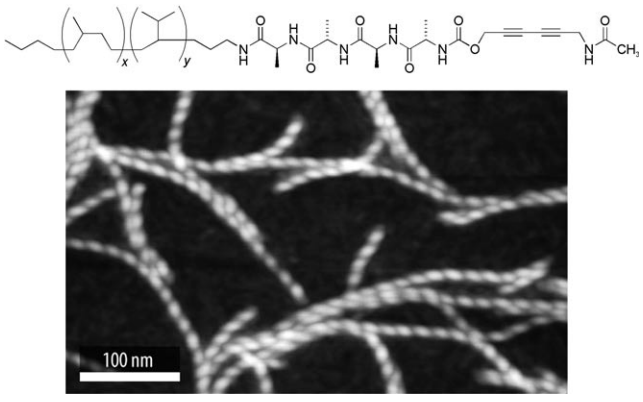


Figure 2. Top: A tetrapeptide–poly(isoprene) conjugate is employed in the solution organization of topochemically polymerizable diacetylene units. Bottom: AFM image of the tube-shaped double helices made up of β sheets.[26]

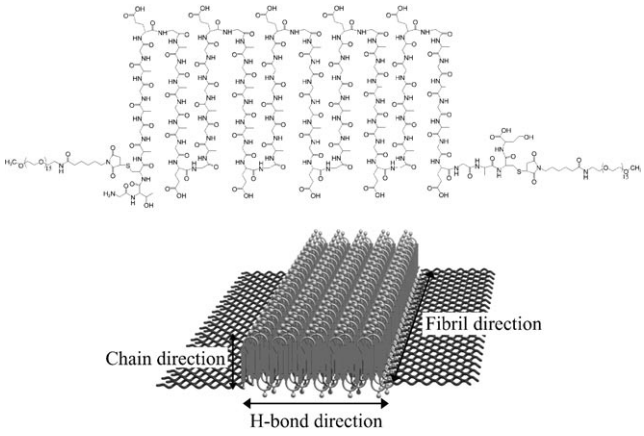


Figure 3. Structural organization of a PEG–peptide–PEG triblock in solution; the peptide 80-mers or 160-mers used were prepared by protein engineering.[27]

3. Cyclic Oligopeptide Copolymers

Self-assembled tubular structures based on various hybrids of β-sheet peptides[28] and shape-persistent macrocycles[29] have also received increasing attention in recent years. One way of constructing hollow tubes is by the sequence-controlled synthesis of cyclic oligopeptides. The first examples of native cyclic peptides built from alternating D and L α-amino acids self-assembling into extended tubes were described by Ghadiri et al.[30–33] The structures formed from cyclic peptides are related to typical pores of β helices, as found, for example, in bacteriophage tail spike proteins[34] and bacterial proteinases.

Polymer chemists have focused on this attractive self-assembling peptide motif only quite recently. The first example of a cyclic peptide–polymer conjugate was reported by Biesalski et al.[35] Lysine residues within the peptide functioned as anchor points for initiator groups for atom-transfer radical polymerization (ATRP). *N*-Isopropylacrylamide (NIPAM) was polymerized from the peptide initiator in a controlled radical polymerization. It could be shown by AFM that the peptide initiator and the copolymer both formed tubular aggregates in water; in the case of the copolymer aggregates with lengths of roughly 80 nm and a height of 12 nm were observed. A core–shell structure could clearly be visualized for the peptide copolymer (Figure 4). It was proposed that stacks of circular two-dimensional β sheets

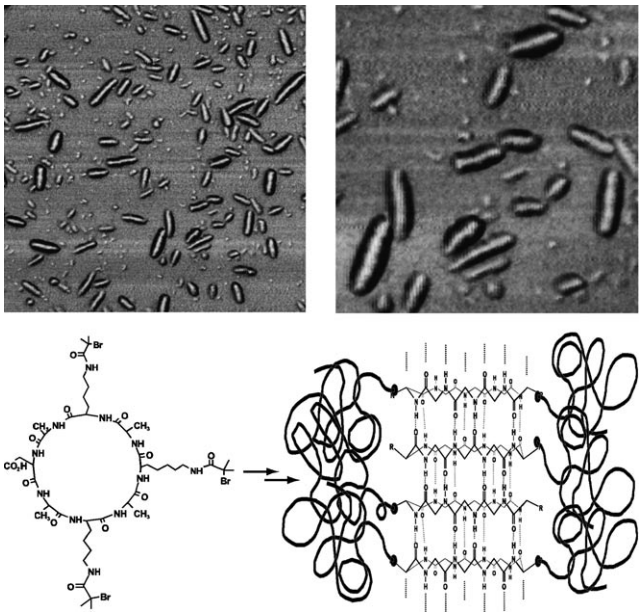


Figure 4. Tubular assemblies of cyclic peptide–polymer conjugates. Top: AFM phase image (left: image edge 2 μm; right: image edge 0.8 μm). Bottom left: Cyclic peptide initiator for ATRP; bottom right: proposed aggregation of the copolymer.[35]

formed the core and poly(NIPAM) made up the shell of the observed aggregates. It could be shown further that the length of the aggregates remained constant up to a critical length of the surrounding polymer.[36] For very long polymer chains, however, the aggregates started to break up and form smaller particles presumably as a result of repulsive forces. No further aggregation of the peptide tubes was observed.

Following up on their work on linear oligopeptide copolymers based on reversible addition–fragmentation chain transfer (RAFT) and ATRP initiators,[37,38] Börner et al. prepared cyclic peptide copolymers in solution on a multigram scale.[39] Tubelike structures with widths of approximately 4.8 nm that organize further into fiber networks were observed by AFM and TEM. In contrast to Biesalski's work,[35,36] lateral aggregation of the tubes was observed. This was explained to occur through entanglement of the polymer side chains and formation of intertubular hydrogen bonds between the L-glutamine side chains.

Cyclic peptides typically stack in a β-sheet-like antiparallel manner. Of course, for the stacking of the rings there are several possible arrangements of peptide rings, which could result in a random orientation of polymer side chains along the aggregate. Yet in all these arrangements, each ring is always stacked onto the previous one in a perfectly parallel way. Further hierarchical self-assembly into larger aggregates is therefore only possible through noncovalent interactions amongst the polymer side chains or peptide residues.

4. Oligoaramide Copolymers

Employing β-sheet peptides composed of α-amino acids as the superstructure-directing motif is very attractive. In related work in synthetic polymer chemistry one of the challenges is to find viable nonbiological compounds mimicking the intriguing organizational characteristics of β-sheet peptides. Oligo(*p*-benzamide)s (OPBAs) are particularly interesting in this context as they form shape-persistent linear rigid rods with hydrogen-bond acceptors and donors pointing towards the edges of the flat oligomer, thereby mimicking peptide strands in β sheets (Figure 5). The shape persistence,

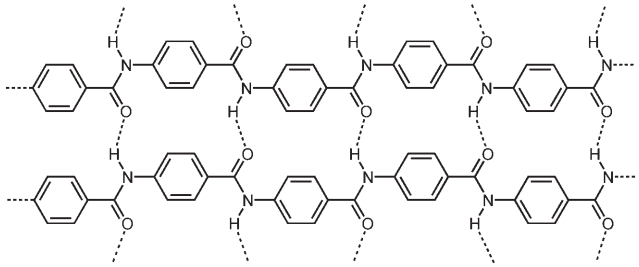


Figure 5. Linear oligo(*p*-benzamide)s mimic β sheets (hydrogen bonds are shows as dashed lines).

that is, the reduced conformational freedom, of the linear oligomers allows the prediction of the geometry and hence simplifies the correlation between molecular shape and superstructure. As oligomers larger than the trimer are virtually insoluble in most organic solvents, several synthetic routes towards longer oligomers were developed in our group using either protected, soluble oligomers or soluble precursors.

The first synthetic route explored made use of the fact that aromatic amides can be transformed into stable imidoyl chlorides. These lack the necessary hydrogen-bond donor and strongly twist the neighboring phenyl groups out of coplanarity. Both effects improve solubility which allowed us to prepare soluble imidoyl chloride precursors up to the tetramer.[40] OPBA–PEG copolymers (Figure 6, top) aggregate strongly in nonpolar solvents.[41] AFM revealed micelles with strongly anisotropic rodlike cores surrounded by a corona of PEG (Figure 6, bottom).[42] In the proposed structure the micellar core is formed by a hydrogen-bonded stack of parallel OPBA chains mimicking a peptide β-sheet. This crystalline micellar core is surrounded by the coil-like PEG block. In all cases, the dimensions of the observed micellar core correlates with the length of the rodlike oligomer. TEM investigations of an OPBA copolymer prepared by a convergent synthetic route confirmed the aggregation observed by AFM.[43]

The synthesis of OPBA was also successfully carried out on a solid support using amide protecting groups to prevent aggregation during synthesis.[44,45] OPBA 7-mers were synthesized with full automation on a solid support and linked to PEG. TEM investigations showed rigid rodlike aggregates with widths of roughly 10 nm, extending up to 1 μm in length. Virtually identical structures were found in chloroform, toluene (Figure 7), and water (not shown). From the data obtained so far, OPBA–PEG copolymers appear to form individual well-defined aggregates that do not assemble further into higher ordered aggregates in solution.

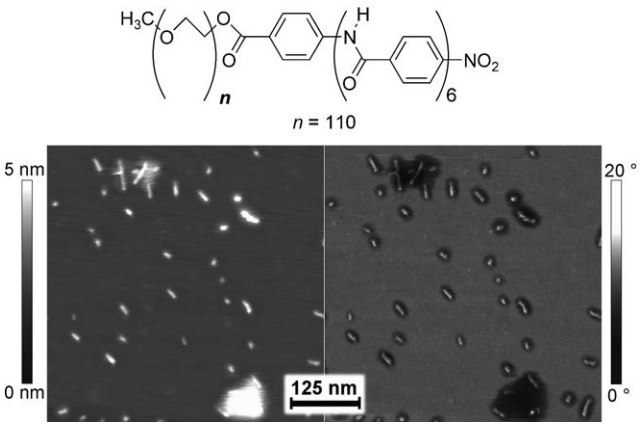
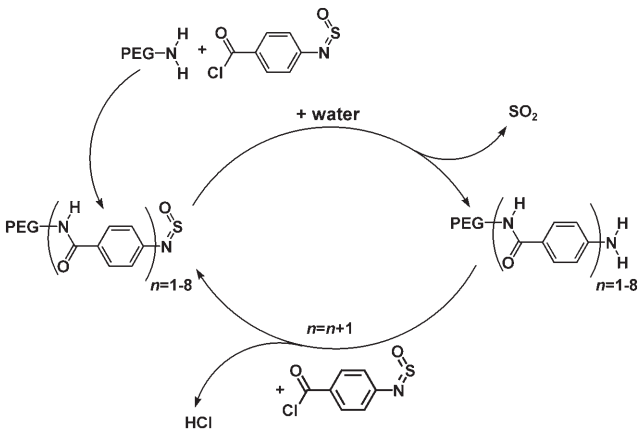


Figure 6. Top: Block copolymer prepared via imidoyl chloride precursors. Bottom: AFM topograph (left) and phase image (right) of a polymer obtained from $CHCl_3$ solution.[42]



Scheme 1. Synthesis of OPBA copolymers on larger scale by automated synthesis.

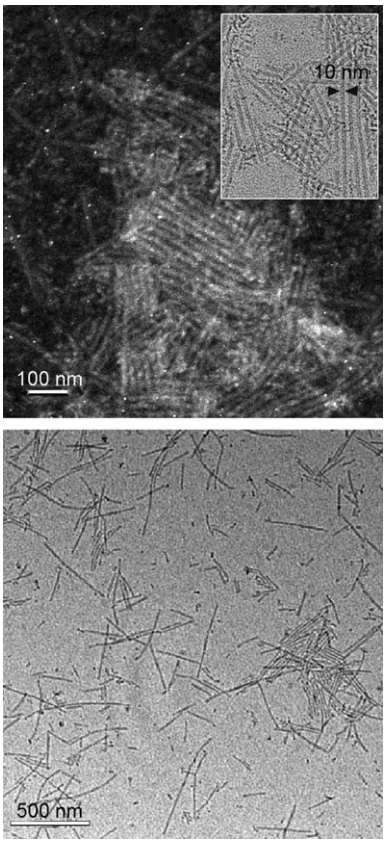


Figure 7. TEM images of an OPBA–PEG rod–coil copolymer. Left: Image from scanning TEM (from chloroform solution); right: TEM image (from toluene). Rodlike micelles can be seen in both images.[45]

Most recently, a fully automated synthesis was developed that allows the stepwise growth of OPBA at the nucleophilic chain end of a polymer.[46] Alternating addition of 4-*N*-sulfinylaminobenzoyl chloride and water to an amine-functionalized PEG allowed the controlled synthesis of OPBA–PEG copolymers on the 150-g scale (Scheme 1). Tapelike aggregates were observed by TEM which were virtually identical to those of the precisely defined materials prepared either on solid support or in solution.[43,45] As noted previously, the width of the aggregate corresponded to the molecular dimensions of the oligoaramide. The straightforward access to larger quantities of OPBA copolymers will enable us to investigate the properties of bulk materials in the near future.

The aggregation motif of the OPBA block copolymers resembles that of the linear β-sheet copolymers. The latter typically form fibrils assembled by a 2D aggregation process (hydrogen bonding and stacking of β sheets) and often aggregate even further yielding networks. The OPBA copolymers form exceptionally linear rigid aggregates as a consequence of their partial π conjugation and lack of chiral substituents. AFM evidence suggests that several linear rods stack on top of each other through π interactions, while hydrogen bonds are responsible for OPBA aggregation parallel to the direction of the fibers.[42] Network formation and aggregation of these fibers has not yet been observed.

5. Summary and Outlook

β-Sheet peptide copolymers and their solution and bulk structures have been of increasing interest in the last decade. Several synthetic pathways towards these hybrid copolymers have been investigated. The convergent synthesis with the peptide prepared on solid support is certainly the approach that gives copolymers with the highest degree of structural perfection, especially for difficult or long peptide sequences. PAP Tentagels have also been used successfully by many groups. To ensure complete coupling of each amino acid, an analytical procedure must follow each coupling step. This approach is convenient for short peptide sequences especially if C-terminal PEG conjugation is required. Peptide ATRP and RAFT initiators are another method of avoiding faulty sequences, as these can typically be purified prior to the controlled radical polymerization.

From the results reported to date on linear β-sheet peptide block copolymers one can conclude that the aggregation of the hybrid copolymers is very similar to that of the native peptides. Typically, tapes of β sheets are formed, and the width of the aggregate correlates directly with the molecular dimensions of the peptide. These flat tapes can further aggregate into infinite stacks as demonstrated by van Hest et al.[27] Twisting of these stacks appears to limit the stacking of β sheets, as observed for the examples reported by Lynn et al.[10–13,18] Surrounding the aggregate with a synthetic polymer block can help to prevent further aggregation of the fibrils and lead to soluble and characterizable aggregates. Most reports so far have focused on aggregation in water. Recent data obtained in organic media of low dielectric constant indicates that residual dipole moments of the peptide sheets can be exploited to explore further aggregation structures.[25]

Examples in which the solution aggregation of peptides is used for the organization of attached functional residues are still rare. Cyclic oligopeptides could potentially carry functional groups on both the inside and the outside of the tubular aggregate; this approach could be used, for example, to devise artificial ion channels.

Oligoaramides (δ peptides) can be derivatized readily, offering the possibility to act as rigid scaffolds for the precise positioning of functional groups at defined distances. Additionally, the well-defined core architectures of copolymer aggregates can serve as anisotropic templates. Removal of the template after cross-linking of the surrounding polymer shell could result in porous polymer networks with defined pore dimensions.

All of the aggregation processes described above can be interpreted as noncovalent polymerizations. In the "covalent world" methods have been established to control the molecular weight and molecular-weight distribution of polymers. In comparison, knowledge about noncovalent polymers is still at an early stage. While many of the above reported examples allow a direct correlation between aggregate width and the molecular dimensions of the peptide building block, ways to control the length of β-sheet copolymer aggregates have not yet been reported. This marks one of the immediate challenges in this field.

In the "polymer world", shape-persistent rodlike macromolecules such as polymer brushes or dendronized polymers have attracted much attention. Peptide–polymer hybrids offer the potential to construct similarly complex and functional macromolecular architectures using the rules of reversible noncovalent self-assembly.

β-Sheet copolymers represent a new area of macromolecular science, which straddles synthetic organic chemistry, polymer chemistry, and materials science. In this emerging field, the most basic of nature's lessons, dealing with the formation of β-sheet secondary structures in peptid copolymers has been learned. In the many lessons to come, the higher levels of hierarchical organization of these β sheets will have to be addressed.

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