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Bio-inspired supramolecular self-assembly towards soft nanomaterials

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Abstract

Supramolecular self-assembly has proven to be a reliable approach towards versatile nanomaterials based on multiple weak intermolecular forces. In this review, the development of bio-inspired supramolecular self-assembly into soft materials and their applications are summarized. Molecular systems used in bio-inspired “bottom-up self-assembly” involve small organic molecules, peptides or proteins, nucleic acids, and viruses. Self-assembled soft nanomaterials have been exploited in various applications such as inorganic nanomaterial synthesis, drug or gene delivery, tissue engineering, and so on.

Keywords

supramolecular self-assembly; soft material; peptide; nucleic acid; virus

1 Introduction

Nature’s power to efficiently create diverse complex biological functions is based on the non-covalent interactions of covalently prefabricated building blocks including bilayered lipid liposomes, protein tertiary structures, DNA double helices, as well as the complex biological process. For example, in proteins, the amino acid sequence (primary structure) pre-determines different chain segments to attain well-defined conformations such as α-helices or β-sheets (types of secondary structures). These chains are then folded into a specific spatial arrangement (tertiary structure) which determines the overall topographic shape of the macromolecules in solution. Finally, the folded macromolecules may self-assemble into the bioactive protein complex or structural protein (quaternary structure). In this way, complex structural proteins with specific functions are created through the method known as the “bottom up approach”. The structural information and functions are programmed on the molecular level and the subsequent self-assembly beyond molecular level.

Inspired by nature, chemists have been endeavored to explore molecular or supramolecular self-assembly to: (1) reveal the mechanism for the biological self-assembly and understand the way in which biological objects are organized; (2) mimic the complicated but efficient self-assembly process in nature to design hierarchical structures possessing bioactivities; (3) create novel structures or materials capable of novel biological functions.

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Supramolecular self-assembly is an active area of current research in modern chemistry. This review primarily focuses on the research progress of supramolecular self-assembly that is: (1) inspired from biological self-assemblies (e.g. DNA base pairing directed helical rosette nanotubes); (2) based on naturally occurring materials (e.g. peptide β-sheets and viruses); (3) based on synthetic molecules or amphiphiles bearing bioactive moiety (e.g. peptide-amphiphiles and novel glycolipids). The review will help to indicate the recent advances of supramolecular self-assembly research in modern chemistry and aid our future work. In the first section, the concept of supramolecular self-assembly will be briefly introduced and the second section will discuss different building blocks used in supramolecular self-assembly. The applications of self-assembled nanomaterials are presented in the third part.

2 Supramolecular self-assembly — concept and principles

Lehn described supramolecular chemistry as the instruction set for the creation of a large complex assembly contained within its constituent components [1–3]. Supramolecular self-assembly can be defined as the spontaneous formation of organized structures from building blocks with the aid of multiple intermolecular forces including hydrophobic or solvophobic effect, electrostatic forces, hydrogen bonding, π-π stacking, coordination interactions, and ion-dipole interactions [4–9]. For the chemists, supramolecular self-assembly represents a powerful synthetic methodology in the creation of large, discrete, ordered structures from relatively simple units. In this review, the emphasis is on the bio-inspired supramolecular self-assembly into hierarchical structures.

3 Molecular systems used in self-assembly and soft nanomaterials

3.1 Small organic molecules

The most important biopolymers in nature include DNA, proteins, and saccharides, which are covalently linked from DNA bases, amino acids, and simple carbohydrates respectively. Synthetic molecules or amphiphiles incorporated with amino acids, carbohydrates, or DNA bases have received special attentions, owing to their advantages of easy synthesis, tailored molecular structures, biocompatibility, self-organization, and potential applications in bio-related fields.

Nucleic acid bases in DNA systems are a key requisite of double helical systems and genetic information storage. This importance, coupled with the unique nucleobase hydrogen-bond interactions has inspired the use of such motifs to construct a variety of novel ensembles [10]. For example, Yanagawa et al. reported a mononucleotide unit covalently linked to hydrophobic groups of phospholipids, which is capable of self-assembly in aqueous solution to form helical strands as in the case of DNA and RNA [11]. Baglioni and Berti et al. synthesized a series of nucleolipids which form giant wormlike micelles and twisted nanofibers (Fig. 1) [12]. Kim and coworkers used uridine-based amphiphile to prepare low molecular weight hydrogels [13]. Barthélémy et al. described the self-assembled vesicles and ribbon-like structures in different nucleotide-based amphiphiles [14].

DNA is distinguished by its predictable Watson-Crick base-pairing, which enables molecular recognition through hydrogen bonding (Fig. 2). Watson-Crick base-pairing rule can be also used to fabricate self-assembled nanostructures from DNA bases. An outstanding example is the helical rosette nanotubes, which is hierarchically self-assembled by the G^C motif fueled by hydrophobic effects in water. Upon self-assembly, a six-membered supermacrocycle is maintained by 18 H-bonds (rosette) and the functional groups covalently attached to G^C motif could be expressed on the nanotube surface, thereby offering a general “built-in” strategy for tailoring the properties and functions of helical

rosette nanotubes (HRNs). Fenniri et al. have reported hierarchical self-assembly of organic nanotubes from supermacrocycles (rosettes) [15–16]. As shown in Fig. 3, the synthesized L-module **1** possesses a hydrophobic base unit bearing Watson-Crick donor-donor-acceptor (DDA) H-bond array of guanine and acceptor-acceptor-donor (AAD) of cytosine. The spatial arrangement of these arrays constrains **1** to form a six-membered supermacrocycle (rosette, Fig. 3(b)). Later, the same group reported helical rosette nanotubes with tunable chiroptical properties and increased nanotube diameters [17–18].

Self-assembled G-quartets, directed by the hydrogen-bonding self-assembly of four guanosine (G) residues and stabilized by alkali-metal cations (Fig. 4), are emerging as another important subject in supramolecular chemistry and biology [19]. The G-quartet architecture represents a dynamic supramolecular system that has been used as a building block for gelators, columnar polymeric aggregates, self-organized surfaces, and prototypes of chemical dynamic devices [20].

Another synthetic motif intensively investigated is the carbohydrate group, which plays an important role in cell recognition and membrane fusion processes [21]. Simple alkyl glycosides can be found as membrane components, whereas more complex glycolipids are reported to serve as secondary messengers [22] and pathogens [23] and some are substructures of complex endotoxins [24]. Over the past decade, the peculiar self-assembly of glycolipids in water and organic solvents has been extensively studied. Hierarchical architectures including lipid nanotubes, twisted/helical nanofibers, low-molecular-weight gels, and liquid crystals are produced through “bottom-up fabrication”.

The research of glycolipid self-assembly was initially reported by Fuhrhop et al. [25–30]. In their research, N-octyl-D-gluconamide (Fig. 5) is found to form helical fibers caused by amide hydrogen bonds [30]. Ultrathin (diameter 3.8 nm) quadruple helices with a magic-angle inclination are trapped possibly because of the equilibrium between the helices and the micellar disks. A detailed electron microscopic study of these helices revealed a helix, which is dictated by the order of electric interactions between the four helices (Fig. 5(c)).

Shimizu and colleagues also systematically investigated the self-assembly behavior of glycolipids, especially on the design of high-aspect-ratio nanostructures. The group synthesized renewable resource-based molecular building blocks included **1** (which is a mixture derived from cardanol) and **2** (saturated analogue d) (Fig. 6(a)) [31–32]. Glycolipid **1** retained a characteristic helical, coiled-ribbon structure (Fig. 6(b)), and **2** retains a twisted structure (Fig. 6(c)). The coiled nanofibers self-assembled from glycolipid **1** gradually turned into tubular structures, while the modified cardanol derivative (saturated analogue **2**) did not form into nanotubes [33]. The authors suggested that glycolipid self-assembly is driven by hydrogen-bonding, π-π stacking, and hydrophobic forces. The presence of aromatic units induces structural rigidity and helps glycolipids stacking in a cylindrical fashion. Shimizu’s group also studied the self-assembly of a series of long chain phenyl glucosides varying in number of *cis* double bonds [34]. It is found that long-chain phenyl glucosides form twisted nanofiber, helical ribbon, and nanotubular structures depending on the unsaturation of the double bonds. A series of bolaamphiphiles with a 1-glucosamide-head group at each end are reported by the same group [35–36].

Engberts et al. synthesized a series of Gemini-type sugar lipids which self-organize into pH-responsive vesicles [37–42]. The same group has investigated the lipoplex structure of DNA and sugar-based cationic Gemini surfactant, which exhibits excellent transfection efficiency [37]. Rico-Lattes and coworkers have systematically investigated catanionic sugar surfactant which can self-assemble into helices, tubules and vesicles [43–47]. As shown in Fig. 7, the

two-chain **1** self-assembles into unilamellar vesicles while Gemini **2** catanionic surfactant can form lamellae or multilamellar vesicles [44].

The constructive supramolecular self-assembly of glycolipids into soft nanostructures has also been explored by several groups such as O'Brien [48–49], Nolte [50], Lee [51–52], Ho [53–56], Cintas [57], and Hong [58]. Besides, Shinkai group studied the combinatorial library of atypical sugar-integrated amphihphiles which exhibit unique organic gelling capabilities with different three-dimensional network [59–64].

3.2 Peptides and proteins

The covalently linked amino acids with specific sequence give rise to peculiar peptides, which can undergo distinctive self-assembly [65–67] and exhibit recognition function [68–69]. Depending on the conformation and stereochemical configuration of the constituent amino acids, peptides exhibit different structures, such as α-helices and β-sheets. Zhang and coworkers described a class of ionic self-complementary peptides, which form β-sheet structures in aqueous solution with two distinct surfaces. The self-assembly of these peptides is facilitated by electrostatic interactions on one side and the hydrophobic interactions on the other, in addition to the β-sheet hydrogen bonds along the backbone. These peptides with alternating hydrophilic and hydrophobic amino acids can spontaneously aggregate to form interwoven nanofibers in the presence of monovalent cations [70–71]. The peptide scaffolds have been demonstrated to serve as substrates for tissue cell attachment promoting extensive neurite outgrowth and the formation of active nerve connections. Zhang's group also designed a series of peptides which undergo self-assembly to form nanotubes and nanovesicles [72–73]. TEM images reveal the surfactant peptides form a dense network of nanotubes and nanovesicles. Interestingly, 3-fold junctions or branches connecting the nanotubes forming the network can be identified, similar to those observed in tree branches (Fig. 8).

In another attempt, Aggeli et al. designed different short peptides that self-assemble into long, semi-flexible peptide nanotapes in non-aqueous solvents [74–76]. Ghadiri et al. have focused on the self-assembled nanotubes made from cyclic D,L-α-peptides and from cyclic β-peptides, which display a wide range of structural and functional capabilities [77–78]. The research focusing on the peptide self-assembly was also reported by the research groups of Deming [79–80], Hartgerink [81–86], Schneider [87–90], Lu [91–92], and Lee [93–94].

Peptide-amphiphiles (PA) which attach hydrophobic tails to peptide segments are found to self-assemble into highly organized nanostructures, wihch may promote cell adhesion, spreading, migration, growth and differentiation [95–100]. The pioneering work of peptide amphiphiles was done by Stupp et al. [101–108]. This group synthesized a peptide-amphiphile consisting of five parts with different functions (Fig. 9(a)) [101]. Region 1 is a long alkyl tail that conveys hydrophobic character to the molecule and makes the molecule amphiphilic. Region 2 is composed of four cysteine residues that can be polymerized by forming disulfide bonds. Region 3 is a hydrophilic flexible linker region of three glycine residues. Region 4 is a single phosphorylated serine residue that is designed to interact strongly with calcium ions and help direct mineralization of hydroxyapatite. Region 5 displays the cell adhesion ligand RGD. Upon acidification of the solution, the PA spontaneously aggregated into birefringent hydrogels. Cryo-TEM revealed a network of fibers with a diameter of ~7.6 nm and lengths up to several micrometers (Fig. 9(b)). After self-assembly of PA molecules into fibers, the cysteine thiol groups were oxidized. These oxidized PA fibers were found to be stable to alkaline solutions (pH 8) for months, whereas fibers that had not been oxidized would disassemble within several minutes.

Later, Stupp's group investigated twelve derivatives of peptide-amphiphiles that self-assemble into nanofibers [102]. The scope of amino acid selection and alkyl tail modification in the peptide-amphiphile molecules were examined, yielding nanofibers varying in morphology, surface chemistry, and potential bioactivity. Self-assembly of unsymmetric peptide bolaamphiphiles into nanofibers with hydrophilic cores and surfaces are also reported by Stupp et al. [103]. The fabrication of mixed nanofibers from two oppositely charged PAs carrying different biological signals over a large pH range is described [104]. The PA can be modified with tryptophan or pyrene chromophores onto the peptide backbone to probe interior information of resulting supramolecular fiber by spectroscopy [106].

The research on PAs are also reported by Löwik and Hest et al. [109–111], Hartgerink et al. [112], Tirrell et al. [95,98], and Wang et al. [96]. Although a variety of peptide-based scaffolds have been studied, most of the reported peptides self-assemblies are limited to round shapes such as spheres, tubes, and rods. In a recent work [113], Lee et al. reported the first example of finite molecular architectures formed by the self-assembly of a helical β-peptide in aqueous solution (Fig. 10). The 3D shapes of the assembled structures can be controlled by simply changing experimental conditions. The ability to construct biocompatible peptide-based molecular architectures with anisotropic shapes should expand the possibilities for the design of molecular machines for diverse applications in biological and materials science.

3.3 Nucleic acids

DNA or nucleic acids are known as the long term carriers and storage of genetic information, benefiting from the code made up of four chemical bases: adenine (A), guanine (G), cytosine (C), and thymine (T). Over the last two decades, DNA has been extensively manipulated as a versatile material to design functional nanostructures, by pre-designed strands with specific nucleic acid sequences. In 1982, Seeman first proposed the construction of ordered arrays by using branched DNA units [114]. Afterwards, DNA has been shown to be versatile building blocks to fabricate nanometer-scale objects and micrometer-scale arrays (Fig. 11) [115–117].

The driving force for DNA self-assembly lies in the predictable base specific interactions and recognition, namely hydrogen bonding of A/G and G/C pairing. Arbitrary sequences of DNA can be conveniently synthesized in the laboratory by automated phosphoramidite chemistry and functional groups can be covalently attached to the DNA at the end or in the middle using chemical strategy. This ability greatly enables the design of DNA self-assembly into complex architectures through complementary base pairing. The research groups focusing on the DNA self-assembled nanoarchitectures include Seeman [114–115,118–122], LaBean [123–125], Yan [117,126–130], Mao [131–135], and Sleiman [136–139]. These DNA self-assemblies have been used in the synthesis and organization of inorganic nanomaterials, the programmed assembly of biomolecules, and as biosensing materials.

3.4 Viruses

Viruses can be regarded as supramolecular objects consisting of a protein coat and nucleic acid (RNA or DNA), in which proteins assemble round the nucleic acid. The nucleic acid encodes the genetic information and the protein is mainly for protection of nucleic acid. Viruses, which can specifically infect their host, are being employed in biotechnology and nanomedicine [140–147]. Three types of viruses may be used as platforms for these applications: bacteriophages, plant viruses, and animal viruses [148–149]. Plant viruses and

bacteriophages have been mostly investigated because of their low toxicity even at high doses.

The plant virus includes the isosahedral, sphere-like virus Cowpea chlorotic mottle virus (CCMV), Brome mosaic virus (BMV), Cowpe mosaic virus (CPMV), and the rod-shaped Tobacco mosaic virus (TMV). CCMV and BMV are tripartite single-stranded RNA-viruses and have icosahedral symmetry with a diameter of ca. 28 nm. CPMV virions exhibit an icosahedral symmetry and show protrusions at the icosahedral five-fold and also at the three-fold axis. The virions are formed by 60 copies of two different types of coat proteins. Viruses are particularly interesting scaffolds for the preparation of novel supramolecular biohybrid materials. In a recent work, Kostiainen and coworkers used CCMV particles as building blocks to self-assemble into well-defined micrometre-sized objects and then reconvert into individual viruses by using optical stimuli. Assembly is achieved using photosensitive dendrons that bind on the virus surface through multivalent interactions and then act as a molecular glue between the virus particles. The author demonstrated that this method is not limited to the virus particles alone, but can also be applied to other functional protein cages such as magnetoferritin [150].

Bacteriophages or phages, which are viruses that can specifically infect bacteria and is nontoxic to human beings, are an important class of viruses. This is because the well-established phage display technique can be used to identify target-recognizing peptides or proteins from a combinatorial phage-displayed random peptide or protein library, which in turn results in the selection of target-specific virus particles [151]. In addition, phages are robust, thermally and chemically stable, and easy to conjugate with other motifs such as biomolecules or nanoparticles. Filamentous phage including f1, fd, and M13 are the most studied phages, which infect *Escherichia coli* through their F pili. The filamentous phage can be pictured as a core-shell biological nanofiber with ~900 nm long and ~700 nm wide (Fig. 12) [152]. An ssDNA of about 6400 bp is packaged within five coat proteins named pVIII, pIII, pVI, pVII, and pIV. The cationic M13 viruses can be used to undergo the layer-by-layer (LBL) assembly with anionic AuNPs, leading to nanocomposite films. The resultant nanocomposite films exhibit unique surface plasmon resonance (SPR) spectra, depending on their nanoarchitectures (specifically their terminating layers and number of layers) as well as on the environmental humidity [152–153].

4 Application of soft nanomaterials formed by supramolecular self-assembly

4.1 Nanomaterial synthesis and assembly

The last two decades have witnessed an influx of research endeavors aimed at developing synthetic methods for the preparation of novel nanomaterials. Soft template-directed synthesis has proved an ideal approach to structural replication, by the design of materials with predetermined structural properties. There are a vast variety of biological species or biomolecular self-assemblies (e.g. peptides, proteins, DNA, viruses, and small molecules or amphiphiles).

With unique sequence-specific self-assembly and recognition properties, peptides play critical roles in controlling the biomineralization of inorganic nanostructures in natural systems. These attributes render them particularly useful molecules for the fabrication of new materials. Researchers from many scientific disciplines now use peptides to direct the synthesis of inorganic nanostructures including SiO_2, TiO_2, GeO_2, Cu_2O, Cr_2O_3, Fe_2O_3, PbO_2, $CaCO_3$, CdS, Ag, Au, Pt, Pd, etc. [154]. For example, Stupp and coworkers used peptide-amphiphile fibers (PA) as templates for the nucleation of hydroxyapatite [101]. Matsui et al. used sequenced histidine-rich peptide nanowires as templates to fabricate Au

nanowires, in which monodisperse Au nanocrystals were uniformly coated on the histidine peptide nanowires [155]. This strategy can be also utilized to control Cu nanocrystal growth on peptide nanotubes [156]. Adschiri et al. identified a peptide using a combinatorial library approach with both an affinity for ZnO and the ability to generate ZnO nanoparticles that assemble into a highly ordered flower-type structure [157].

Compared with the naturally occurring peptides or DNA, the synthetic amphiphiles or biomolecules exhibits more flexibility in self-assembled structures. For example, Shinkai et al. have described a self-assembly route to organogel and tunable right- and left-handed chiral fibers, which can be readily transcripted into inorganic materials (SiO_2) by the sol-gel transcription method (Fig. 13). This work illustrates the versatility and adaptability of soft templates in the creation of inorganic nanomaterials [158]. Stupp et al. reported the design of single and double helices of cadmium sulfide (CdS) from self-assembled nanoribbons [159–160]. Huang and coworkers synthesized single and double-stranded silica nanohelices templated by self-assembled nanostructures [161].

Nanosized inorganic particles are often classified as “artificial atoms” and may act as potential building blocks for novel materials with multi-functions. To harness the potential of inorganic nanoparticles as building blocks, scientists have devised various approaches to assemble inorganic nanoparticles into one-, two-, and three-dimensional hierarchical architectures [162–164]. For example, Fenniri et al. used self-assembled rosette nanotubes (RNTs) which are a new class of biocompatible materials obtained through self-assembly of G^C motif, to nucleate and assemble monodisperse gold nanoparticles [165]. Pochan et al. have prepared nanosheets of gold nanoparticles, in which laminated β-sheet peptide fibrils acted as templates, and negatively charged gold nanoparticles intercalated within fibril laminates [164]. The formation of the aggregates was induced by electrostatic interactions with the positively charged lysine side chains of the fibrils. Recently, Rosi and coworkers selected the water-soluble peptide AYSSGAPPMPPF to mineralize chloroauric acid to form spherical gold nanoparticles in the presence of HEPES buffer [162,166]. In the presence of HEPES buffer, peptide self-assembles into a unique left-handed twisted nanoribbon. The addition of chloroauric acid was found to assist the formation of twisted nanoribbons. Moreover, the observed self-assembly process and the formation of gold nanoparticles were successfully coupled into one simultaneous process to form structurally complex and highly ordered left-handed double helices of gold nanoparticles (Fig. 14).

4.2 Drug and gene delivery

The pharmacological properties of conventional drugs can be improved through better drug delivery systems (DDS), which include carriers and their associated therapeutics [167]. In the last two decades, the development of supramolecular self-assembly has offered new choices for versatile nanocarriers used in drug delivery. The drug carrier can be lipid liposomes, polymer micelles, peptide hdyrogel, polymeric multilayer capsules, and viruses [168–173].

The primary advantage of using supramolecular self-assembled nanomaterials as drug carriers lies with their external stimuli-responsive release ability, triggered by external input such as light, pH, temperature, or ionic strength. This property allows facile structural transformation of self-assemblies by subtle environmental changes. For example, John et al. reported a novel approach for the controlled delivery of an anti-inflammatory, chemo-preventive drug by an enzyme-triggered drug release mechanism via the degradation of encapsulated hydrogels [174]. Recently, Kataoka et al. have shown the intracellular localization of pH-sensitive polymeric micelles whose functions are controlled by live cells. As a multifunctional biomolecular device, the micelles undergo dynamic changes in

structure and/or function in response to environmental stimuli which enable its utilization as a pH-triggered drug cargo [175].

Owing to the cell-specific property, bacteriophage is exploited as nanocarriers to deliver drugs. For example, Mao et al. reported the self-assembled phage–liposome complex of cationic ZnPc-entrapped liposomes and anionic genetically engineered M13 phage, which was utilized as a novel nanocarrier for targeted drug delivery [153,176]. M13 phage is a rod-like virus that specifically infects bacteria and is nontoxic to human beings. The side wall of phage is made of ~3000 copies of a genetically modifiable major coat protein called pVIII. The two ends of the rod-like virus can be engineered to identify and display a peptide that can recognize a specific target (e.g., cells, tissues, or organs) through phage display. On the other hand, lipid liposomes are regarded as the best containers to entrap drugs either within the inner aqueous compartment or within the hydrophobic domain of the lipid bilayer. The self-assembled phage-liposome complex (Fig. 15) driven by electrostatic interactions is therefore anticipated to be a target-recognized cargo for zinc phthalocyanine (ZnPc), which is a photosensitizer for photodynamic therapy.

4.3 Biomaterials and tissue regeneration

Biomaterials play central roles in modern strategies in regenerative medicine and tissue engineering as designable biophysical and biochemical milieus that direct cellular behavior and function. One important aspect of biomaterial research is the bioactivity of materials and devices, especially in the fields of tissue engineering and regenerative medicine. Until now, peptides were the most promising candidates for functionalizing interfaces and incorporating cell binding ability and recognition into biomaterials.

The peptide-amphiphiles provide a convenient mechanism for self-assembly into 1D nanostructures associated with 3D network formation, which make them ideal candidates as cell culture matrixes or scaffolds in tissue engineering and regenerative medicine. Extensive studies have already indicated their good biocompatibility. Thus, the composition and orientation of molecules on the surface is well controlled, enabling optimal presentation of active binding sites. Furthermore, these long chains can also improve the stability and activity of the peptide relative to the parent protein by imparting secondary structures. Current and past research into the utility of peptide-amphiphiles has focused on several aspects, including, but not limited to, binding specificity; the effect of surface composition, and ligand availability on binding; factors affecting cell spreading and migration; and the effect of ligand structures on the binding capability. One of the most desirable qualities in any bioactive material is the ability to interact specifically with cells of interest.

Apart from peptides or proteins, molecular self-assembly has provided various potential biomaterials. For example, Fenniri et al. reported the application of RGDSK (Arg-Gly-Asp-Ser-Lys) modified rosette nanotube–hydrogel composites with unique surface chemistry and favorable cytocompatibility properties for bone repair [177]. Incorporated with nanocrystalline hydroxyapatite hydrogel, helical rosette nanotubes (HRNs) were successfully used to design a novel biomimetic nanocomposite with improved mechanical and cytocompatibility properties for bone tissue engineering applications [22].

5 Summary and outlook

In summary, we have highlighted the progress in supramolecular self-assembly into well-organized nanostructures as well as their applications in various areas. Driven by the hydrophobic interactions, electrostatic forces, hydrogen bonds, π-π packing, or their synergic effects, the biofunctional molecules can give birth to and stabilize the self-assembled architectures on different scales, including vesicles, fibers, tubes, ribbons,

lamella, and helices. The self-assembled structures can vary in shape, size, helicity, and handness. Particularly, the 1D nanostructures can be fabricated from biomolecular self-assembly by the directing forces of the hydrogen bonding and π-π stacking. The self-assembled nanostructures and soft materials can be exploited in biomedicine such as biomaterials synthesis, drug and gene delivery, tissue engineering and regenerative medicine. Despite the vast work on the bio-inspired supramolecular self-assembled nanomaterials, we believe more work needs to be dedicated to the following areas: (i) responsive biomaterials whose structure and function can be manipulated by environmental stimulus; (ii) complex hierarchical self-assemblies that can mimic naturally occurring structures; (iii) the incorporation of biofunctional segments into the emerging nanomaterials to improve their biofunctionality and bioactivity for better performance in biomedical applications. Therefore, the combination of supramolecular chemistry, material science, and biology has generated multidisciplinary research areas in nanomedicine and biotechnology.

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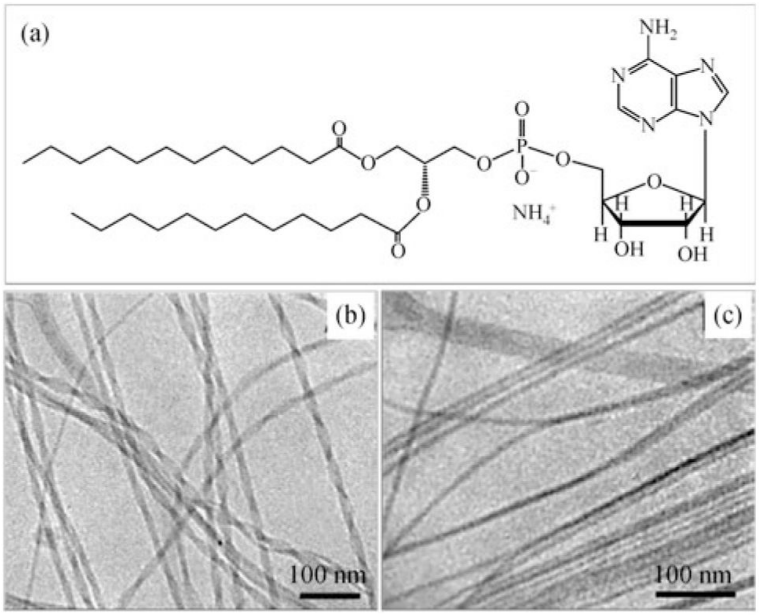

Fig. 1.

(a) Molecular structure of 1, 2-dilauroyl-phosphatidyl-adenosine (DLPA). Cryo-TEM images of DLPA micellar solutions in 0.1 mol/L PBS: **(b)** aged samples at 25°C; **(c)** after an overnight annealing at 35°C. (Reproduced with permission from Ref. [12], Copyright 2008 Royal Society of Chemistry)

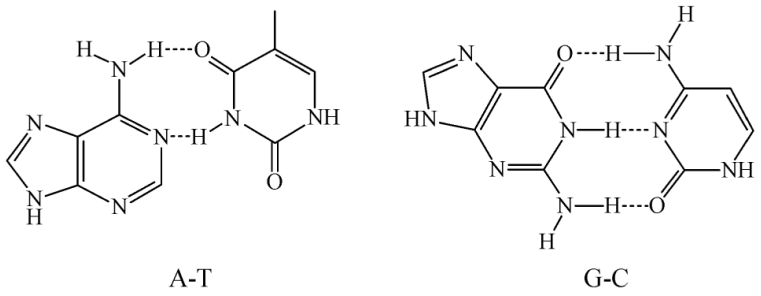

Fig. 2.
The Watson–Crick hydrogen-bonding motifs between DNA bases.

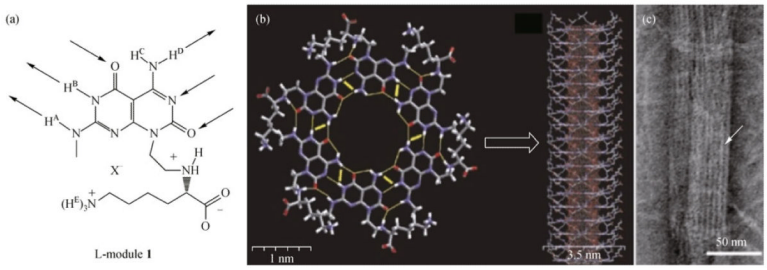

Fig. 3.
(a) Modules **1** investigated. **(b)** Molecular model of rosette structure and the proposed nanotubes. **(c)** TEM of rosette nanotubes. (Reproduced with permission from Ref. [15], Copyright 2001 American Chemical Society)

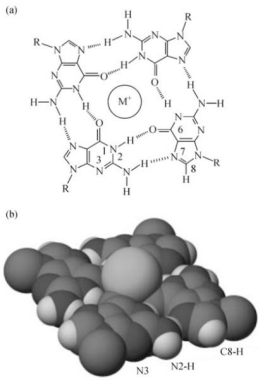

Fig. 4.

(a) The G-quartet and **(b)** a space-filling model showing a G-quartet with a K^+ bound above the plane of the G-quartet. (Reproduced with permission from Ref. [20], Copyright 2004 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim)

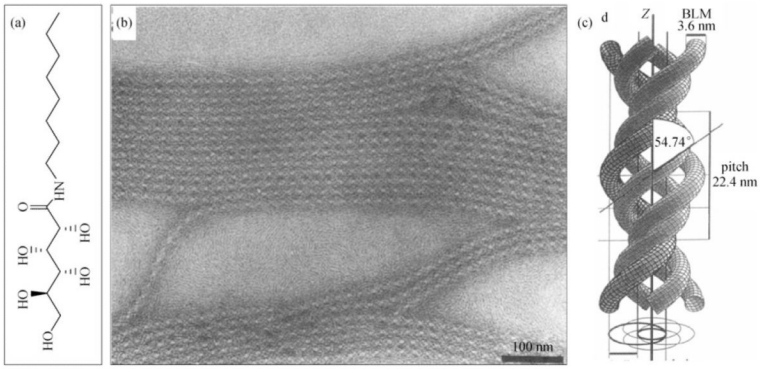

Fig. 5.

(a) Molecular structure of N-octyl-D-gluconamide. **(b)** TEM image of a fiber bundle. **(c)** Computer model of the helical fiber. (Reproduced with permission from Ref. [30], Copyright 1993 American Chemical Society)

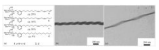

Fig. 6.

(a) Molecular structure of renewable resource-based molecular building blocks. **(b)** EF-TEM image of an individual coiled nanofiber of **1**. **(c)** EF-TEM image of an individual twisted nanofiber of **2**. (Reproduced with permission from Ref. [31], Copyright 2001 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim)

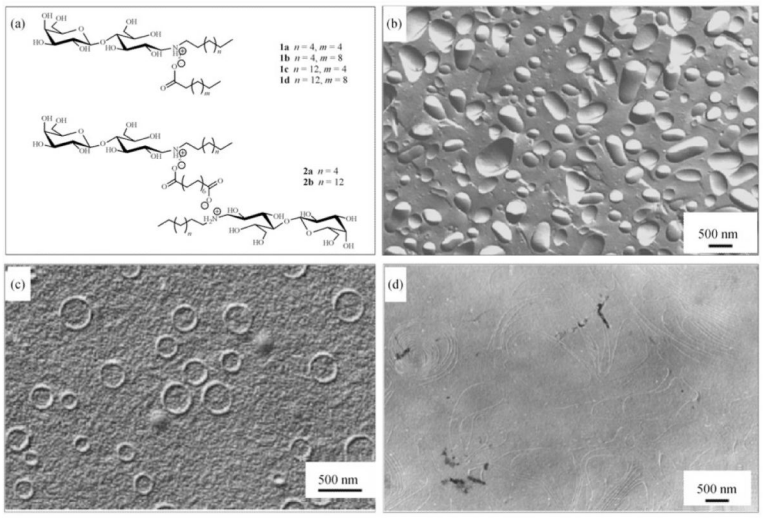

Fig. 7.

(a) Molecular structures sugar-based cationic-anionic surfactants systems. Freeze-fracture images of catanionic amphiphiles: **(b)** two-chain analogue **1b**; **(c)** Gemini **2a**; **(d)** Gemini **2b**. (Reproduced with permission from Ref. [44], Copyright 2003 Royal Society of Chemistry)

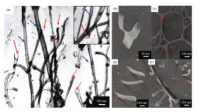

Fig. 8.
(a) TEM image of A6D and V6D in water. **(b)(c)** Three-way junctions. **(d)** There are openings at the ends indicated by red arrows, with the other ends possibly buried inside the replica. **(e)** Example of vesicles that are budding off a nanotube. (Reproduced with permission from Ref. [72], Copyright 2002 Proceedings of the National Academy of Sciences USA)

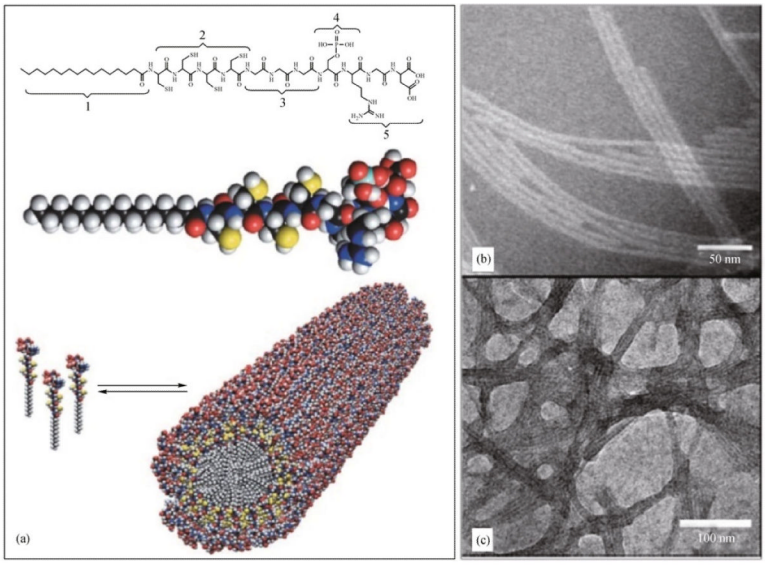

Fig. 9.

(a) Chemical structure and model of peptide amphiphile. **(b)** TEM of the nanofibers before covalent capture. Fibers are arranged in ribbon-like parallel arrays. **(c)** TEM of nanofibers after oxidative cross-linking. (Reproduced with permission from Ref. [101], Copyright 2001 American Association for the Advancement of Science)

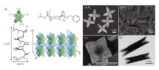

Fig. 10.
(a) Schematic representation of possible molecular packing of ACPC7. SEM of ACPC7 self-assemblies prepared from: **(b)** distilled water and **(c)** aqueous solution of P123. **(d)** Long-axis view of RP. **(e)** TEM image of RP. (Reproduced with permission from Ref. [113], Copyright 2010 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim)

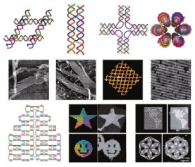

Fig. 11.
Models of representative DNA tiles and their assemblies into periodic 2D arrays.
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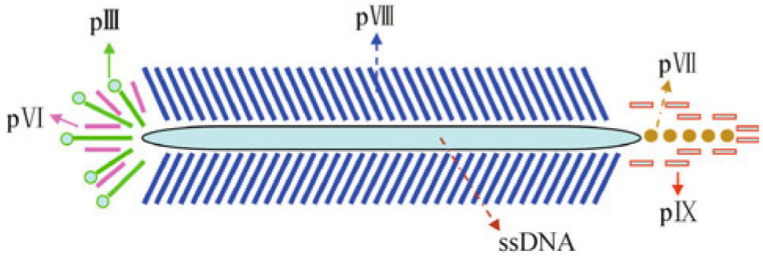

Fig. 12.
Schematic illustration of M13 virus (not scaled). (Reproduced with permission from Ref. [152], Copyright 2009 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim)

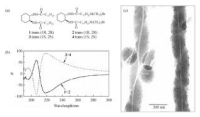

Fig. 13.

(a) Molecular structures of organogelators. **(b)** CD spectra of **1** + **2** (1:1 wt.%) and **3** + **4** (1:1 wt.%) in acetonitrile. **(c)** Left- and right-handed SiO_2 fiber. (Reproduced with permission from Ref. [158], Copyright 2000 American Chemical Society)

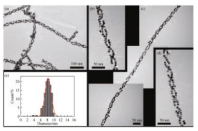

Fig. 14.
(a)(b)(c)(d) TEM images of double helical arrays of gold nanoparticles. **(e)** Size distribution of gold nanoparticles. (Reproduced with permission from Ref. [162], Copyright 2008 American Chemical Society)

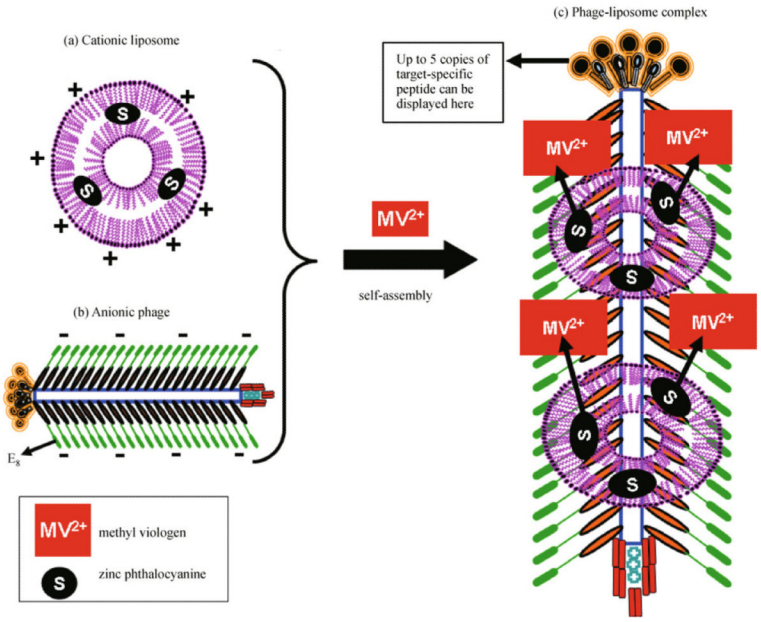

Fig. 15.

Schematic representation of the self-assembled complex: **(a)** cationic ZnPc-entrapped liposome; **(b)** anionic genetically engineered phage; **(c)** rod-like phage–liposome complex. (Reproduced with permission from Ref. [153], Copyright 2009 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim)