Rod–coil block molecules: their aqueous self-assembly and biomaterials applications†

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Past decades have witnessed rapidly growing interest in nanometer-sized structures, which have great potential to be used in a variety of applications, such as electronics, sensors, coatings, and biomaterials. Supramolecular chemistry in particular has been actively applied to the development of such materials. Nanostructures can readily be accessed using bottom-up supramolecular approaches as they are composed of small molecules (supramolecular building blocks) requiring fewer steps to synthesize. Among various types of supramolecular building blocks, rod–coil molecules, due to their anisotropic molecular shape, are well-suited for tailoring nanostructural properties such as size and shape. This Feature Article highlights the self-assembly of rod–coil molecules in aqueous solution and introduces an emerging approach to the application of rod–coil nanostructures in biomaterials applications.

1. Introduction

Construction of nano-sized structures by molecular self-assembly of designed supramolecular building blocks has been the subject of intensive research during the past decades.[1] In aqueous solution, the spontaneous self-organization of the supramolecular building blocks is driven by noncovalent interactions including hydrophobic, electrostatic, π–π stacking, and hydrogen bonding.[2,3] Supramolecular scientists make use of those interactions alone or in concert to form desired nanostructures. Depending on the molecular structure of the building blocks, it has been possible to fabricate various supramolecular architectures, such as spherical micelles, vesicles, fibers, supramolecular helices, nanoribbons, and nanotubes. As the research in the field goes on, an increasing repertoire of rationally designed supramolecular building blocks is being continuously added, yielding a variety of morphology controlled, stimuli responsive, and functional nanostructures. Most widely investigated basic supramolecular building blocks include amphiphilic block copolymers,[4–8] surfactants,[9,10] peptides/peptide derivatives,[11–18] and rod–coil amphiphiles.[19–27]

Among many types of supramolecular building blocks, rod–coil block molecules (rod–coils) offer ample opportunities to construct a variety of well-defined nanostructures of controlled size and shape in selective solvents (good solvent for one block and poor solvent for the other). Rod–coils consist of rigid, rod-like blocks and flexible, coil-like blocks in the same molecular backbone. For the aqueous self-assembly of rod–coils, one of the blocks is designed to be hydrophilic, while the other block is hydrophobic. The self-assembly of rod–coils is directed by microphase separation of the two dissimilar blocks similarly to conventional coil–coil amphiphiles (coil–coils). In contrast to coil–coils, rod–coils can form well-ordered structures even at low molecular weights because the anisotropic molecular shape and stiff rod-like conformation of the rod blocks impart orientational organization.[11,28–31] Moreover, rod–coils can form unique

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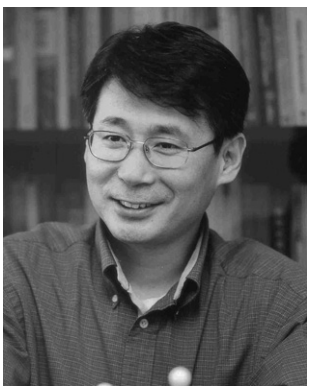

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structures such as hockey puck micelles.[32] The difference in chain rigidity of the stiff rod-like and flexible coil-like blocks is expected to greatly affect the details of molecular packing and thus the nature of thermodynamically stable supramolecular structures. The energetic penalties associated with chain stretching of the coil block and interfacial energy results in the self-assembly of rod–coils into a variety of supramolecular nanostructures depending on the relative volume fraction of the rod segments and temperature.[32,33] In addition to the hydrophobic interactions, the rigid rod block drives the self-assembly of the molecules *via* π–π interactions. In β-sheet peptide rod–coils, hydrogen bonding plays an important role in stabilizing the rod structure as well as hydrophobic and π–π interactions. As the rod block has restricted conformational freedom, it retains its rod-like character under virtually all circumstances.

It is becoming a major challenge for supramolecular chemists to utilize self-assembled nanostructures in biomaterials applications. In biological systems, myriads of molecular recognition events take place in a multivalent manner.[34–39] This is because multivalent interactions provide a significant increase in binding affinity that is not achievable with monovalent interactions. Given the fact that a basic principle of supramolecular chemistry is the iterative and regular array of monomeric building blocks, the self-assembled nanostructures are excellent platforms for displaying multiple functionalities.[40–43] Therefore, there is a vast potential of developing self-assembled nanostructures as modulators of biological interactions. For example, carbohydrate molecules on the mammalian cell surface are the targets of many pathogenic viruses and bacteria in their initial cell recognition events.[44–46] The pathogens utilize multivalent interactions for tight binding and specific recognition of the cells, which is then followed by infection of host cells. If the self-assembled nanostructures, decorated with the same carbohydrates, are used as decoys of the pathogens, the result should be the inhibition of pathogen infection. Moreover, formation of most biological entities, such as cell membranes, DNA double helices, protein folding, and cytoskeleton formation *etc.*, are molecular self-assembly in essence. Therefore, it is our belief that synthetic nanostructures have vast potential in biological applications.

In this Feature Article, we focus on the recent progress on the aqueous self-assembly behavior of rod–coils. We will mainly introduce the burgeoning field, in which self-assembled rod–coil nanostructures are being developed as functional biomaterials. Here, we classified rod–coils into three types (Fig. 1). The first section deals with the most widely studied rod–coils, in which the rod blocks are based on rigid aromatic scaffolds. The aromatic rod blocks are typically derived from traditional mesogens. Liquid crystal self-assembly of behavior of aromatic rod–coils in the bulk state has been studied extensively. In the bulk state, the anisometric shape of the rigid rod is important for long range orientational order and amphiphilic character of rod–coils for microphase segregation and positional order. The vast amount of knowledge gained from the study of the bulk state can be applied to the research of aromatic rod–coils in the aqueous state. In the second section, rod–coils in which rod blocks are based on helical scaffolds are highlighted. The last section is focused on the self-assembly and bio-applications of β-sheet peptide-based rod–coil peptides. We do not want to present a complete overview on reported rod–coils here. Instead, we highlight the most recently synthesized and biologically applicable rod–coils.

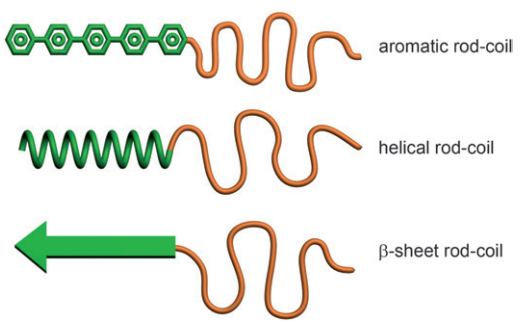


Fig. 1 Schematic models of an aromatic rod–coil, a helical rod–coil, and a β-sheet rod–coil.

2. Rod–coil molecules based on aromatic rods

Most of the rigid rod blocks in aromatic rod-based rod–coils are derived from mesogens. For that reason, investigations on the liquid crystalline self-assembly behavior of aromatic rod–coils in the bulk state have been the subjects of much research.[47–52] In this Feature Article, however, we will focus mainly on the aqueous self-assembly behavior of aromatic rod–coils. Notably, self-assembly in aqueous solution has its advantages due to environmental friendliness and direct applicability as biomaterials.

2.1 Carbohydrate-decorated aromatic rod–coils

It has been shown that rod–coils adopt various morphologies depending on the molecular structure, relative volume fraction of rod and coil, chirality, and hydrogen bonding capability. Supramolecular morphology of amphiphiles depends highly on the relative volume fraction of hydrophobic and hydrophilic blocks. It has been proposed that self-assembled aggregates of amphiphiles consisting of a hydrophobic chain and a hydrophilic head can be predicted by the packing parameter, $P = v/(a_0 l_c)$, where v is the volume of the hydrophobic chain, a_0 is the polar head surface area at the critical micelle concentration (cmc), and l_c is the chain length (Fig. 2).[53]

Lee and co-workers applied this packing parameter concept in designing carbohydrate conjugated aromatic rod–coils.[54,55] The molecular design was implemented by varying either the PEO coil length or the rod number (Fig. 3). From this molecular design approach, the authors were able to fine-tune the size and shape of carbohydrate-decorated nanostructures from spheres to vesicles and cylinders. The nanostructures were shown to act as multivalent ligands in the presence of carbohydrate-binding lectin protein, concanavalin A (Con A). From the increased object sizes in TEM images, lectin proteins were thought to tightly surround the supramolecular object through multivalent interactions. Such a specific binding event was found exclusively in mannose-decorated nanostructures, as the control experiment with non-specific galactose-decorated objects did not show the specific object–Con A association. Through a hemagglutination inhibition assay with Con A, the authors investigated the influence of object architecture on the binding activity.

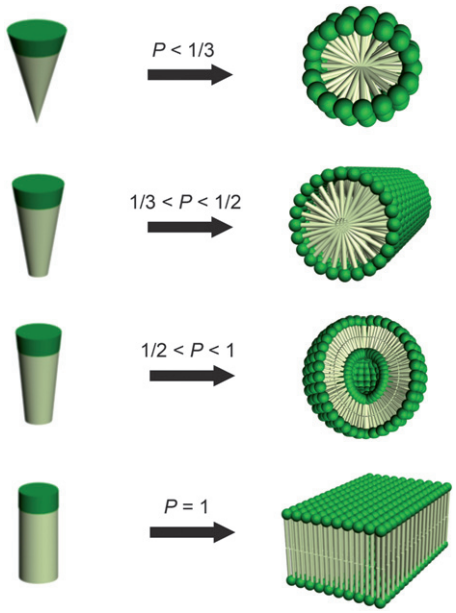


Fig. 2 Dependence of nanostructure morphologies on the relative volume fraction of hydrophobic and hydrophilic blocks.

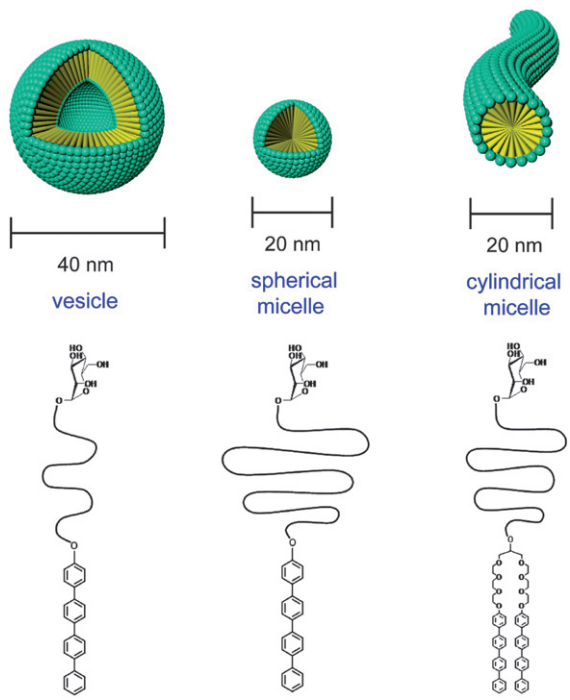


Fig. 3 Mannose-conjugated aromatic rod–coils self-assemble into nanostructures of various sizes and shapes.

Hemagglutination assay measures the extent of inhibition of Con A-mediated erythrocyte agglutination. The results showed that, depending on the size and shape of the nanostructures, the inhibitory potency varied from 800 to 1800 fold compared to monomeric carbohydrate. Lessons from these results are that molecular self-assembly is well suited for constructing multivalent carbohydrate ligands and the biological activity of carbohydrate-decorated supramolecular objects is critically dependent on their size and shape.

Thoma and co-workers explored dynamic properties of self-assembly in which optimization of size and shape of the polyvalent carbohydrate ligand could occur during a multivalent receptor binding process.[56] Dendritic rods coupled with carbohydrate ligands (glycodendrimers) were found to self-assemble into noncovalent nanoparticles which could function as polyvalent ligands (Fig. 4). They tested the potency of carbohydrate-decorated nanoparticles in decavalent antibody IgM binding assays.[57] Compared to monomeric carbohydrate or glycodendrimers that could not self-assemble, self-assembled glyconanoparticles showed much higher potency in the binding assays. The individual protein–carbohydrate interactions are generally weak ($K_d = 10^{-3}$–10^{-4} M^{-1}).[39] The results clearly demonstrate the enhancement in protein–carbohydrate binding affinity by the self-assembly and the resulting multivalent carbohydrate presentation. The authors suggest that noncovalent polyvalent ligands are optimized with respect to size and shape in the presence of natural polyvalent receptors.

Dependence of object size and shape in supramolecular multivalent interactions has also been investigated in carbohydrate-decorated rod–coil nanostructures and bacterial cell interaction systems.[58] For this, triblock rigid-flexible dendritic block molecules consisting of a rigid aromatic segment as a stem segment, carbohydrate-branched dendrons as a flexible head, and a hydrophobic alkyl chain were synthesized, and characterized in both the bulk and solution states. In solution, both molecules were observed to self-assemble into carbohydrate-coated cylindrical nanostructures with a uniform diameter. Notably, these cylindrical objects were reversibly transformed into spherical objects upon encapsulation (intercalation) of hydrophobic guest molecules (Fig. 5). The cylinder to sphere transition was explained as the loosening of rod packing due to the intercalation. Investigation on the interactions of the carbohydrate-coated nanostructures with *E. coli* cells showed that both cylindrical and spherical nano-objects could immobilize the bacterial cells, while the degree of immobilization was significantly dependent on the shape of the nanostructure. TEM investigation showed that a number of cylindrical and spherical objects were clearly observed to be located along the pili of *E. coli* (ORN178), indicative of strong binding of the objects to the pili. The pili of the *E. coli* ORN178 strain contain mannose binding proteins.[59]

2.2 Membrane-active rod–coil nanostructures

Matile and co-workers have developed synthetic ion channels and pores that can function in lipid bilayer membranes using rigid-rod molecules such as *p*-oligophenyls.[60–63] They found that hydrophobic matching of rod length and the bilayer thickness were the key for the construction of functional transmembrane architecture. As representative examples, they developed rigid push–pull rods, α-helix mimics, which helped to clarify contributions of axial rod dipoles to the voltage gating of ion channels and pores. Push–pull rods are conjugated rigid rods with an electron donating π donor D at one terminus and a π acceptor A at the other terminus (Fig. 6). Push–pull rods are equipped with ion-conducting azacrown modules. Voltage-gated ion channel

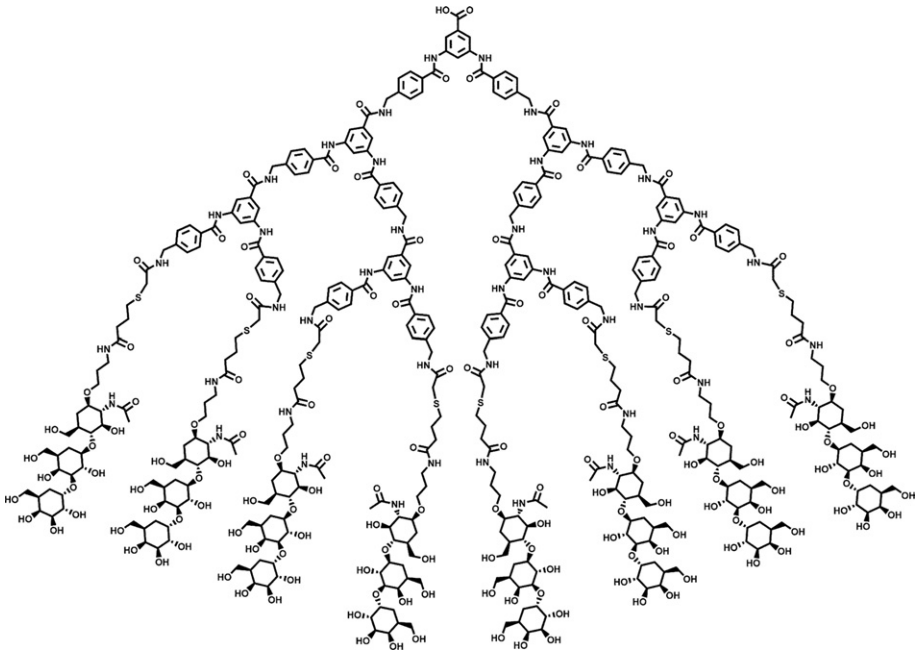


Fig. 4 Structure of glycodendrimer.

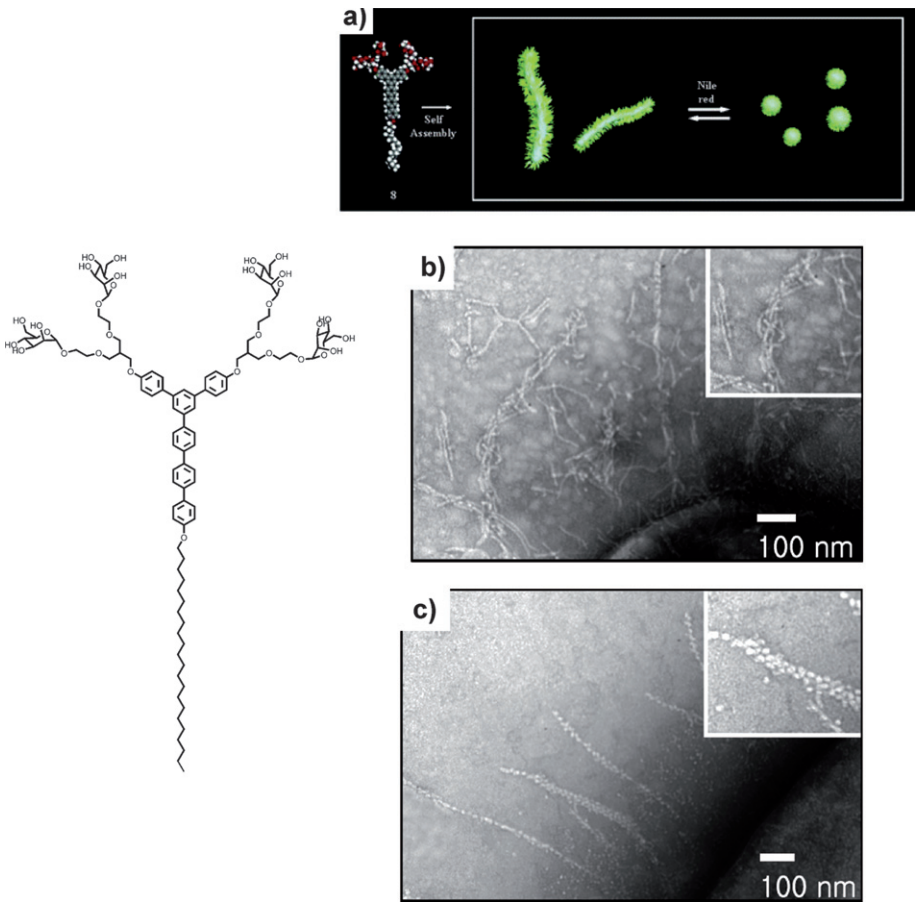
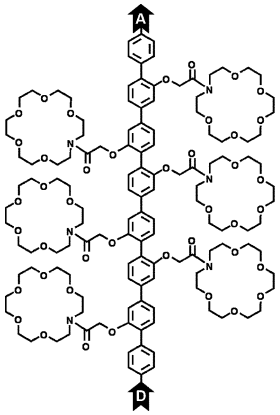


Fig. 5 a) Schematic representation of reversible transformation of cylindrical micelles into spherical micelles upon encapsulation of guest molecules. TEM images of *E. coli* pili bound with b) cylindrical and c) spherical micelles. Reproduced in part from ref. 58, © 2007 American Chemical Society. Used with permission.



	A	D	recognition
11	$-SO_2Me$	-SMe	+
12	-SMe	-SMe	-
13	$-SO_2CH_2CH_2NH_3^+$	-SMe	+
14	$-SO_2Me$	$-SCH_2CH_2NH_3^+$	-
15	-SMe	$-SCH_2CH_2NH_3^+$	-

Fig. 6 Rigid-rod molecules with hydrogen-bonded chains for selective proton transport as rigid push–pull rods with axial dipoles for the recognition of polarized membranes.

formation was determined in planar bilayers and elaborated in doubly labeled neutral (EYPC) and anionic (egg yolk phosphatidylglycerol) spherical bilayers (SUVs) with inside negative membrane potentials, an internal pH-sensitive dye, and an external potential-sensitive dye. More in depth discussion of related systems can be found in recent reviews.[60,61]

Recently, Lee and co-workers reported an unusual example of supramolecular barrels in the solid and in aqueous solution, based on the self-assembly of amphiphilic rod–coil macrocycles (Fig. 7).[64] As compared to acyclic molecules, it is quite probable that cyclic rod–coils show a distinct self-assembly in bulk and solution as the coil blocks will inevitably be concentrated near rod blocks in a packing structure, significantly inhibiting inter-rod packing. Despite such a straightforward expectation, it has been challenging to study the self-assembly of macrocyclic systems due to difficulties in synthesis. The macrocyclic molecules that form these aggregates consist of a hexa-*p*-phenylene rod and a poly(ethylene oxide) (PEO) coil that are fused together into a macrocyclic ring. Aside from interesting bulk morphologies such as supramolecular ribbons and barrel-like micelles with ordered superlattices, the most striking is the formation of a barrel-like tubular structure in an aqueous environment. In an aqueous solution, the discrete tubular objects have a hydrophilic exterior and interior consisting of PEO coils and water molecules. Preliminary transport experiments indicated that the amphiphilic macrocycles are active in lipid bilayer membranes.

3. Rod–coil molecules based on helical rods

Helical structures are abundant in biological systems. For example, a number of helical structures are found in proteins, which include α-helix,[65] polyproline helix,[66] collagen helix,[67] 3_{10}-helix,[68] and π-helix.[69] The polypeptide helices are stabilized by hydrogen bonding and/or steric effects, rendering them to have stiff rod-like characters. For example, the α-helix, one of the most common motifs in the secondary structure of proteins, adopts a right-handed coiled conformation, in which every backbone N–H group donates a hydrogen bond to the backbone C═O group of the amino acid four residues earlier ($i + 4 \rightarrow i$ hydrogen bonding).

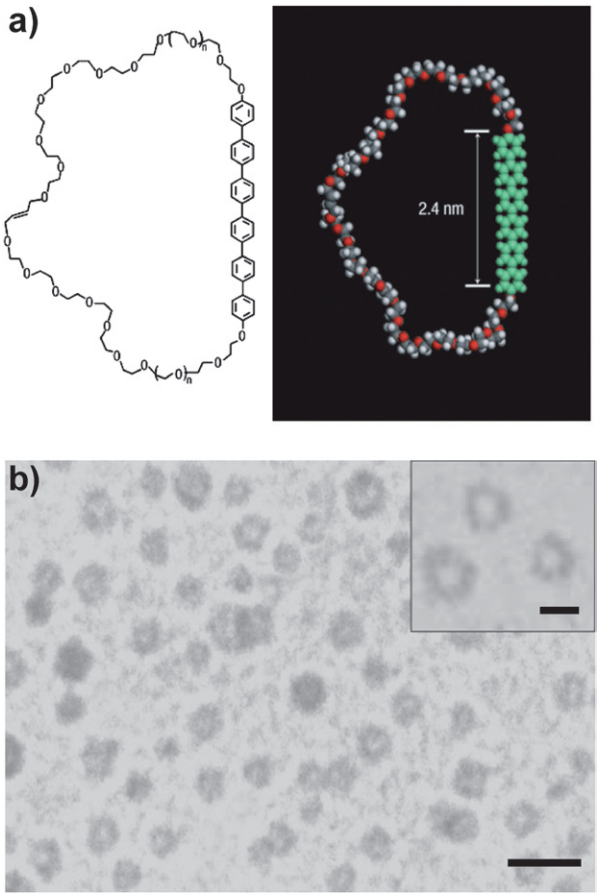


Fig. 7 a) Chemical structure of a rigid–flexible macrocycle. b) TEM image of barrel-like tubular structures in an aqueous solution. Reproduced in part from ref. 64. © 2005 Nature Publishing Group. Used with permission.

Nolte and co-workers prepared amphiphilic block copolymers containing a poly(styrene) tail and a rod-like helical poly(isocyanide) headgroup (Fig. 8).[70] The block copolymers self-assembled in aqueous systems to form a variety of morphologies such as micelles, vesicles, and bilayer aggregates. The morphology of these aggregates could be controlled by varying the length of the poly(isocyanide) block, the pH, and the anion–headgroup interactions. The chirality of the macromolecules results in the formation of helical superstructures that have a helical sense opposite to that of the constituent block copolymers.

Self-assembly of stimuli-responsive polypeptide diblock copolymer has recently been reported by Rodríguez-Hernández and Lecommandoux (Fig. 9).[71] The polypeptide consists of a zwitterionic diblock copolymer poly(L-glutamic acid)-*b*-poly(L-lysine) (PGA-*b*-PLys), which was synthesized by sequential ring-opening polymerization of the corresponding α-amino acid *N*-carboxyanhydrides. Upon neutralization of the polypeptide block, the block changed from a random coil conformation (charged form) into a neutral and compact α-helical structure (rod). At acidic pH, the PGA block is neutralized, thereby rod-like PGA forming the core of the aggregates (vesicles) while the PLys block forms the shell. In contrast, under basic conditions, the protonated PLys block ($-NH_3^+$) is transformed into neutral and insoluble $-NH_2$ groups, forming the core of the aggregates.

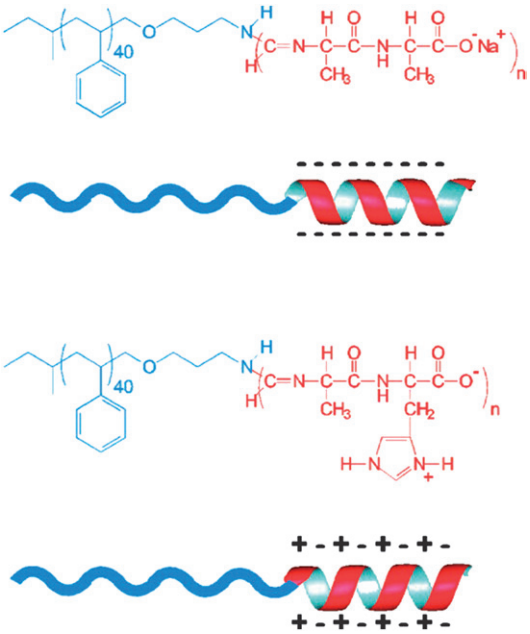


Fig. 8 Structures of helical rod–coil block copolymers. Reproduced in part from ref. 70. © 1998 American Association for the Advancement of Science. Used with permission.

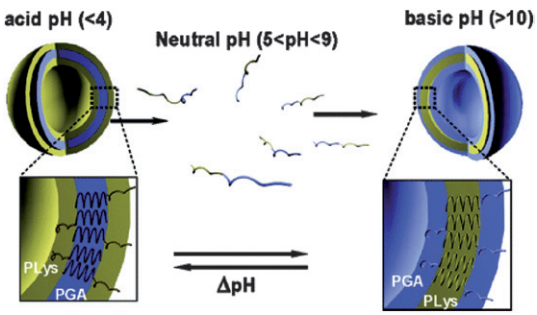


Fig. 9 Reversible inside–out micellization of pH-responsive and water-soluble vesicles based on polypeptide diblock copolymers. Reproduced in part from ref. 71. © 2005 American Chemical Society. Used with permission.

Deming and co-workers reported the self-assembly behavior and bio-application of poly(L-lysine)-*b*-poly(L-leucine), poly(L-glutamic acid)-*b*-poly(L-leucine), and poly(L-arginine)-*b*-poly(L-leucine) diblock polypeptides.[72–74] The driving force underlying the aggregation of the diblock polypeptides was the α-helical hydrophobic rod formation of the poly(L-leucine) block. Notably, the diblock polypeptides formed vesicular structures at low hydrophobic residue contents (10–40 mol%). Conventional amphiphilic diblock copolymers within this composition range would be expected to form small spherical or cylindrical micelles in aqueous solution, whereas stable vesicles would usually form at higher hydrophobic contents (approximately 30–60 mol%).[75] The copolypeptides should deviate from this trend due to the rigid chain conformation and strong interactions between chains. The formation of micelles with a large degree of interfacial curvature between the hydrophobic and hydrophilic domains is thus disfavored, as the rod-like

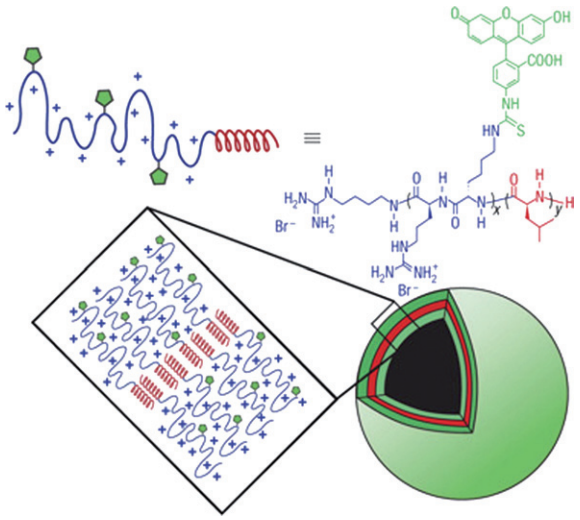


Fig. 10 Schematic diagram of proposed self-assembly of poly(L-arginine)-*b*-poly(L-leucine) vesicles. Reproduced in part from ref. 74. © 2007 Nature Publishing Group. Used with permission.

amphiphiles would rather laterally associate into a flat membrane of relatively low interfacial curvature. The poly-arginine-coated vesicles showed potential as intracellular delivery carriers following entrapment of water soluble molecules (Fig. 10). The guanidinium residues of arginines, essential residues for the function of cell-penetrating peptides (CPPs),[76,77] were responsible for the effective intracellular delivery of vesicles and cargos.

Recently, Lee and co-workers reported self-assembly of peptide rod–coils composed of a polyproline rod and a CPP Tat coil.[78] Among the 20 naturally occurring amino acids, proline is the only one in which the side chain atoms form a pyrrolidine ring with the backbone atoms. As the cyclic structure of proline induces conformational constraints among the atoms in the pyrrolidine ring, the proline-rich sequences tend to form a stiff helical rod structure, called a polyproline type II (PPII) helix, in aqueous solution. The hydrophobicity of proline itself as an isolated amino acid is rather small. However, three nonpolar methylene groups are aligned at the outer part of the rod after PPII helix formation. Based on these facts, they hypothesized that the stiff rod character and the nonpolar nature of the outer surface of the PPII helix might impart microphase separation characteristics to the rod–coil of a PPII rod and a hydrophilic Tat CPP coil, leading to the anisotropic orientational ordering of the rod and self-assembly. The results showed that the peptide rod–coil did self-assemble into a vesicular structure (Fig. 11). To assess the potential of the CPP-coated capsule in intracellular delivery of hydrophilic drugs, a water-soluble fluorescent dye, rhodamine B, was entrapped within the aqueous space of the capsule. The intracellular delivery experiment performed in mammalian cell line showed the efficient cell delivery potential of the CPP-coated capsule.

4. Rod–coil molecules based on β-sheet rods

Artificially designed β-sheet peptides have gained growing attention for their potential to be used as biomaterials.[79–84] The

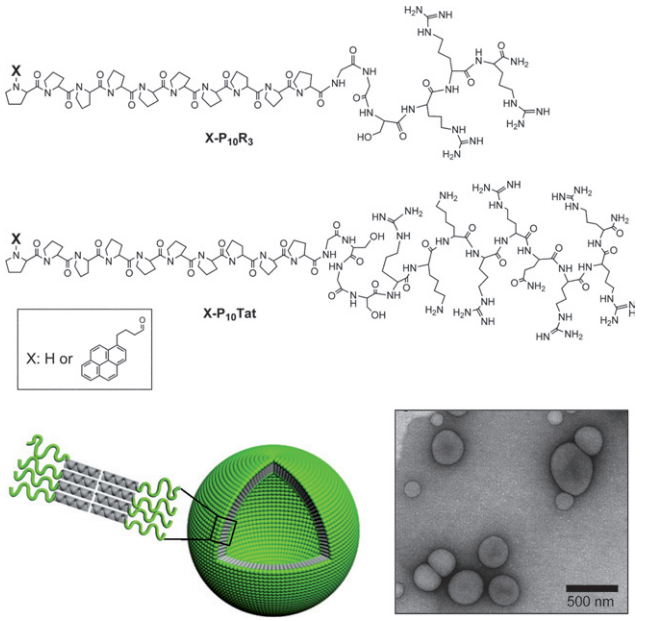


Fig. 11 Self-assembly of PPII–Tat CPP rod–coils. Reproduced in part from ref. 78. © 2008 The Royal Society of Chemistry. Used with permission.

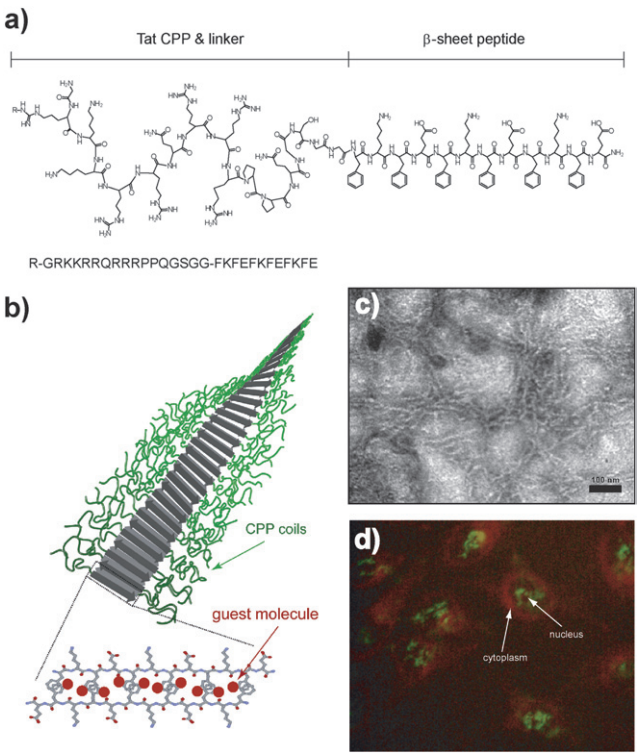


Fig. 12 a) Structure and sequence of TβP peptide building block. b) Representation of the nanoribbon formed by self-assembly of TβP and encapsulation of hydrophobic guest molecules. c) TEM image of nanoribbon. d) Intracellular delivery of encapsulated guest molecules by CPP-coated β-ribbon. In this confocal laser scanning microscope (CLSM) image of the cells, TβP and encapsulated guest molecules are shown in green and red, respectively. Reproduced in part from ref. 93. © 2007 Wiley-VCH Verlag GmbH & Co. KGaA. Used with permission.

polypeptide chains are nearly fully extended in β-sheet structures in which regular hydrogen bonds form between the polypeptide backbone amide protons and carbonyl oxygen groups of adjacent chains.[85,86] By this reason, β-sheet can be considered as another class of rod segment. Nanofibers of β-sheets are organized in such a way that each β-strand runs perpendicular to the fibril axis. The design principle for most artificial β-sheet peptides is the alternating placement of charged (or polar) and hydrophobic amino acids. This type of arrangement promotes the proper β-sheet hydrogen bonding arrangement between amide hydrogen and carbonyl oxygen. When one face of the one-dimensional β-sheet (β-tape) consists of predominantly hydrophobic amino acid side chains, the removal of the hydrophobic side chains from contact with water drives two β-tapes to associate into a bilayered β-sheet nanoribbon (β-ribbon) structure.

It has been demonstrated that many peptides having a propensity for β-sheet nanofiber formation often laterally interact to form higher order aggregates. Coupling of hydrophilic macromolecules (coils) on the N- or C-terminus of β-sheet peptides significantly inhibits the formation of higher order aggregates.[87,88] Investigations on the self-assembly and bio-applications of β-sheet rod-functional coil block molecules are beginning to emerge.

Several reports described the successful attachment of proteins such as green fluorescent protein (GFP) and cytochrome (Cyt) in their active form to β-sheet nanofibers.[89,90] Barker and co-workers reported that a β-sheet fiber forming SH3 domain was fused with Cyt.[91] Cyt is a porphyrin binding protein that catalyzes redox reactions in the cell.[92] TEM, X-ray diffraction (XRD), and circular dichroism (CD) analyses showed that the fusion protein forms β-sheet fibers coated densely with Cyts. The UV-Vis spectra of SH3-Cyt fibrils bound to iron(II) and iron(III) protoporphyrin IX were identical to those of the wild type Cyt and other spectroscopic analyses further confirmed that activity of Cyt was not impaired by the fibril formation. The results demonstrate that this fibril provides a novel nanostructured material for the study of charge transfer in supramolecular systems.

Lee and co-workers recently reported the self-assembling block peptide (TβP) consisting of a CPP Tat and a β-sheet assembly peptide (FKFEFKFEFKFE) was synthesized for intracellular delivery applications (Fig. 12).[93] It was found that TβP formed β-ribbon structures in which β-sheet interaction was the main driving force for the self-assembly. The TβP β-ribbons were able to encapsulate hydrophobic guest molecules such as pyrene and Nile red in the hydrophobic interface between two β-tapes, showing the possibility of use in drug delivery applications, similarly to conventional amphiphilic block copolymer micelles. It turned out that the cell penetration efficiency of the TβP β-ribbon was much higher than that of unimolecular Tat CPP, suggesting that the multivalent coating of CPPs is advantageous in increasing cellular uptake efficiency.[94]

In another example, multivalent protein–carbohydrate interaction was explored with carbohydrate-decorated β-ribbons.[95,96] The building block consists of a carbohydrate mannose, an oligo(ethylene glycol), and a β-sheet assembly peptide (Fig. 13). GP1 and GP2 building blocks were found to form long and short β-ribbons, respectively. To investigate interactions between the

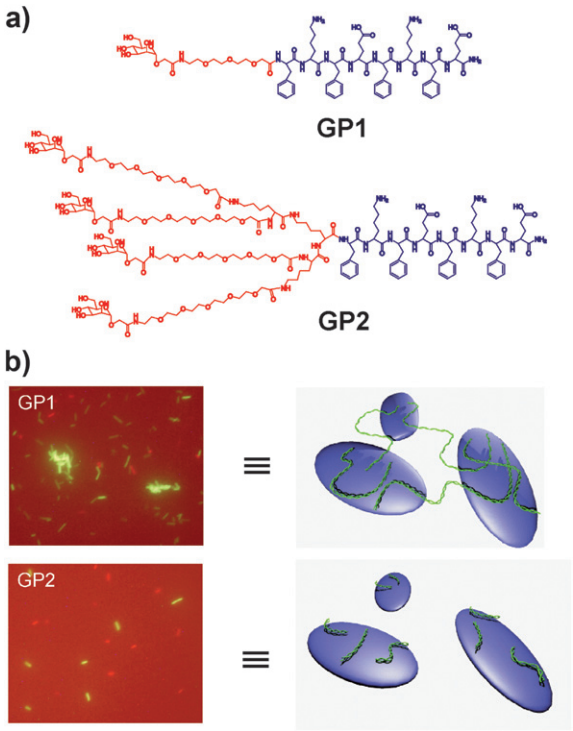


Fig. 13 a) Structures of carbohydrate-conjugated peptide building blocks. b) Overlaid fluorescence microscopy images of fluorescent bacteria. GP1 nanoribbons induced bacterial agglutination and inhibited bacterial motility, whereas GP2 nanoribbons only inhibited bacterial motility. ORN178-GFP *E. coli* (specific to mannose), green; ORN208-RFP *E. coli* (nonspecific to mannose), red. Reproduced in part from ref. 95. © 2007 American Chemical Society. Used with permission.

mannose-coated β-ribbon and the bacterial cells, an *E. coli* strain containing mannose binding adhesin FimH in its type I pili (ORN178) was chosen as a model pathogen. Upon addition of the mannose-coated long β-ribbon from GP1 to the bacterial suspension, the bacteria lost their motility and agglutinated, whereas short β-ribbons from GP2 only inhibited bacterial motility. Agglutination and motility inhibition of microbial cells such as bacteria and viruses might be developed as a way to inactivate pathogens. A similar observation has recently been reported that carbohydrate-coated long carbon nanotubes could aggregate anthrax spores, whereas carbohydrate-coated spherical nanoparticles could not.[97] Overall, these observations highlight an important phenomenon regarding interactions at the supramolecular level; the size and morphology of nanostructures are critically important even if their chemical properties are similar.

5. Conclusion

Fundamental studies on the self-assembly behavior of rod–coils have provided structural controls for the preparation of well-defined nanoscopic objects, which include small spherical micelles, long cylindrical micelles, nanorings, helical fibers, and nanotubes. This unique structural diversity seems to originate from the combination of organizing forces by amphiphilic characteristics and anisotropic molecular shape that show the tendency of their lipophilic and lipophobic parts to segregate in space into distinct microdomains and molecular architectures. Relative to phase-rich bulk morphologies, self-assembled nanostructures in solution have not been studied widely. Supramolecular rod–coil building blocks can provide powerful tools to create tailor-made functional nanomaterials.

Conventional pharmacophores, such as small molecule drugs and protein drugs, have been designed to act only on one target site. In addition, the desired effects of conventional pharmacophores have mostly been the inhibition of target protein's function. Considering the huge size and multivalent properties of supramolecular nanostructures, nano-pharmacophores are likely to offer quite novel and unexpected biological properties, which could not be achievable with conventional pharmacophores. Given the exquisiteness and extremely well-controlled nature of biological processes, the usefulness of bioactive nanostructures should rely heavily on the capability to control the properties (*e.g.*, size and shape) of the nanostructures.

As the field is very young, this is still a very unexplored area. Considering the interdisciplinary nature of the field, knowledge from various scientific disciplines should be combined synergistically. From the supramolecular point of view, control of nanostructural properties, such as morphology, size, and stability, should be one of the most imminent issues to address. In addition, novel types of rod–coil building blocks need to be designed to get unforeseen and unexpected properties of supramolecular materials. From the biological perspective, biomaterials applications of supramolecular nanostructures have been such as to use them as drug delivery, gene delivery, membrane-active, and pathogen aggregation materials. Expanding the repertoire of biomaterials applications should be one of the most important tasks to do, as there remain a myriad of potential bioprocesses to explore. Among many types of supramolecular building blocks, rod–coil type building blocks offer advantages in that a variety of controllable, well-defined, and dynamic nanostructures can be constructed. Therefore, it should be the one of the best starting points to utilize rod–coils in developing the growing field of supramolecular nanobiomaterials.

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References

1 (*a*) J.-M. Lehn, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 4763; (*b*) L. Brunsveld, B. J. B. Folmer, E. W. Meijer and R. P. Sijbesma, *Chem. Rev.*, 2001, **101**, 4071; (*c*) J. A. A. W. Elemans, A. E. Rowan and R. J. M. Nolte, *J. Mater. Chem.*, 2003, **13**, 2661; (*d*) K. Kinbara and T. Aida, *Chem. Rev.*, 2005, **105**, 1377; (*e*) A. Mueller and D. F. O'Brien, *Chem. Rev.*, 2002, **102**, 727; (*f*) D. Chen and M. Jiang, *Acc. Chem. Res.*, 2005, **38**, 494.
2 V. Berl, M. Schmutz, M. J. Krische, R. G. Khoury and J. M. Lehn, *Chem.–Eur. J.*, 2002, **8**, 1227.
3 G. B. W. L. Ligthart, H. Ohkawa, R. P. Sijbesma and E. W. Meijer, *J. Am. Chem. Soc.*, 2005, **127**, 810.
4 D. E. Discher and A. Eisenberg, *Science*, 2002, **297**, 967.
5 S. Jain and F. S. Bates, *Science*, 2003, **300**, 460.

6 D. J. Pochan, Z. Chen, H. Cui, K. Hales, K. Qi and K. L. Wooley, *Science*, 2004, **306**, 94.
7 X. Wang, G. Guerin, H. Wang, Y. Wang, I. Manners and M. A. Winnik, *Science*, 2007, **317**, 644.
8 K. Kataoka, A. Harada and Y. Nagasaki, *Adv. Drug Delivery Rev.*, 2001, **47**, 113.
9 T. Shimizu, M. Masuda and H. Minamikawa, *Chem. Rev.*, 2005, **105**, 1401.
10 F. M. Menger and J. S. Keiper, *Angew. Chem., Int. Ed.*, 2000, **39**, 1906.
11 Y.-b. Lim, E. Lee and M. Lee, *Angew. Chem., Int. Ed.*, 2007, **46**, 9011.
12 S. G. Zhang, *Nat. Biotechnol.*, 2003, **21**, 1171.
13 M. R. Ghadiri, J. R. Granja, R. A. Milligan, D. E. Mcree and N. Hazanovich, *Nature*, 1993, **366**, 324.
14 G. A. Silva, C. Czeisler, K. L. Niece, E. Beniash, D. A. Harrington, J. A. Kessler and S. I. Stupp, *Science*, 2004, **303**, 1352.
15 E. B. Hadley and S. H. Gellman, *J. Am. Chem. Soc.*, 2006, **128**, 16444.
16 S. Ghosh, M. Reches, E. Gazit and S. Verma, *Angew. Chem., Int. Ed.*, 2007, **46**, 2002.
17 D. Eckhardt, M. Groenewolt, E. Krause and H. G. Börner, *Chem. Commun.*, 2005, 2814.
18 R. J. Mart, R. D. Osborne, M. M. Stevens and R. V. Ulijn, *Soft Matter*, 2006, **2**, 822.
19 M. Lee, B.-K. Cho and W.-C. Zin, *Chem. Rev.*, 2001, **101**, 3869.
20 K.-S. Moon, H.-J. Kim, E. Lee and M. Lee, *Angew. Chem., Int. Ed.*, 2007, **46**, 6807.
21 J.-K. Kim, E. Lee, Z. Huang and M. Lee, *J. Am. Chem. Soc.*, 2006, **128**, 14022.
22 S. I. Stupp, S. Son, H. C. Lin and L. S. Li, *Science*, 1993, **259**, 59.
23 A. Halperin, *Macromolecules*, 1990, **23**, 2724.
24 G. N. Tew, M. U. Pralle and S. I. Stupp, *Angew. Chem., Int. Ed.*, 2000, **39**, 517.
25 H. M. König, T. Gorelik, U. Kolb and A. F. M. Kilbinger, *J. Am. Chem. Soc.*, 2007, **129**, 704.
26 C. Tschierske, *Chem. Soc. Rev.*, 2007, **36**, 1930.
27 (*a*) B. Chen, X. Zeng, U. Baumeister, G. Ungar and C. Tschierske, *Science*, 2005, **307**, 96; (*b*) B. Chen, U. Baumeister, G. Pelzl, M. K. Das, X. Zeng, G. Ungar and C. Tschierske, *J. Am. Chem. Soc.*, 2005, **127**, 16578.
28 L. H. Radzilowski, J. L. Wu and S. I. Stupp, *Macromolecules*, 1993, **26**, 879.
29 H.-A. Klok, J. F. Langenwalter and S. Lecommandoux, *Macromolecules*, 2000, **33**, 7819.
30 J.-Z. Chen, C.-X. Zhang, Z.-Y. Sun, L.-J. An and Z. Tong, *J. Chem. Phys.*, 2007, **127**, 024105.
31 C. Singh, M. Goulian, A. J. Liu and G. H. Fredrickson, *Macromolecules*, 1994, **27**, 2974.
32 D. R. M. Williams and G. H. Fredrickson, *Macromolecules*, 1992, **25**, 3561.
33 A. N. Semenov, *Mol. Cryst. Liq. Cryst.*, 1991, **209**, 191.
34 S.-K. Choi, *Synthetic multivalent molecules*, John Wiley & Sons, Inc., New Jersey, 2004.
35 M. Mammen, S.-K. Choi and G. M. Whitesides, *Angew. Chem., Int. Ed.*, 1998, **37**, 2755.
36 J. S. Kim and C. O. Pabo, *Proc. Natl. Acad. Sci. U. S. A.*, 1998, **95**, 2812.
37 C. R. Bertozzi and L. L. Kiessling, *Science*, 2001, **291**, 2357.
38 J. J. Lundquist and E. J. Toone, *Chem. Rev.*, 2002, **102**, 555.
39 Y. C. Lee and R. T. Lee, *Acc. Chem. Res.*, 1995, **28**, 321.
40 Y.-b. Lim and M. Lee, *Org. Biomol. Chem.*, 2007, **5**, 401.
41 K. Larsen, M. B. Thygesen, F. Guillaumie, W. G. T. Willats and K. J. Jensen, *Carbohydr. Res.*, 2006, **341**, 1209.
42 X. Chen, U. C. Tam, J. L. Czlapinski, G. S. Lee, D. Rabuka, A. Zettl and C. R. Bertozzi, *J. Am. Chem. Soc.*, 2006, **128**, 6292.
43 J. E. Kingery-Wood, K. W. Williams, G. B. Sigal and G. M. Whitesides, *J. Am. Chem. Soc.*, 1992, **114**, 7303.
44 W. J. Lees, A. Spaltenstein, W. J. E. Kingery and G. M. Whitesides, *J. Med. Chem.*, 1994, **37**, 3419.
45 M. Mammen, G. Dahmann and G. M. Whitesides, *J. Med. Chem.*, 1995, **38**, 4179.
46 I. Connell, W. Agace, P. Klemm, M. Schembri, S. Marild and C. Svanborg, *Proc. Natl. Acad. Sci. U. S. A.*, 1996, **93**, 9827.
47 L. H. Radzilowski and S. I. Stupp, *Macromolecules*, 1994, **27**, 7747.
48 M. Lee, N.-K. Oh, H.-K. Lee and W.-C. Zin, *Macromolecules*, 1996, **29**, 5567.
49 S. I. Stupp, V. LeBonheur, K. Walker, L. S. Li, K. E. Huggins, M. Keser and A. Amstutz, *Science*, 1997, **276**, 384.
50 V. Francke, H. J. Räder, Y. Geerts and K. Müllen, *Macromol. Rapid Commun.*, 1998, **19**, 275.
51 H. Kukula, U. Ziener, M. Schops and A. Godt, *Macromolecules*, 1998, **31**, 5160.
52 M. Lee, B.-K. Cho, H. Kim, J.-Y. Yoon and W.-C. Zin, *J. Am. Chem. Soc.*, 1998, **120**, 9168.
53 J. N. Israelachivili, *Intermolecular and Surface Forces*, Academic Press, New York, 1985.
54 B.-S. Kim, W.-Y. Yang, J.-H. Ryu, Y.-S. Yoo and M. Lee, *Chem. Commun.*, 2005, 2035.
55 B.-S. Kim, D.-J. Hong, J. Bae and M. Lee, *J. Am. Chem. Soc.*, 2005, **127**, 16333.
56 G. Thoma, A. G. Katopodis, N. Voelcker, R. O. Duthaler and M. B. Streiff, *Angew. Chem., Int. Ed.*, 2002, **41**, 3195.
57 J.-Q. Wang, X. Chen, W. Zhang, S. Zacharek, Y. Chen and P. G. Wang, *J. Am. Chem. Soc.*, 1999, **121**, 8174.
58 J.-H. Ryu, E. Lee, Y.-b. Lim and M. Lee, *J. Am. Chem. Soc.*, 2007, **129**, 4808.
59 S. L. Harris, P. A. Spears, E. A. Havell, T. S. Hamrick, J. R. Horton and P. E. Orndorff, *J. Bacteriol.*, 2001, **183**, 4099.
60 N. Sakai, J. Mareda and S. Matile, *Acc. Chem. Res.*, 2005, **38**, 79.
61 S. Bhosale, A. L. Sisson, N. Sakai and S. Matile, *Org. Biomol. Chem.*, 2006, **4**, 3031.
62 J.-Y. Winum and S. Matile, *J. Am. Chem. Soc.*, 1999, **121**, 7961.
63 N. Sakai, D. Gerard and S. Matile, *J. Am. Chem. Soc.*, 2001, **123**, 2517.
64 W.-Y. Yang, J.-H. Ahn, Y.-S. Yoo, N.-K. Oh and M. Lee, *Nat. Mater.*, 2005, **4**, 399.
65 L. Pauling, R. B. Corey and H. R. Branson, *Proc. Natl. Acad. Sci. U. S. A.*, 1951, **37**, 205.
66 L. Crespo, G. Sanclimens, B. Montaner, R. Perez-Tomas, M. Royo, M. Pons, F. Albericio and E. Giralt, *J. Am. Chem. Soc.*, 2002, **124**, 8876.
67 L. E. Bretscher, C. L. Jenkins, K. M. Taylor, M. L. DeRider and R. T. Raines, *J. Am. Chem. Soc.*, 2001, **123**, 777.
68 M. Crisma, M. Saviano, A. Moretto, Q. B. Broxterman, B. Kaptein and C. Toniolo, *J. Am. Chem. Soc.*, 2007, **129**, 15471.
69 T. M. Weaver, *Protein Sci.*, 2000, **9**, 201.
70 J. J. L. M. Cornelissen, M. Fischer, N. A. J. M. Sommerdijk and R. J. M. Nolte, *Science*, 1998, **280**, 1427.
71 J. Rodríguez-Hernández and S. Lecommandoux, *J. Am. Chem. Soc.*, 2005, **127**, 2026.
72 E. G. Bellomo, M. D. Wyrsta, L. Pakstis, D. J. Pochan and T. J. Deming, *Nat. Mater.*, 2004, **3**, 244.
73 E. P. Holowka, D. J. Pochan and T. J. Deming, *J. Am. Chem. Soc.*, 2005, **127**, 12423.
74 E. P. Holowka, V. Z. Sun, D. T. Kamei and T. J. Deming, *Nat. Mater.*, 2007, **6**, 52.
75 B. M. Discher, D. A. Hammer, F. S. Bates and D. E. Discher, *Curr. Opin. Colloid Interface Sci.*, 2000, **5**, 125.
76 P. A. Wender, D. J. Mitchell, K. Pattabiraman, E. T. Pelkey, L. Steinman and J. B. Rothbard, *Proc. Natl. Acad. Sci. U. S. A.*, 2000, **97**, 13003.
77 S. Futaki, T. Suzuki, W. Ohashi, T. Yagami, S. Tanaka, K. Ueda and Y. Sugiura, *J. Biol. Chem.*, 2001, **276**, 5836.
78 Y.-R. Yoon, Y.-b. Lim, E. Lee and M. Lee, *Chem. Commun.*, 2008, 1892.
79 G. T. Dolphin, P. Dumy and J. Garcia, *Angew. Chem., Int. Ed.*, 2006, **45**, 2699.
80 C. W. G. Fishwick, A. J. Beevers, L. M. Carrick, C. D. Whitehouse, A. Aggeli and N. Boden, *Nano Lett.*, 2003, **3**, 1475.
81 T. S. Burkoth, T. L. S. Benzinger, D. N. M. Jones, K. Hallenga, S. C. Meredith and D. G. Lynn, *J. Am. Chem. Soc.*, 1998, **120**, 7655.
82 J. Hentschel, E. Krause and H. G. Börner, *J. Am. Chem. Soc.*, 2006, **128**, 7722.
83 R. Mimna, M.-S. Camus, A. Schmid, G. Tuchscherer, H. A. Lashuel and M. Mutter, *Angew. Chem., Int. Ed.*, 2007, **46**, 2681.
84 Y.-b. Lim and M. Lee, *J. Mater. Chem.*, 2008, **18**, 723.
85 C. L. Nesloney and J. W. Kelly, *Bioorg. Med. Chem.*, 1996, **4**, 739.
86 H. J. Dyson, J. R. Sayre, G. Merutka, H. C. Shin, R. A. Lerner and P. E. Wright, *J. Mol. Biol.*, 1992, **226**, 819.
87 J. H. Collier and P. B. Messersmith, *Adv. Mater.*, 2004, **16**, 907.

88 J. M. Smeenk, M. B. J. Otten, J. Thies, D. A. Tirrell, H. G. Stunnenberg and J. C. M. van Hest, *Angew. Chem., Int. Ed.*, 2005, **44**, 1968.
89 U. Baxa, V. Speransky, A. C. Steven and R. B. Wickner, *Proc. Natl. Acad. Sci. U. S. A.*, 2002, **99**, 5253.
90 N. Sondheimer and S. Lindquist, *Mol. Cell*, 2000, **5**, 163.
91 A. J. Baldwin, R. Bader, J. Christodoulou, C. E. MacPhee, C. M. Dobson and P. D. Barker, *J. Am. Chem. Soc.*, 2006, **128**, 2162.
92 M. Gouterman and D. Dolphin, *The Porphyrins*, Academic Press., New York, 1978.
93 Y.-b. Lim, E. Lee and M. Lee, *Angew. Chem., Int. Ed.*, 2007, **46**, 3475.
94 M. Sung, G. M. K. Poon and J. Gariépy, *Biochim. Biophys. Acta: Biomembranes*, 2006, **1758**, 355.
95 Y.-b. Lim, S. Park, E. Lee, H. Jeong, J.-H. Ryu, M. S. Lee and M. Lee, *Biomacromolecules*, 2007, **8**, 1404.
96 Y.-b. Lim, S. Park, E. Lee, J.-H. Ryu, Y.-R. Yoon, T.-H. Kim and M. Lee, *Chem.–Asian J.*, 2007, **2**, 1363.
97 H. Wang, L. Gu, Y. Lin, F. Lu, M. J. Meziani, P. G. Luo, W. Wang, L. Cao and Y.-P. Sun, *J. Am. Chem. Soc.*, 2006, **128**, 13364.

