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Self-assembly of supramolecularly engineered polymers and its biomedical applications

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Abstract

Noncovalent interactions provide a flexible method of engineering various chemical entities with tailored properties. Specific noncovalent interactions between functionalized small molecules, macromolecules or both of them bearing complementary binding sites can be used to engineer supramolecular complexes that display unique structure and properties of polymers, which can be defined as supramolecularly engineered polymers. Due to their dynamic tunable structures and interesting physical/chemical properties, supramolecularly engineered polymers have recently received more and more attention from both academia and industry. In this feature article, we summarize the recent progress in the self-assembly of supramolecularly engineered polymers as well as its biomedical applications. In view of different molecular building units, the supramolecularly engineered polymers can be classified into the following three major types: supramolecularly engineered polymers built by small molecules, supramolecularly engineered polymers built by small molecules and macromolecules, and supramolecularly engineered polymers built by macromolecules, which possess distinct morphologies, definite architectures and specific functions. Owing to the reversible nature of the noncovalent interactions, the supramolecularly engineered polymers have exhibited unique features or advantages in molecular self-assembly, for example, facile preparation and functionalization, controllable morphologies and structures, dynamic self-assembly

process, adjustable performance, and so on. Furthermore, the self-assembled supramolecular structures hold great potential as promising candidates in various biomedical fields, including bioimaging, drug delivery, gene transfection, protein delivery, regenerative medicine and tissue engineering. Such developments on the self-assembly of supramolecularly engineered polymers and its biomedical applications greatly promote the interdisciplinary researches among supramolecular chemistry, polymer materials, biomedicine, nano-science and technology.

1. Introduction

Polymer chemistry has witnessed a remarkable development since the original discovery of the main-chain supramolecular polymers based on triple hydrogen bonding in 1990 by Lehn.¹ Different from the conventional polymers in which monomer units are connected by covalent bonds, supramolecular polymers are polymeric arrays of monomer units held together with directional and reversible noncovalent interactions, such as hydrogen bond, host-guest recognition, metal coordination or electrostatic interaction.²⁻⁵ The resulting materials therefore maintain their polymeric properties in dilute and concentrated solutions, as well as in the bulk. Due to the dynamic nature of noncovalent interactions, the supramolecular polymers exhibit a wide range of unique properties, such as reversibility and responsiveness to stimuli, which can be complementary to conventional polymers.⁶ For example, the reversibility of noncovalent interactions endows the supramolecular polymers with the ability of self-healing and adaptation, which provides a major advantage over covalent bonded polymers.

With the rapid development of supramolecular polymers, noncovalent interactions have been gradually extended to engineer various chemical entities from small molecules to macromolecules with complex properties. In this context, supramolecularly engineered polymers generate. Supramolecularly engineered polymers are a class of polymers built through noncovalent interactions among the monomer units, polymeric units, or both of them instead of covalent bonds. These dynamic supramolecularly engineered polymers represent a topic of increasing interest due to their enormous potential in a variety of applications and have received more and more attention in both academic and industrial fields in the last twenty years.⁷⁻¹²

In recent years, driven by an increasing need to create materials and devices with well-controlled and highly functional architectural features at different scales, polymer scientists have begun to use self-assembly as a powerful fabrication tool.¹³⁻¹⁸ In general, macromolecular self-assembly refers to the assembly of synthetic polymers, biomacromolecules and supramolecular polymers.¹⁹ In particular, the

self-assembly of supramolecularly engineered polymers, which could generate hierarchically ordered and complicated materials with novel structures and properties, has attracted wide interest in fields ranging from energy and medicine to environmental sustainability.²⁰⁻²⁸ In the past few years, a rapidly increasing amount of publications related to the synthesis strategies of supramolecularly engineered polymers, characterizations and applications have been reported.²⁹⁻³⁶ However, a systematic review on the self-assembly and potential biomedical applications of supramolecularly engineered polymers has not yet been published.

In this feature article, we consider only supramolecularly engineered polymeric systems with a molecular weight high enough to show at least oligomer behavior (e.g. molecular weight > 1 kDa). Depending on the building units, supramolecularly engineered polymers can be classified as the following three main types, including supramolecularly engineered polymers built by small molecules (SEPS), supramolecularly engineered polymers built by small molecules and macromolecules (SEPSM) as well as supramolecularly engineered polymers built by macromolecules (SEPM). Therefore, we are going to discuss the self-assembly of supramolecularly engineered polymers, including SEPS self-assembly, SEPSM self-assembly, SEPM self-assembly, and hybrid self-assembly. In addition, the biomedical applications of these supramolecularly engineered polymer assemblies are also summarized in this article. Despite it is impossible to cover all related topics completely within the frame of a single feature article, we try to identify the important trends in this field, as well as the significant achievements and challenges. We hope to stimulate new ideas and inspire continued endeavors in this promising research area of supramolecularly engineered polymers.

2. Self-assembly of supramolecularly engineered polymers

Macromolecular self-assembly involves spontaneous formation of supramolecular aggregates and structures in various states.¹⁷ During the past twenty years, the self-assembly of coil-coil or rod-coil typed block copolymers in solution or solid states has been widely studied.³⁷⁻⁴⁵ In recent years, progress in the self-assembly of supramolecularly engineered polymers has also been achieved. Up till now, supramolecularly engineered polymers have proved to be excellent precursors in macromolecular self-assembly, and many delicate supramolecular structures and hybrids at all scales have been generated. More importantly, these supramolecular materials have shown unique characteristics in comparison with conventional polymeric materials, such as simple morphology control, smart responsiveness, excellent template ability, facile functionalization, and unusual physical/chemical properties. These advantages pave the way for biomedical applications of

supramolecularly engineered polymer assemblies. In the following section, the self-assembly behaviors of various supramolecularly engineered polymers and their hybrids will be briefly introduced on the basis of different building units.

2.1 Self-assembly of supramolecularly engineered polymers built by small molecules (SEPS)

The polymeric backbone of SEPS is typically composed of low-molecular-weight building units that are held together via noncovalent connections. The physicochemical properties of such noncovalent bonded SEPS are not only determined by their intrinsic features of molecular building units, but also greatly depend on the nature of noncovalent interactions. The SEPS derived from small molecules exhibits several advantages, including ease to synthesis, versatile design, controlled structure and tunable function compared to covalent polymers.¹⁰ To date, a variety of noncovalent forces including hydrogen bonding, host-guest interaction, metal-ligand coordination, ionic interaction, and π - π stacking, etc., have been used to construct small molecule-based SEPS that is very sensitive to external stimuli, further imparting unique properties and functions to the supramolecular assemblies.⁴⁶⁻⁴⁹ In contrast to conventional polymeric assemblies, the supramolecularly engineered polymeric materials self-assembled from SEPS are more sensitive to external stimuli, and can achieve reversible switching of structure and properties under certain conditions due to dynamic noncovalent connections between molecular building units.

Geometrical matching and directionality of hydrogen bonding provide an effective method to form highly ordered supramolecular nanostructures self-assembled from low-molecular-weight building units.⁵⁰ By using self-complementary triple hydrogen bonding, Yagai and coworkers constructed SEPS through the self-assembly of melamine-anchored perylene bisimide and *N*-dodecylcyanurate in aliphatic media.⁵¹ The flexible hydrogen-bonded SEPS self-assembled into ribbon-like aggregates in cyclic alkanes and rope-like aggregates in acyclic alkanes, which were driven by π - π stacking between the perylene chromophores. Such solvent-dependent nanoscopic morphologies might be derived from the difference in the crystallinity of the self-organized SEPS in the solvents. These one-dimensionally elongated nano-objects containing electronically active chromophores would hold promise as nanoscale conducting wires.

Nowadays, the reversible metal-ligand interaction has been widely used to build metallo-supramolecular polymeric systems, which can bestow the resulting self-assembled materials with the ability to light-emitting behaviors and multi-responsive characteristics. In a typical example, Rowan and coworkers prepared multi-responsive metallo-supramolecular polymer utilizing metal-ligand interaction between metal ions with a ditopic ligand (Fig. 1a).⁵² The resultant SEPS exhibited

thermo-, chemo-, and mechano-induced sol-gel phase transition in chloroform/acetonitrile ($\text{CHCl}_3/\text{CH}_3\text{CN}$) (Fig. 1b). One particularly interesting property of the metallo-induced SEPS was its sensitivity to mechanical perturbation, resulting in a thixotropic shear-thinning behavior. It is obvious that the metallo-based SEPS opens up the possibility of designing multi-responsive organic-inorganic hybrid materials, whose properties can be easily tuned by changing the combination of metal ions. Furthermore, the incorporation of metal ions imparts the functional properties of the metal ions, for example, catalysis, light-emitting, conducting, gas binding, etc., to the resulting materials. As one example, Terech and coworkers have reported the metallo-supramolecular polymers based on the metal-ligand complexation between metal ions and a polytopic bis-terpyridine-cyclam ligand, giving multi-sensitive gels in dimethylformamide (DMF).⁵³ These new SEPS gels exhibit interesting properties: (i) chemosensitivity: the gelation is dependent on the type of metal, stoichiometry of metal ions/ligand, solvent, and counterion; (ii) electrosensitivity: among these systems, the Co(II)/ligand gel system is electrochemically and reversibly changed between the gel (red) and liquid (green) states; and (iii) mechanical sensitivity: the system is able to cycle from weakly to highly viscous states upon fast application/suppression of a shearing stress. The variety of colors and reversible gelation of the metallo-induced SEPS gels gained by multiple stimuli clearly demonstrates the advantages of incorporating metal ions into SEPS.

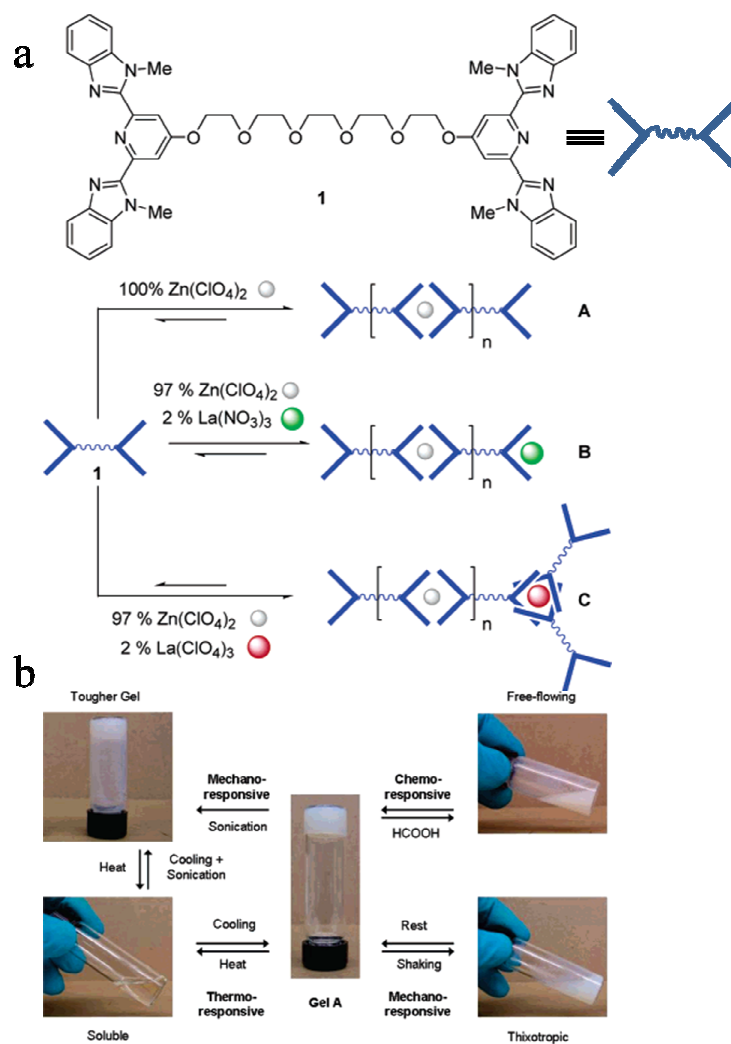


Fig. 1 (a) Schematic representation of the formation of metallo-supramolecular polymeric aggregates using ditopic ligand end-capped monomers with metal salts: A, $\text{Zn}(\text{ClO}_4)_2$, B, $\text{Zn}(\text{ClO}_4)_2$ and $\text{La}(\text{NO}_3)_3$, and C, $\text{Zn}(\text{ClO}_4)_2$ and $\text{La}(\text{ClO}_4)_3$, mixed with monomer **1** in acetonitrile as solvent. (b) Gel A (11 wt% in acetonitrile) exhibits the typical multi-stimuli responsive behavior observed for this class of metallo-supramolecular gels. Reproduced with permission from ref. 52. Copyright 2006, American Chemical Society.

Among various noncovalent interactions, host-guest interaction endows the resulting supramolecular materials with unique physical/chemical properties accompanied with easily switched efficiencies and functions. Harada and coworkers used cyclodextrin (CD) derivatives to prepare supramolecularly engineered polymers based on host-guest interaction, and the resulting SEPS further self-assembled into supramolecular gels driving by hydrogen bonding.⁵⁴⁻⁵⁶ On the other hand, Huang and coworkers reported a dual-responsive SEPS through the molecular recognition of crown ether.⁵⁷ In their design, the linear SEPS was constructed by the reversible host-guest recognition motif between the dibenzo[24]crown-8 unit and its

complementary guest dibenzylammonium salt moiety, linked by a long aliphatic chain in solution. The resulting SEPS exhibited reversible sol-gel transition by alteration of heating and cooling, or acidification and neutralization. This thermo- and pH-dual-responsive SEPS gel was used for the controlled release of rhodamine B, which shows potential in biomedical fields such as personal-care products and drug delivery systems. Recently, they further developed a novel quadruple-responsive SEPS gel in the presence of a metal cross-linker, $[\text{PdCl}_2(\text{PhCN})_2]$, which possessed excellent shape-persistent and elastic properties.⁵⁸ Firstly, a linear SEPS was constructed through the host-guest interaction between the benzo[21]crown-7 host unit and dialkylammonium salt guest moiety in solution (Fig. 2a). Then, a gel network was formed via direct cross-linking of SEPS by $[\text{PdCl}_2(\text{PhCN})_2]$ since the 1,2,3-triazole group acted as a ligand for coordination with palladium(II). The gel displayed pH-, thermo-, cation-, and metallo-induced reversible sol-gel transition (Fig. 2b). In their system, the morphology of the SEPS gel was well controlled by the amount of cross-linker. Moreover, the material could be molded into shape-persistent and free-standing objects with elastic behavior. The responsive features and good mechanical properties of cross-linked SEPS networks were derived from reversible host-guest interaction, making them excellent soft materials. In addition, by utilization of the cucurbit[n]uril (CB[n])-based host-guest interaction, Zhang and coworkers prepared the supramolecular gel self-assembled from a water-soluble SEPS (Fig. 3).⁵⁹ They successfully utilized multiple host-stabilized charge transfer interaction between a multifunctional monomer and CB[8] to obtain SEPS with a high degree of polymerization, and found that this SEPS could self-assemble into supramolecular gel in water, which might be driven by the interaction between carbonyl group portals and hydronium ions of CB[8] and also between CB[8] themselves. Upon addition of potassium cations, the gel collapsed because the interaction between the polymer chains was destroyed.

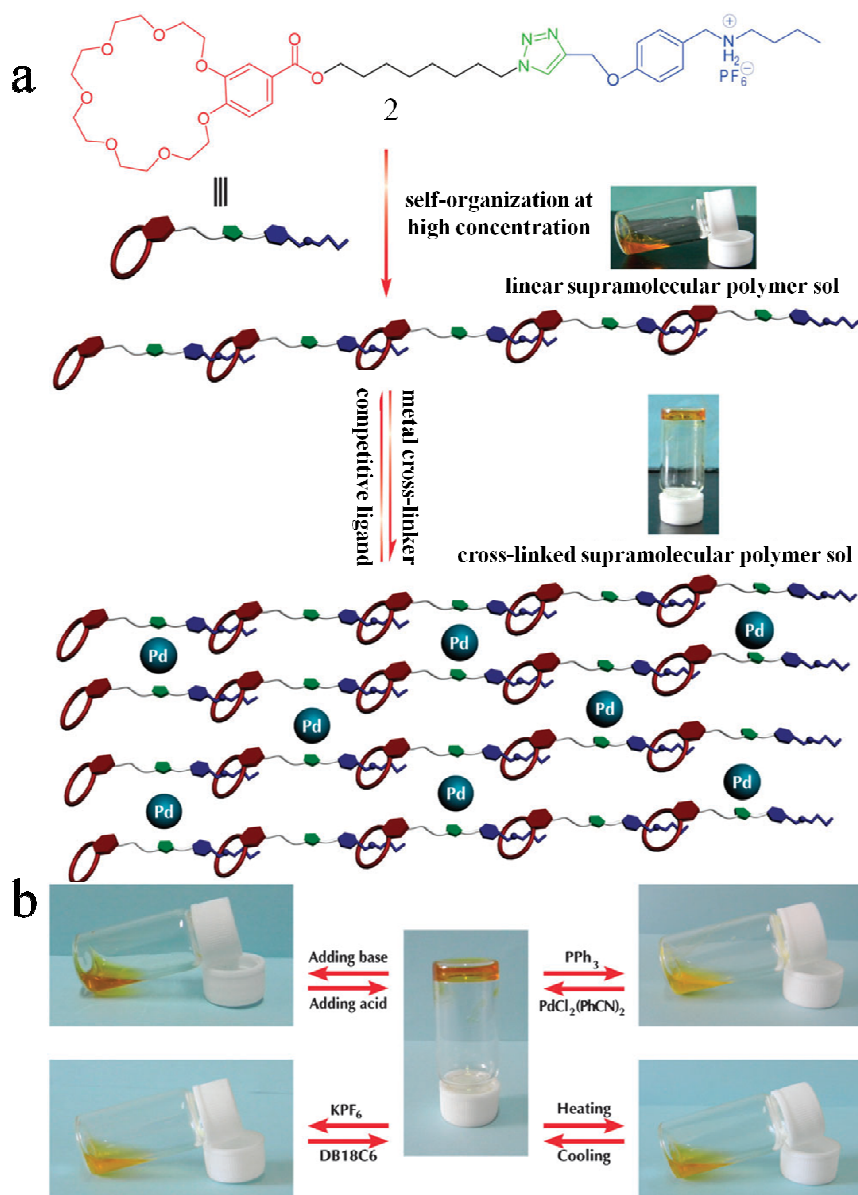


Fig. 2 (a) Schematic representation of the formation of linear and crosslinked SEPS from **2**. (b) The reversible gel-sol transition of the SEPS network gel triggered by four different stimuli (pH-, thermo-, cation-, and metallo-induced). Reproduced with permission from ref. 58. Copyright 2012, Royal Society of Chemistry.

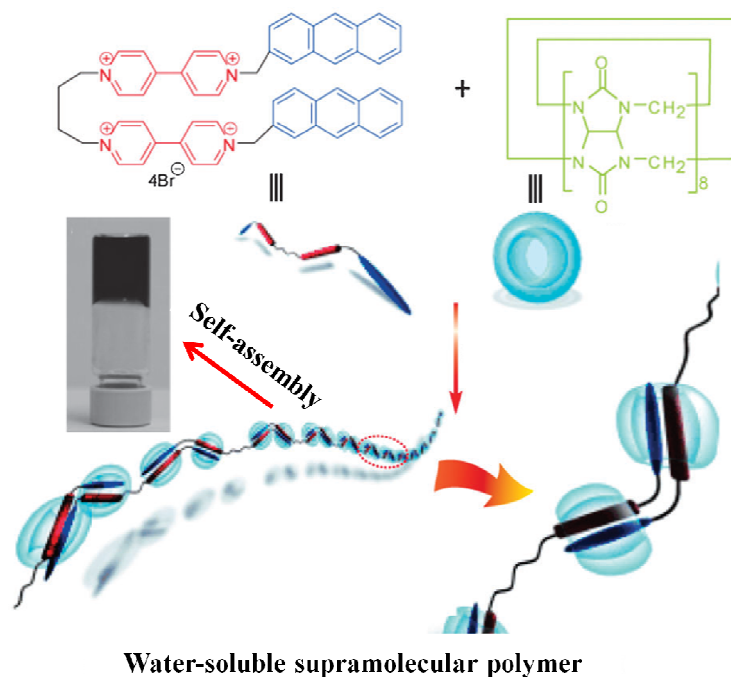


Fig. 3 Schematic representation of the formation of gel based on water-soluble SEPS. Reproduced with permission from ref. 59. Copyright 2012, Royal Society of Chemistry.

In general, supramolecularly engineered polymers based on single noncovalent interaction display several drawbacks including low degree of polymerization, poor stability, and simple structure. Thus, to combine multiple noncovalent interactions in the same supramolecularly engineered polymers is a valuable tool for improving their degree of polymerization and stability. Recently, Stang and Huang et al. prepared SEPS with tunable topologies based on low-molecular-weight molecules through a hierarchical design strategy, which could further self-assemble into nano-fibers and macroscopic fibers in dichloromethane (CH_2Cl_2).⁶⁰ Here, the driving forces for the construction of SEPS were metal-ligand coordination and hydrogen bonding interaction. The linear SEPS self-assembled into tightly packed nanoscale fibers with a diameter of ~ 300 nm in solution; while the cross-linked supramolecular hexagonal networks aggregated into long and flexible fibers with a diameter of ~ 8 μm after swelling in CH_2Cl_2 . The resultant macroscopic fibers possessed enough strength and flexibility to arrange into stable knots which could persist over 24 h without cracking and agglomeration. Deformation of these supramolecular assemblies under mechanical stress could reform due to the reversibility of the metal-ligand coordination and hydrogen bonding, ultimately increasing the robustness of the materials. These features could be attributed to the dynamic reversibility of noncovalent interactions and good mechanical properties of the cross-linked SEPS network, making these fibers an intelligent soft material. Besides, Stupp's group reported a novel hairpin-shaped small molecule based on thiophene-capped

diketopyrrolopyrrole unit and the *trans*-diamidocyclohexane, which formed SEPS by a combination of hydrogen bonding and π - π stacking and further self-assembled into long supramolecular nanowires.⁶² This nanostructure exhibited better charge transport characteristics in devices that were 54% more efficient than the corresponding control. Very recently, Ghosh' group reported stimuli-responsive self-assembly of a naphthalene diimide (NDI) and its coassembly with a pyridine-functionalized pyrene (PY), which were driven by multiple noncovalent interactions, including hydrogen bonding interaction, π - π stacking and charge transfer interaction.⁶¹ As shown in Fig. 4, the building block NDI (3) containing hydrazide (H1) and hydroxy (H2) groups self-assembled into reverse vesicles in methylcyclohexane via orthogonal H-bonding (H1-H1 and H2-H2) and π - π stacking. Above the lower critical solution temperature (LCST), the assembled structure was changed and turned into macroscopic precipitation owing to the thermal dissociation of the H2-H2 H-bonding while H1-H1 H-bonding retained unaltered. Interestingly, the precipitated SEPS redissolved in the medium and self-assembled into reverse-micellar structure above the upper critical solution temperature (UCST). In the presence of the PY donor, a transient segregated supramolecular dyad (NDI-PY) was formed by H2-H3 H-bonding, which was gradually transformed into an alternate NDI-PY stack due to an enthalpy-driven charge-transfer interaction between NDI and PY. Notably, the LCST of NDI-PY was about 10 °C higher than that of NDI alone, which might be attributed to the synergistic assistance of multiple hydrogen bonding interaction and charge transfer interaction. The mixed NDI-PY assembly displayed a morphology transition from a reverse micelle (with a NDI-PY core) below the LCST to another reverse micelle (with a NDI core) above the UCST through a “denatured” intermediate.

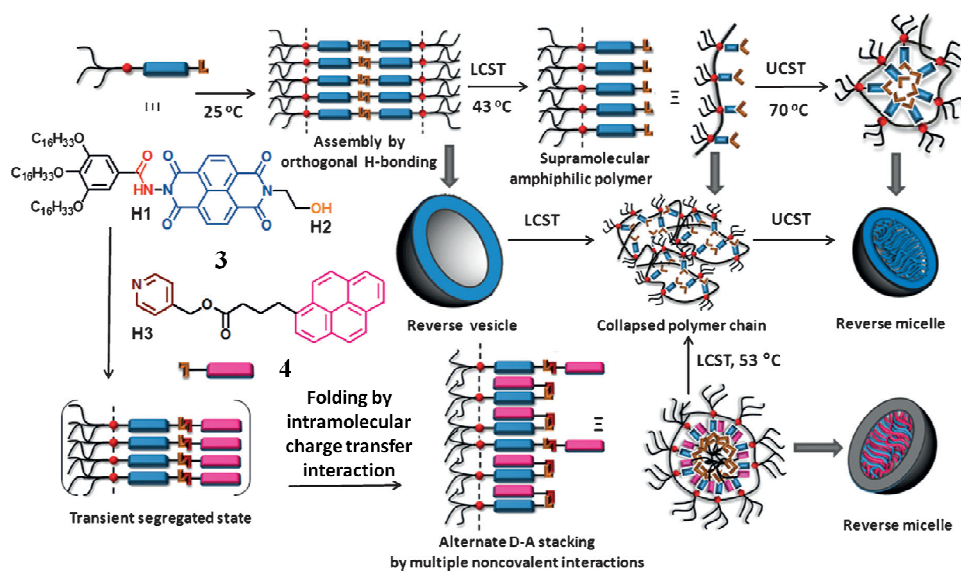


Fig. 4 Schematic representation of the formation of SEPS driven by multiple noncovalent interactions and the self-assembly of 1 and its coassembly with 2. Reproduced with permission

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Owing to the existence of many noncovalent connections, it is a great challenge to construct stable SEPS with sufficient length in polar solutions and control their formation reversibly under external stimuli. By utilization of two orthogonal binding interactions, metal-ligand binding and ion pair formation, Schmuck and coworkers fabricated a new kind of switchable SEPS built by the low-molecular-weight heteroditopic monomer (terpyridine attached to a self-complementary guanidiniocarbonyl pyrrole carboxylate zwitterion) and the metal ion (Fe(II)).⁶³⁻⁶⁵ The resultant SEPS of considerable length exhibited a sufficient stability in polar dimethylsulfoxide (DMSO) and even aqueous solutions. The SEPS further self-assembled in solution into larger globular aggregates with a densely packed core and a loose shell. The state of the assembly could be reversibly switched on and off either by addition of a competing ligand to remove the metal ion and subsequent re-addition of the metal ion or by reversible protonation and deprotonation of the zwitterion upon adjusting of pH value. Such system might provide a new strategy for designing functional materials in the future.

2.2 Self-assembly of supramolecularly engineered polymers built by small molecules and macromolecules (SEPSM)

SEPSM refers to supramolecules where low-molecular-weight molecules are associated with covalent bonded polymer by noncovalent interactions such as hydrogen bonding, metal coordination, van der Waals forces, electrostatic attraction and π - π interaction. In recent years, self-assembly of SEPSM has attracted enormous attention for its application as functional nanomaterials at different length scales. Design and preparation of SEPSM is the vital precondition for its self-assembly. Generally, the synthesis of well-defined functional covalent bonded polymers is an expensive and time-consuming process. In contrast, the preparation of SEPSM consisting of small molecule and conventional polymer is facile, diverse and inexpensive. Due to the dynamic-tunable property of supramolecularly engineered polymers, the self-assembled morphologies of SEPSM can be easily tuned by simply changing the sorts or ratios of small molecule monomers. In addition, the specific or multiple functions can be introduced into SEPSM systems through a modularization strategy by using noncovalent interactions.

As CDs can form inclusion complexes with various guest molecules, they constitute an important building block for SEPSM and then become an elegant platform for the generation of self-assembled nanoparticles and hydrogels. Dong and coworkers reported a reverse micellar hydrogel formed between polypeptide-based copolymer and α -CD by utilizing host-guest interaction.⁶⁶ The CD-based SEPSM first

self-assembled into α -CD/poly(ethylene oxide) (PEO) polypseudorotaxane-cored reverse micelles with a polypeptide corona. Then, the reverse micelles further aggregated into hydrogels via the hydrogen bonding interaction among the polypeptide corona. These hydrogels were also thermally and pH-reversible, which could load and release anticancer drug efficiently and afford them to be an injectable controlled drug release system. Craig and coworkers reported the hierarchical self-assembly of SEPSM composed of an alkylated β -CD and poly(ethylene glycol) (PEG)-conjugated adamantane (AD) via host-guest interaction. Above a critical concentration, the SEPSM self-assembled into highly ordered fibrous structures, which responded to environment variation through the defining molecular recognition. Furthermore, Jiang and coworkers reported the reversible self-assembly of SEPSM composed of β -CD-terminated poly(*N*-isopropylacrylamide) (β -CD-PNIPAM) and Fréchet-type benzyl ether dendron with an azobenzene group driven by the host-guest interaction between the CD ends and the azobenzene groups.⁶⁷ The obtained SEPSM self-assembled into thin-layer vesicles in water. The assembly and disassembly of vesicles could be realized by alternating visible and UV irradiation or heating and cooling. Very recently, we reported the self-assembly of linear-hyperbranched SEPSM consisting of AD-functionalized alkyl chain (AD-C_n, n = 12, 18, 30) and hyperbranched polyglycerol grafted from β -CD (CD-g-HPG) through the specific AD/CD host-guest interaction, which self-assembled into unilamellar vesicles in water (Fig. 5).⁶⁸ The SEPSM-based vesicles possessed good stability and ductility under external force and could be disassembled readily under a competitive host of β -CD.

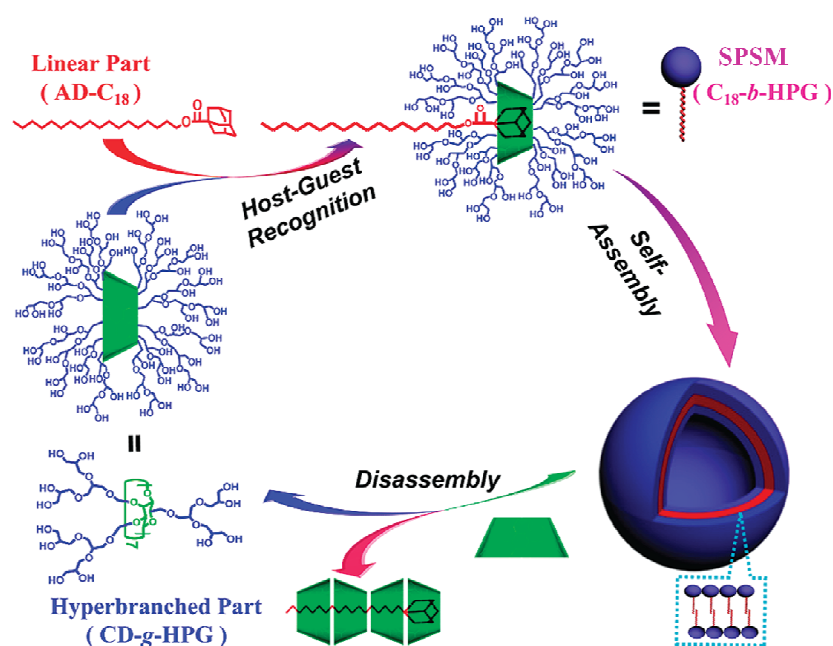


Fig. 5 Cartoon representation for self-assembly and disassembly processes of SEPSM. Reproduced with permission from ref. 68. Copyright 2012, American Chemical Society.

CB[n], as a newly emerged host molecule, has received increasing research interest in construction of SEPSM and plays an important part in macromolecular self-assembly. CB[8] is able to bind two organic guest molecules simultaneously with high association constants ($K_a \geq 10^{11} \text{ M}^{-2}$) in an aqueous environment, thus enhancing the charge transfer interaction between these two guests which serve as a charge donor and a charge acceptor, respectively.⁶⁹⁻⁷¹ Scherman and coworkers introduced CB[8] to link 2-naphthol-terminated *cis*-1,4-poly(isoprene) and methylviologen (MV)-terminated PEG to build a host-stabilized charge transfer connected SEPSM, and found it self-assembled into micelles or vesicles in aqueous solution.⁷² Further, Chen and coworkers investigated the self-assembly of supramolecular graft copolymer in which CB[8] linked viologen-containing copolymer and naphthalene-ended PNIPAM via host-stabilized charge transfer interaction.⁷³ They found that the self-assembled micelles were sensitive to temperature and reducing agents because of the temperature sensitive property of PNIPAM moiety and the noncovalent connection, respectively. In addition, Ji and coworkers fabricated reducible supramolecular assemblies of SEPSM based on CB[8], indole-terminated poly(lactic acid) and MV-terminated PEO (PEO-MV) via host-stabilized charge transfer interaction.⁷⁴ These SEPSM-based assemblies could load the anticancer drug doxorubicin (DOX) and release them successfully after adding a reducing agent $\text{Na}_2\text{S}_2\text{O}_4$ because of the redox chemistry of MV.

As one important kind of supramolecular hosts, crown ethers are also frequently used to construct the SEPSM. For instance, Huang and coworkers reported the aqueous self-assembly of supramolecular diblock polymer consisting of a crown ether appended hydrophobic supramolecular polymer and a conventional hydrophilic polymer PEG between which the host-guest and electrostatic interactions acted as supramolecular linkers (Fig. 6).⁷⁵ The SEPSM was obtained through the association of the negatively charged bis(m-phenylene)[32]crown-10 host unit and its complementary viologen dication guest moiety. Interestingly, self-assembled morphologies of the amphiphilic SEPSM could be well-controlled by varying the block length ratio of the supramolecular polymer block to the conventional polymer block by just changing the proportion of the polymer unit to small molecules in solution, avoiding intricate organic and/or polymer synthesis. When the chain length of the traditional polymer PEG was longer than that of the supramolecular polymer, micelles were obtained, which could encapsulate and release hydrophobic molecules. In contrast, under the opposite condition, the self-assembled vesicles were formed with the function of transporting both hydrophobic and hydrophilic molecules. The combination of conventional polymers with the dynamic features and responsiveness of supramolecular polymers endows the self-assembled supramolecular materials with

unique functions and properties. For example, the degradation of supramolecular aggregates from SEPSM can be triggered by external stimuli due to the responsiveness of noncovalent interactions.

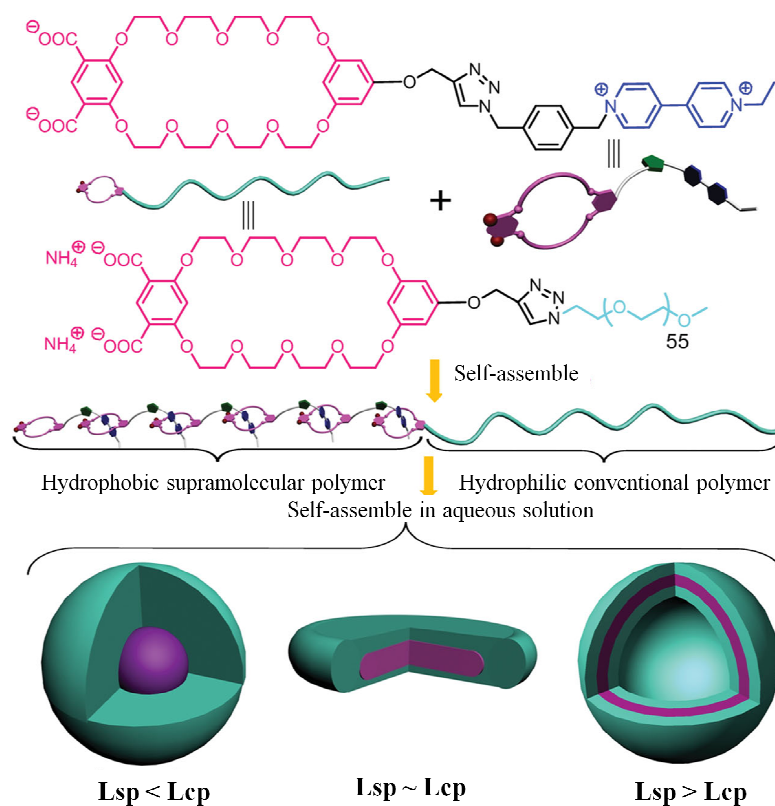


Fig. 6 Cartoon representation of the formation of SEPSM and its self-assembly in aqueous solution. Lsp represents the extended length of the supramolecularly engineered polymers, and Lcp represents the extended length of the conventional polymer. Reproduced with permission from ref. 75. Copyright 2013, Wiley.

It should be mentioned that the self-assembly of hydrogen bonded SEPSM in the solid state has received enormous research interest for years. The groups of Ikkala and ten Brinke have pioneered the research on self-assembly of supramolecular comb-like coil hydrogen bonded polymers consisting of H-acceptor polymers, including commercially available poly(styrene-*block*-4-vinylpyridine) (PS-*b*-P4VP), and a variety of H-donor surfactant-type small molecules.⁷⁶⁻⁷⁹ These hydrogen bonding connected SEPSM could self-assemble into highly ordered morphologies such as hexagonal cylindrical and lamellar structures. Subsequently, Priimagi, del Barrio and coworkers investigated the self-assembly of supramolecular hydrogen bonded polymers based on vinylpyridine group-containing polymers and a variety of azobenzene compounds.⁸⁰⁻⁸³ Very recently, del Barrio and coworkers reported hydrogen-bonding-assisted self-assembly of dendronized SEPSM composed of a carboxy-terminated azodendron (dAZO), an H-donor azodendron, and two H-acceptor

polymers: P4VP and PS-*b*-P4VP block copolymer (Fig. 7a).⁸³ It was found that the hydrogen bonded SEPSM self-assembled into lamellar, cylindrical, and spherical morphologies by altering the ratio of dAZO and vinylpyridine repeating unit (Fig. 7b). Photo-induced orientation of the azobenzene moieties was obtained in films of the SEPSM by using 488 nm linearly polarized light. Compared to their previous report, highly sensitive photo-induced response was obtained for dAZO-containing supramolecular materials even at azobenzene contents as low as 2.7 wt%.⁸⁴ The optimized combination of supramolecularly engineered polymer self-assembly and “chromophore synthons” demonstrated the enhanced optical properties of these materials efficiently. Similarly, Kuila and Stamm groups have extensively studied supramolecular assembly in thin film from SEPSM built by block copolymer and small molecule via hydrogen bonding interaction, and reviewed the recent development of these supramolecular assemblies as functional nanomaterials.⁸⁵

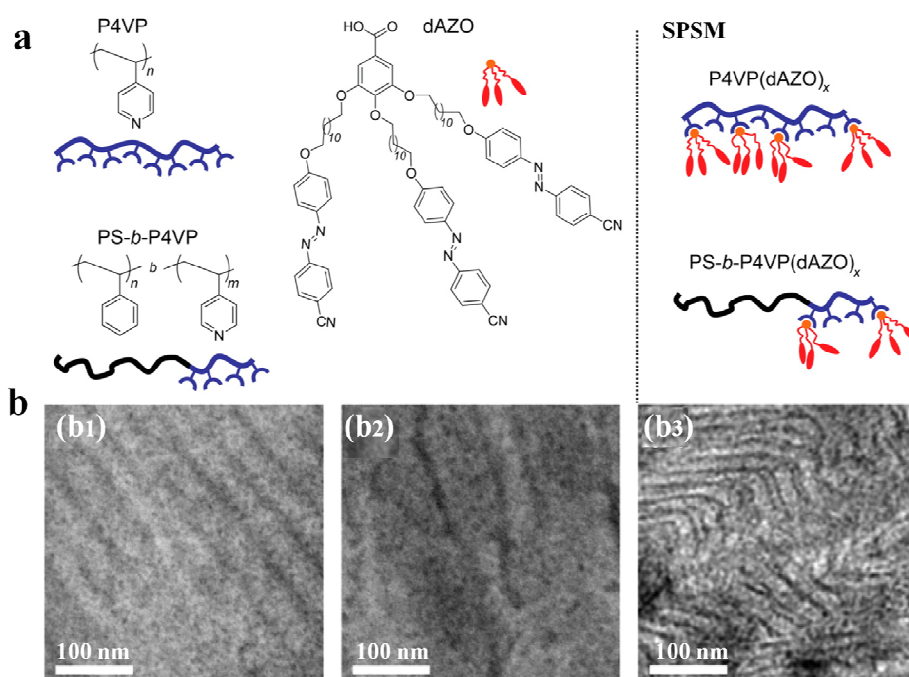


Fig. 7 (a) Chemical structures and schematic representations of hydrogen bonding connected SEPSM. (b) TEM bright-field micrographs of assemblies from SEPSM: (b₁) PS-*b*-P4VP(dAZO)_{0.06}, (b₂) PS-*b*-P4VP(dAZO)_{0.25}, and (b₃) PS-*b*-P4VP(dAZO)_{0.50}. Reproduced with permission from ref. 83. Copyright 2014, American Chemical Society.

It has been reported that through electrostatic attraction, molecules with cationic and anionic head groups can be held together to form SEPSM. Based on this strategy, SEPSM can be prepared and further self-assembled into various nanostructures. For example, Thayumanavan and coworkers reported the polymeric assemblies from SEPSM of small molecule surfactants with positive charge and negatively charged polyelectrolytes connected by electrostatic interaction.⁸⁶ The disassembly of these

supramolecular aggregates was accomplished with variations in redox environment, ionic strength, and pH of the medium, wherein the electrostatic interaction between the polymer and the surfactant was weakened by the stimuli. Recently, Zhang and coworkers constructed a phosphatase-responsive SEPSM based on the electrostatic complexation of a double hydrophilic block copolymer methoxy-poly(ethylene glycol)₁₁₄-*block*-poly(L-lysine hydrochloride)₂₀₀ (PEG-*b*-PLKC) and a natural multi-charged adenosine 5'-triphosphate (ATP) (Fig. 8).⁸⁷ It was found that the SEPSM could self-assemble into spherical aggregates in aqueous solution. The spherical aggregates exhibited good responsiveness and disassembled after treating with phosphatase because the negatively charged ATP was hydrolyzed to single-charged phosphate and a neutral adenine group. In the subsequent work, they fabricated a series of SEPSM based on the electrostatic interaction and obtained various assemblies with different morphologies in aqueous solution, including micelles, sheet-like aggregates and spherical aggregates.⁸⁸⁻⁹¹ The resultant assemblies from SEPSM could respond to external stimuli and hold great promise as smart materials.

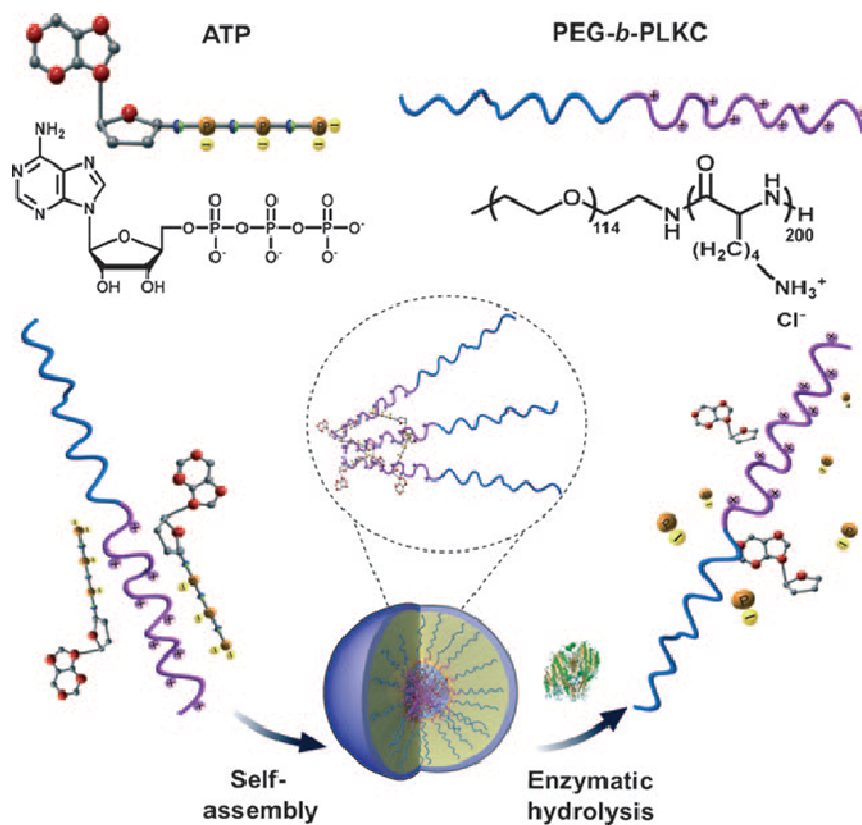


Fig. 8 Schematic representations of the self-assembled aggregates from SEPSM based on electrostatic interaction. Reproduced with permission from ref. 87. Copyright 2010, Wiley.

2.3 Self-assembly of supramolecularly engineered polymers built by macromolecules (SEPM)

The supramolecularly engineered polymers can also be constructed with merely macromolecules. In SEPM-type polymers, macromonomers are linked together by noncovalent interactions. To date, a large amount of SEPM containing supramolecular linkers along the main chain or side chain have been successfully synthesized by using hydrogen bond, metal-ligand coordination, host-guest complexation, electrostatic interaction, et al.⁹²⁻⁹⁶ The resultant SEPM combines the characteristic features of conventional covalent bonded polymers with those of supramolecular systems (e.g., reversibility, tunability, strength, stability). Thus the self-assembly of the SEPM possesses unique features compared with that of conventional covalent bonded polymers and has received considerable attention. In this section, we mainly focus on the self-assembly of SEPM based on metal-ligand coordination, host-guest interaction, and hydrogen bond, since these three kinds of SEPM are well-studied recently.

Metal-ligand coordination is particularly interesting since the coordination bond is highly directional and the strength of the interaction can be readily tuned by changing the metal ions.⁹⁷ Therefore, it has been extensively employed in the synthesis of SEPM, which offers many advantages for the self-assembled aggregates from SEPM. For example, the reversibility of the metal-ligand bond allows for improved control over the properties of assembled materials. Furthermore, the presence of a metal complex brings additional electrochemical, photophysical, and catalytic properties for the aggregate structures. Schubert and Gohy et al. reported the self-assembly of metallo-supramolecular block copolymers in which metal-ligand coordination acted as linkers between two polymers.⁹⁸⁻¹⁰⁰ They published a series of excellent works, focusing on the construction of metallo-induced supramolecularly engineered copolymers and their self-assembly behavior. The initial studied system was the self-assembly of metal-ligand connected SEPM, PS-[Ru]-PEO, in which 2,2':6',2''-terpyridine was used as a ligand (Fig. 9a).⁹⁸ The PS-[Ru]-PEO self-assembled into spherical micelles with uniform size, which showed a strong tendency to aggregate. Compared to conventional micelles from covalent bonded polymers, the core and shell of the supramolecular micelles were connected only by metal-ligand coordination rather than by covalent connection. In addition, these micelles contained charged entities located at the interface between core and corona and thus significantly different from "neutral" ones. The experimental results proved that micelles self-assembled from metallo-induced SEPM were stable in various environments. However, the metal complexes in micelles could be readily opened after adding a huge excess of a competitive water-soluble ligand (such as hydroxyethyl ethylenediaminetriacetic acid trisodium salt, HEEDTA), followed by heating the micellar solution.^{99,100} It indicated that disassembly of metallo-induced polymeric micelles could be realized by adding the competing ligands and heating.

Similarly, O'Reilly and coworkers prepared the hollow responsive functional nanocages using supramolecular self-assembly of polystyrene-[Ru]-poly(acrylic acid) (PS-[Ru]-PAA) in which the tripyridine-Ru complexes were used as a linker.¹⁰¹ First, the metallo-induced SEPM self-assembled into micelles with a PAA shell and a PS core in aqueous solution. Then the PAA shell of the micelles was stabilized via cross-linking chemistry reported by Wooley.¹⁰² The micelles reacted with a huge excess of a competing ligand HEEDTA at 60 °C and made the tripyridine-Ru complexes open. The nanocages could be obtained by dialysis of the micellar solution against tetrahydrofuran/water (THF/H₂O: 2/1) to remove the released PS block. Subsequently, they designed and prepared metal-ligand connected micelles self-assembled from an unsymmetrical supramolecularly engineered metallo-diblock copolymer, in which PS block modified with a relatively weak coordinating pyridine ligand and PAA modified with a strong pincer ligand were connected by the Pd(II) metal (Fig. 9b).¹⁰³ As expected, metal-functionalized hollow nanocages could be obtained by removing hydrophobic PS from the noncovalent connected micelles under the acidic condition (pH 5). Compared to the SEPM with the terpyridine-Ru linkage, this SEPM with the unsymmetrical metal-ligand bond exhibited a significant advantage in its readiness to realize the selective cleavage of the assemblies.

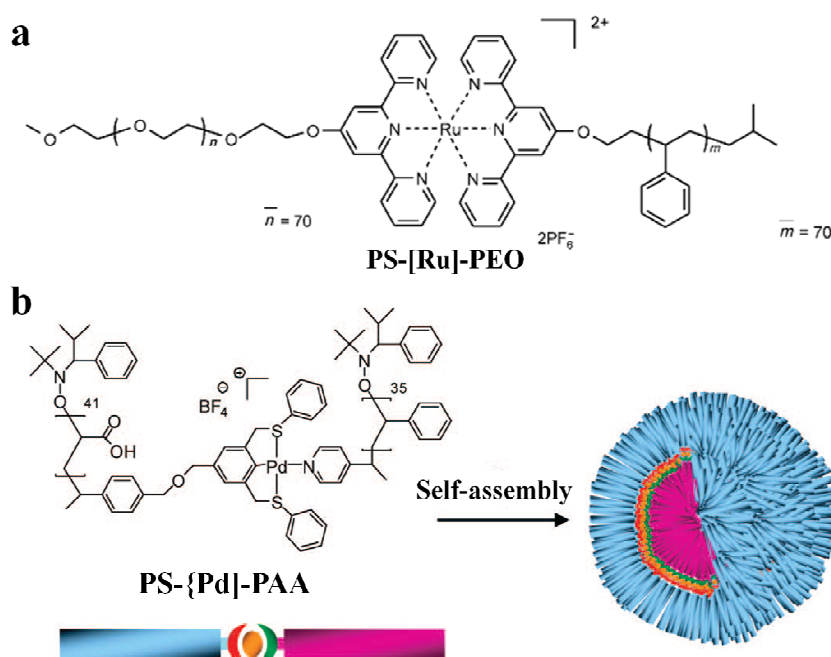


Fig. 9 (a) Chemical structure of SEPM PS-[Ru]-PEO. (b) Chemical structure and self-assembly of unsymmetrical SEPM PS-{Pd}-PAA. Reproduced with permission from ref. 103. Copyright 2008, American Chemical Society.

The self-assembly of PS-[Ru]-PEO in a selective solvent and in the bulk was investigated by Schubert and coworkers.^{104,105} Interestingly, the thin SEPM films with

various morphologies and tunable domain size were obtained from supramolecularly engineered copolymer PS-[Ru]-PEO containing different PS block lengths. This supramolecular combinatorial approach exhibited a significant advantage compared with classical covalent polymers. Apart from controlling the morphology of assemblies, another advantage of the metallo-induced SEPM is the reversibility of the bis-terpyridine complexes. For example, the same research group prepared nanoporous thin films from the supramolecularly engineered copolymer PS-[Ru]-PEO.¹⁰⁵ Firstly, cylinders oriented normal to the substrate were obtained directly by spin-coating a solution of the SEPM in a non-selective solvent. Then adding the cerium(IV) sulfate, Ru^{II} was oxidized to Ru^{III}, and the initial bis-complexes turned into mono-complexes, which led to the release of minor block PEO and subsequently formed the nanoporous films. Such reversibility could be utilized to create well-ordered nanoporous structures.

Host-guest inclusion complexation has promoted the development of the supramolecular chemistry field. Typical host molecules are crown ethers, CDs and CBs. The SEPM based on the host-guest interaction has been extensively investigated due to its high association constant. Compared to conventional assemblies, the supramolecular assemblies from SEPM provide several advantages, such as structural adaptability, additional responsiveness to guest molecules, and robust combination of different building blocks. Shi and coworkers reported the self-assembly of supramolecular double hydrophilic block copolymer through the host-guest complexation between β -CD-P4VP and AD-PNIPAM.¹⁰⁶ Depending on pH and temperature, the obtained SEPM could self-assemble into two distinctly different micelles because of the pH-responsive P4VP polymer and the thermo-responsive PNIPAM. Similarly, Liu and coworkers reported the assemblies from supramolecular double hydrophilic block copolymer consisting of β -CD-PNIPAM and AD-terminated poly(2-(diethylamino)ethyl methacrylate) (AD-PDEA) driven by host-guest interaction, and they found that the SEPM assemblies showed interesting multi-responsive and reversible micelle-to-vesicle transition behavior in response to solution pH and temperature.¹⁰⁷ Interestingly, this kind of thermo- and pH-responsive micelle-to-vesicle transition was fully reversible. Moreover, Li and coworkers studied the self-assembly thermosensitive micellization phenomena of ABA-type dual thermo-responsive supramolecularly engineered copolymer. Host-guest complexation between a star-shaped PNIPAM with a β -CD core and bis(adamantyl)-modified poly(propylene glycol) (PPG) was utilized to construct the SEPM, which could self-assemble into micelles and further aggregate with increasing temperature because of the existence of two kinds of thermoresponsive segments, PPG and PNIPAM.¹⁰⁸ Different from conventional polymeric micelles, the core and shell of these supramolecular micelles from SEPM were connected by host-guest interaction rather

than chemical bond. The size of the SEPM micelles could be easily tuned by altering the temperature, concentration of the components, ratio of host/guest, and length of the PPG block in the guest polymer, respectively. Recently, we constructed a supramolecular Janus hyperbranched polymer with AZO-functionalized hyperbranched poly(3-ethyl-3-oxetanemethanol) (HBPO) and CD-functionalized HPG connected by noncovalent host-guest coupling.¹⁰⁹ This amphiphilic SEPM self-assembled into unilamellar bilayer vesicles in aqueous solution under visible light. Alternatively, the vesicles disassembled into unimers under the irradiation of UV light (365 nm) because of the *trans-to-cis* isomerization of the AZO groups.

The self-assembly of supramolecular miktoarm copolymer is rarely found in the literature. An example for the self-assembly of a supramolecular ABC miktoarm star-shaped terpolymer comes from our laboratory.¹¹⁰ The supramolecular polymeric host-guest system consists of a β -CD-modified hydrophilic diblock copolymer with two different blocks (PEG- β -CD-PDMAEMA) and the hydrophobic AD-modified poly(methyl methacrylate) (AD-PMMA), which self-assembles into spherical nanoparticles in aqueous solution due to its amphiphilicity. The disassembly of supramolecular nanoparticles can be readily achieved by adding competitive pure β -CD host or sodium 1-adamantane carboxylate (AD-COONa) guest because of the noncovalent connection. As illustrated in Fig. 10A, the size of PEG- β -CD-PDMAEMA/AD-PMMA micelles become smaller after the addition of competitive β -CD host or AD-COONa guest, which demonstrates the disassembly of the SEPM assemblies.

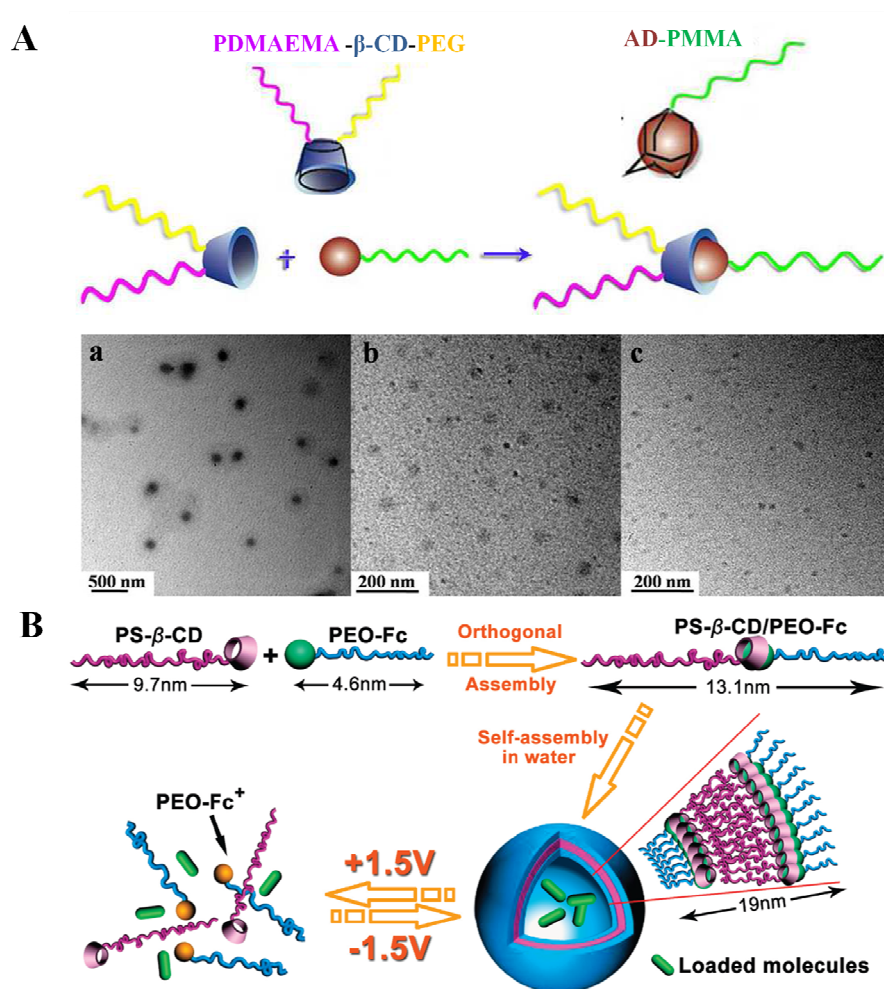


Fig. 10 (A) Chemical structure of PEG-β-CD-PDMAEMA/AD-PMMA and TEM images of assemblies from SEPM before (a) and after (b) being treated with β-CD or (c) treated with AD-COONa. (B) Schematic of the assembly and disassembly of PS-β-CD/PEO-Fc vesicles. Reproduced with permission from ref. 110 and 112. Copyright 2012 and 2010, American Chemical Society.

The self-assembly of SEPM based on host-guest complexation of CD and ferrocene (Fc) is also reported in recent years. It has been demonstrated that β-CD can exactly form a 1:1 inclusion complex with uncharged Fc species or its derivatives. However, the charged Fc species (Fc^+) would dissociate from the β-CD cavity, and this process can be reversibly achieved by changing the external voltage.¹¹¹ Yuan and coworkers employed β-CD-decorated PS (PS-β-CD) and ferrocene-decorated PEO (PEO-Fc) to form supramolecular diblock copolymer (PS-β-CD/PEO-Fc) via host-guest interaction between the β-CD and the Fc (Fig. 10B).¹¹² This SEPM self-assembled into supramolecular vesicles in aqueous solution, which remained stable for 3 months without external disturbance. Upon +1.5 V voltage stimuli, the uncharged PEO-Fc was oxidized into charged PEO-Fc^+ , resulting in the dissociation of SEPM

accompanied by disassembly of the vesicles. After 5 h of electrostimulation, the vesicles disaggregated into small fragments. The process of assembly and disassembly of the vesicles was reversible and well-controlled by exerting a reductive voltage or upon an oxidative voltage. More importantly, the disassociation rate of the vesicles could be tuned by controlling the voltage intensities. Thus, the self-assembled supramolecular vesicles could serve as smart nanocapsules that could control the release of functional molecules or drugs by altering artificial voltage. Similarly, Chen and coworkers reported the self-assembly of amphiphilic supramolecular block copolymer formed by the host-guest interaction between benzimidazole-terminated poly(ϵ -caprolactone) (BM-PCL) and β -CD-functionalized dextran (Dex- β -CD).¹¹³ The BM was protonated under acidic conditions, inducing the dissociation of β -CD and BM. Therefore, the resultant SEPM micelles exhibited pH-sensitive behavior.

The pioneer work about the self-assembly of SEPM through the hydrogen bonding interaction was reported by Jiang's group.¹¹⁴⁻¹¹⁸ They developed the noncovalent connected micelles, in which the core and shell were mainly connected by hydrogen bonding. For example, Jiang and coworkers constructed a graft-like supramolecularly engineered polymer containing P4VP and mono-carboxy terminated PS (MCPS) through the hydrogen bonding association of the P4VP backbone and the carboxyl ends of MCPS in the common solvent CHCl_3 (Fig. 11a).¹¹⁶ After changing the medium to a selective solvent toluene for MCPS, the SEPM self-assembled into stable micelles, with P4VP as the core and MCPS as the shell. The obtained hydrogen bonding connected micelles from this SEPM differed from the micelles of conventional covalent bonded block copolymers because of the hydrogen bonding linkage between the core and the shell instead of covalent bond. The similar self-assembly of SEPM composed of P4VP and carboxyl-ended polybutadiene (CPB) occurred in an appropriate selective solvent n-hexane/ CHCl_3 or nitromethane/ CHCl_3 .¹¹⁸ Similarly, Pispas and coworkers prepared the hydrogen bonding micelles self-assembled from SEPM between poly(2-vinylpyridine) (P2VP) and PS or polyisoprene (PI) end-modified with one sulfonic acid group in the mixed solutions of THF and decane.¹¹⁹

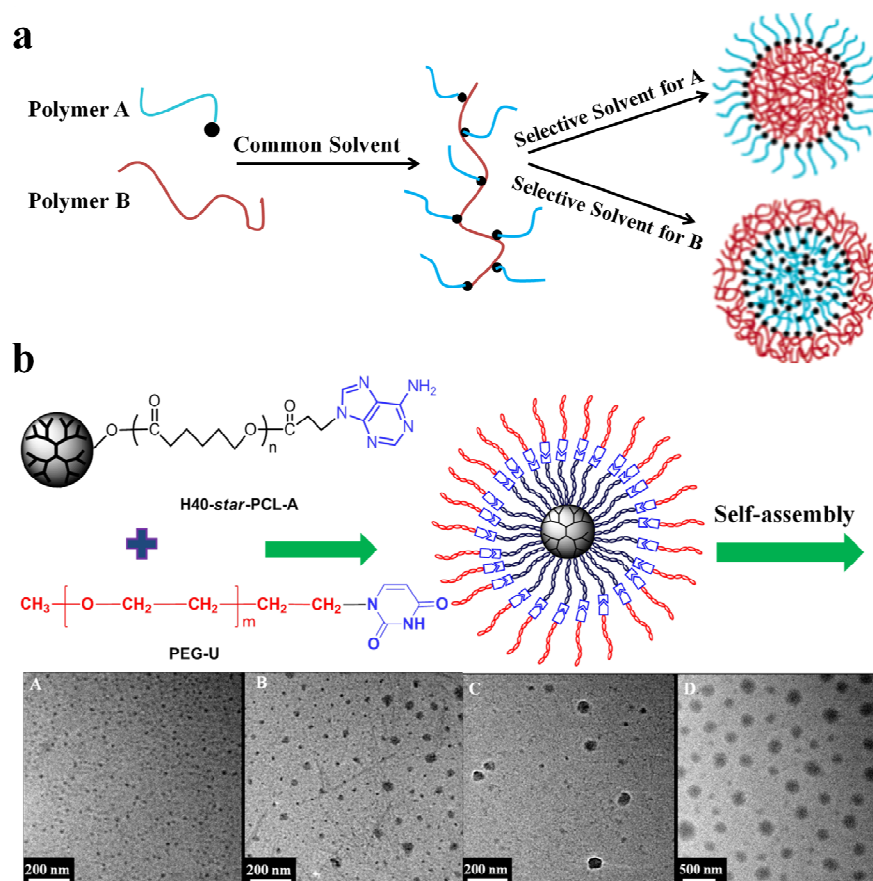


Fig. 11 (a) Schematic representation of the formation of hydrogen bonding grafting SEPM and its assembly in selective solvents. (b) Schematic illustration of the self-assembly of the supramolecular amphiphilic multiarm hyperbranched copolymer micelles through complementary hydrogen bonding interactions. Reproduced with permission from ref. 116 and 121. Copyright 2005, American Chemical Society and 2013, Royal Society of Chemistry.

Inspired by the nucleotide-based biological systems such as DNA and RNA, our group reported a class of SEPM based on complementary multiple hydrogen bonding interactions, which could further self-assemble into hydrogen bonding connected micelles in aqueous solution.¹²⁰ This SEPM system contained adenine-ended PCL (PCL-A) and uracil-terminated PEG (PEG-U), which formed SEPM in the common apolar solvent through the hydrogen bonding interaction. After the addition of water, a selective solvent for PCL, into the SEPM solution, the micelles with the PCL core and PEG shell connected by hydrogen bonding were obtained. The hydrophobic microenvironment provided by the PCL core would ensure the base pair to form stable hydrogen bonds inside micelles, making it possible to obtain stable micelles in aqueous solution. The resultant micelles were very sensitive to acidic pH, which could be ascribed to the protonation of the nucleobase nitrogen atoms. Correspondingly, the disassembly of the micelles occurred at low pH conditions. Furthermore, we

developed size-controlled SEPM micelles using complementary multiple hydrogen bonding interactions. In this system, the adenine-terminated H40-*star*-poly(ϵ -caprolactone)-adenine (H40-*star*-PCL-A) and PEG-U formed supramolecular amphiphilic multiarm hyperbranched copolymer through the molecular recognition between A and U moieties, which further self-assembled into pH-responsive micelles with low critical micelle concentration (CMC) due to the hydrogen bonding connection and the unique hyperbranched architecture.¹²¹ Interestingly, the size of the self-assembled micelles could be well-controlled by adjusting the ratio of hydrophobic H40-*star*-PCL-A building block and hydrophilic PEG-U arm. As shown in Fig. 11b, the diameter of these SEPM micelles changes from 10 nm to 200 nm when the ratio of adenine and uracil is (A) 1:1; (B) 1:0.8; (C) 1:0.6; (D) 1:0.4. Recently, we also prepared salt/pH dual-responsive micelles self-assembled from supramolecular amphiphilic brush copolymers consisting of brush-like poly(2-hydroxyethyl methacrylate)-*g*-(PCL-A) and linear PEG-U via the molecular recognition of nucleobases.¹²² These micelles could be destroyed by lowering the pH or increasing the concentration of salt due to the special architecture of brush polymer and hydrogen bonding connection, which represents a new generation of stimuli-responsive delivery vehicles for a wide variety of biomedical applications.

2.4 Hybrid self-assembly of supramolecularly engineered polymers

Hybrid self-assembly provides a facile and robust tool for the design of high performance supramolecularly engineered polymer-inorganic hybrid materials in which both components contribute to the whole functionality. Supramolecularly engineered polymers possess conventional polymer's properties and dynamic nature of noncovalent bonds, which provides a unique advantage in encapsulating inorganic nanoparticles (NPs) and directing the self-assembly of inorganic precursors.¹²³⁻¹²⁶ In general, the supramolecularly engineered polymers in polymer-inorganic hybrids can serve the following purposes: 1) the use of a supramolecularly engineered polymer self-assembly strategy could assemble the inorganic phases into composite materials; 2) the supramolecularly engineered polymers can serve as matrix that causes the inorganic phase ordering and anisotropic orientation; 3) the supramolecularly engineered polymers can act as a functional components. The intramolecular noncovalent connections of supramolecularly engineered polymers include hydrogen bonding, metal-ligand coordination, host-guest complexation, electrostatic attraction/repulsion, hydrophobic interaction, and so on. These interactions can induce hybrids into controlled structures and modulate their chemical and physical properties. Nevertheless, the ordered supramolecular structures through hybrid self-assembly of supramolecularly engineered polymers and inorganics have been reported. Most of

the prepared hybrids are limited in the use of supramolecularly engineered polymeric assemblies as templates to direct the formation of hybrid nanoparticles or nanopores, construction of functional hybrid composites, utilization of inorganic particles as templates to direct the formation of supramolecularly engineered polymeric assemblies, and preparation of novel supramolecularly engineered polymer-inorganic hybrids.

Supramolecularly engineered polymers offer an alternative strategy to fabricate polymeric assemblies. First of all, the way to prepare supramolecularly engineered polymers avoids the complicated synthesis and purification procedures, which are usually required for synthesizing the covalent bonded polymers. More importantly, compared to the assemblies of covalent copolymers, the noncovalent connected assemblies hold great potential for further functionalization at the noncovalent combination interfaces. Therefore, supramolecular assemblies might provide a possibility to control the distribution of metal/inorganic nanoparticles in specific areas of the assemblies. For example, Ji and coworkers reported the use of novel bowl- and porous sphere-shaped supramolecular assemblies for the encapsulation and templating of gold nanoparticles.¹²⁷ The hydrophilic amino-ended poly(2-methacryloyloxyethyl phosphorylcholine) (PMPC-NH₂) and hydrophobic carboxyl-end PS (PS-COOH) formed supramolecularly engineered copolymers via electrostatic interaction, and further self-assembled into bowl- and porous sphere-shaped assemblies. The bowl-shaped supramolecular assemblies acted as templates for the confined assembling of weakly positively charged gold nanoparticles with an average diameter of 3.6 ± 0.5 nm. When the mass ratio of gold nanoparticle to PS-COOH was 1/15, the gold nanoparticles preferentially located at the inner interface of the bowls (Fig. 12a and 12f). It should be noted that the mass ratio of gold nanoparticles to PS-COOH had an important influence on the morphology of the aggregates. When the molar ratio of gold nanoparticles to PS-COOH increased gradually from 1/10 and 1/5 to 1/1, the morphology of the assemblies changed and the holes in the shallow bowls became smaller and smaller (Fig. 12a-c, respectively). This phenomenon might be attributed to the fact that positively charged gold nanoparticles as the competitors disturbed the interaction between the PS-COOH and PMPC-NH₂. They also found that the morphologies of the supramolecular assemblies could not be changed by lowering the mass ratio of gold nanoparticles to polymer. Interestingly, a series of gold nanoparticle-polymer assemblies with different morphologies could be prepared by using the template method, including supramolecular spheres, bowls, shallow bowls, porous spheres and shallow porous spheres (Fig. 5 a-e).

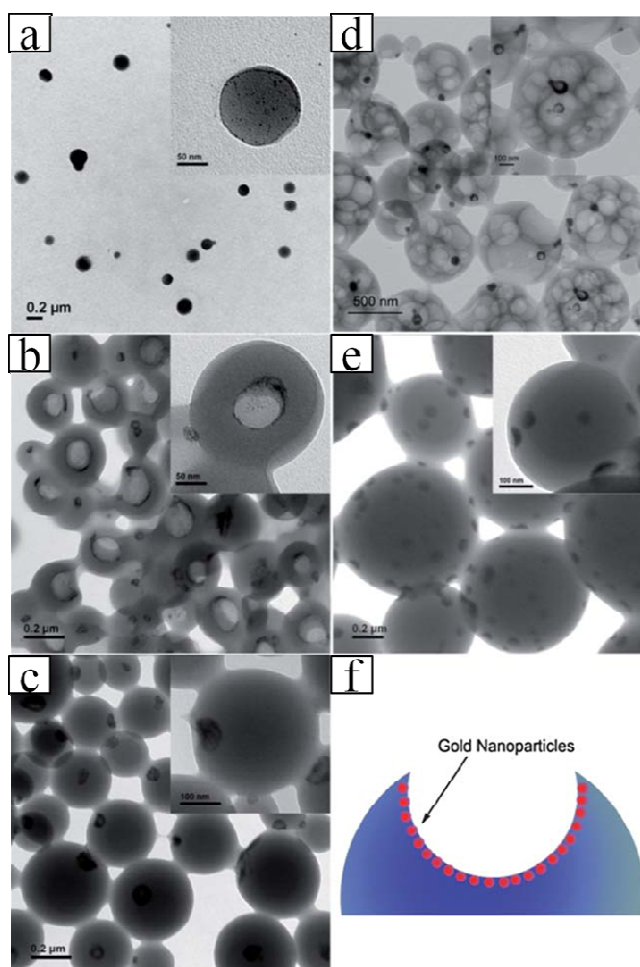


Fig. 12 Representative TEM images of gold nanoparticle-supramolecularly engineered polymer composite particles of different morphologies. The initial polymer concentration: (a) 1 C_0 , (b) 2.8 C_0 , (c) 10 C_0 , (d) 30 C_0 , (e) 60 C_0 , (mass ratio of gold nanoparticles to polystyrene was 1/20, molar ratio of the polymer blocks was 1/1, THF content is mixed solvent was 50% for all samples). The insert shows an enlarged view of the particles. (f) Gold nanoparticles preferentially located at the inner surface. Reproduced with permission from ref. 127. Copyright 2011, Royal Society of Chemistry.

Another example of hybrid self-assembly is to create functional hybrid materials consisting of supramolecularly engineered polymers and inorganic phases. Li and coworkers reported the multifunctional supramolecular hybrids with β -CD, cationic oligoethylenimine (OEI), anticancer drug paclitaxel (PTX) and fluorescent quantum dot (QD) (β -CD-OEI/PTX@QD), which took advantages of these two species for cooperative drug and gene delivery as well as cellular imaging.¹²⁸ First of all, they synthesized a red fluorescent CdSe-CdS QDs functionalized with the sodium salt of thioglycolic acid (TGA) to form the anionic water-soluble TGA@QD with an average diameter of 4.6 nm. Meanwhile, the supramolecularly engineered polymer β -CD-OEI/PTX was prepared by encapsulating PTX into the cavity of the star-shaped

cationic β -CD polymer (β -CD-OEI) with a β -CD core and multiple OEI arms. Then cationic β -CD-OEI/PTX and the anionic TGA@QD formed hybrid assemblies in water through the electrostatic interaction. The β -CD-OEI/PTX@QD hybrids could condense plasmid DNA (pDNA) into nanoparticles for simultaneous dual therapeutics and cellular imaging.

The preparation of functional polymeric materials using hybrid self-assembly of supramolecularly engineered polymers has also been reported. In this regard, inorganic nanoparticles are used as a template for controlling the structure of polymeric assemblies. For example, Caruso and coworkers described a modular hybrid assembly approach for the preparation of degradable capsules using polyrotaxanes and azide-modified silica particles as components (Fig. 13).¹²⁹ The supramolecularly engineered polymer polyrotaxanes were constructed from α -CD and PEG, driven by hydrophobic interaction. The modular assembly was formed by grafting polyrotaxanes with three alkyne moieties at each end-capping group onto the azide-functionalized silica particles (2.76 μm diameter) that were used as templates. Then the assembled polyrotaxanes were cross-linked using a degradable linker in order to form a stable architecture. At last, polymeric capsules were obtained after dissolving the template silica particles with buffered hydrofluoric acid (HF). The resultant capsules could be further functionalized as they possessed free OH groups of the threaded α -CDs and the alkyne moieties at the surface of the cross-linked polyrotaxanes.

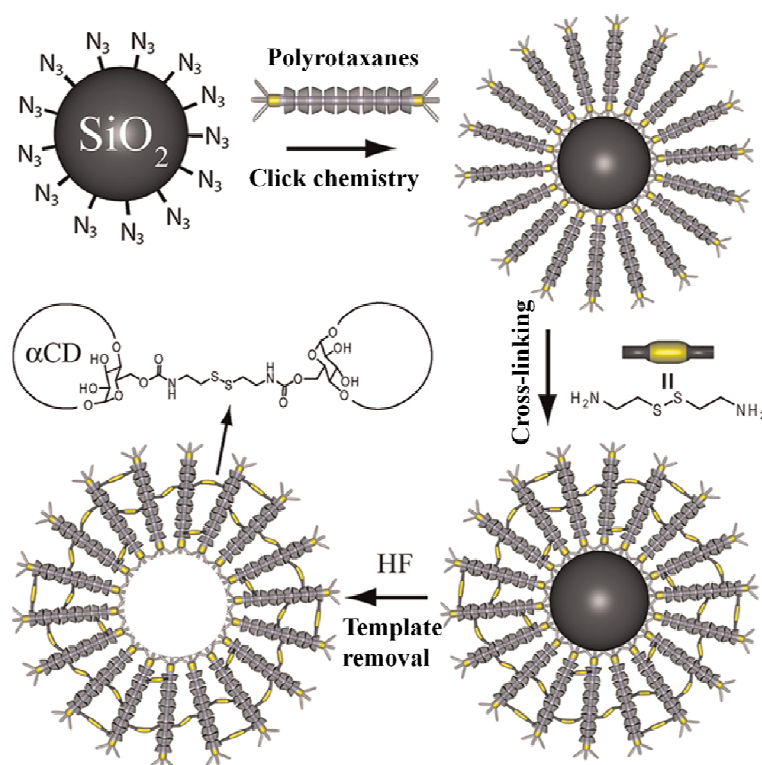


Fig. 13 (a) Schematic representation of the hybrid self-assembly of supramolecularly engineered

polymer polyrotaxanes and silica nanoparticles. Reproduced with permission from ref. 129. Copyright 2012, American Chemical Society.

At present, most of the reported supramolecularly engineered polymers are constructed from organic building blocks, except for the metal-ligand coordination supramolecularly engineered polymers in which the metal ions are incorporated. Supramolecularly engineered polymers composed of organic-inorganic hybrid units are few reported. Very recently, Wu and coworkers reported a novel kind of organic-inorganic hybrid supramolecularly engineered polymers using polyoxometalate (POMs) clusters as monomers and investigated the hybrid self-assembly of them.¹³⁰ It is well known that POMs include a large class of discrete and molecularly well-defined metal-oxide clusters and have proved promising inorganic building blocks. POMs exhibit unusual structural diversity and unique functionalities in optics, catalysis, electronics, magnetics, and so on. In particular, the POM surface can be modified with organic molecules, which provides a great advantage for fabricating hybrid nanostructures and materials. Wu et al. synthesized adenine-difunctionalized Anderson-type disc-like cluster $[\text{MnMo}_6\text{O}_{24}]^{3-}$ (abbreviated as MnMo_6) and thymine-difunctionalized MnMo_6 , which formed a hybrid supramolecularly engineered polymer via the complementary hydrogen bonding interaction of the base pairs. The hybrid supramolecularly engineered polymer could be easily prepared into different shaped monoliths by mold casting (Fig. 14a). At a suitable concentration, the hybrid supramolecularly engineered polymer self-assembled into fibers with the length over several hundred micrometers and the width in the range from dozens to hundreds of nanometers via the electrospinning technique (Fig. 14b). The organic phases of the fibers could be removed by calcination at 650 °C in air for 1 h and the linearly arranged nanoparticles of Mn and Mo oxides were obtained. This approach demonstrates that the fibers might be used as a template to prepare metal-oxide nanostructures.

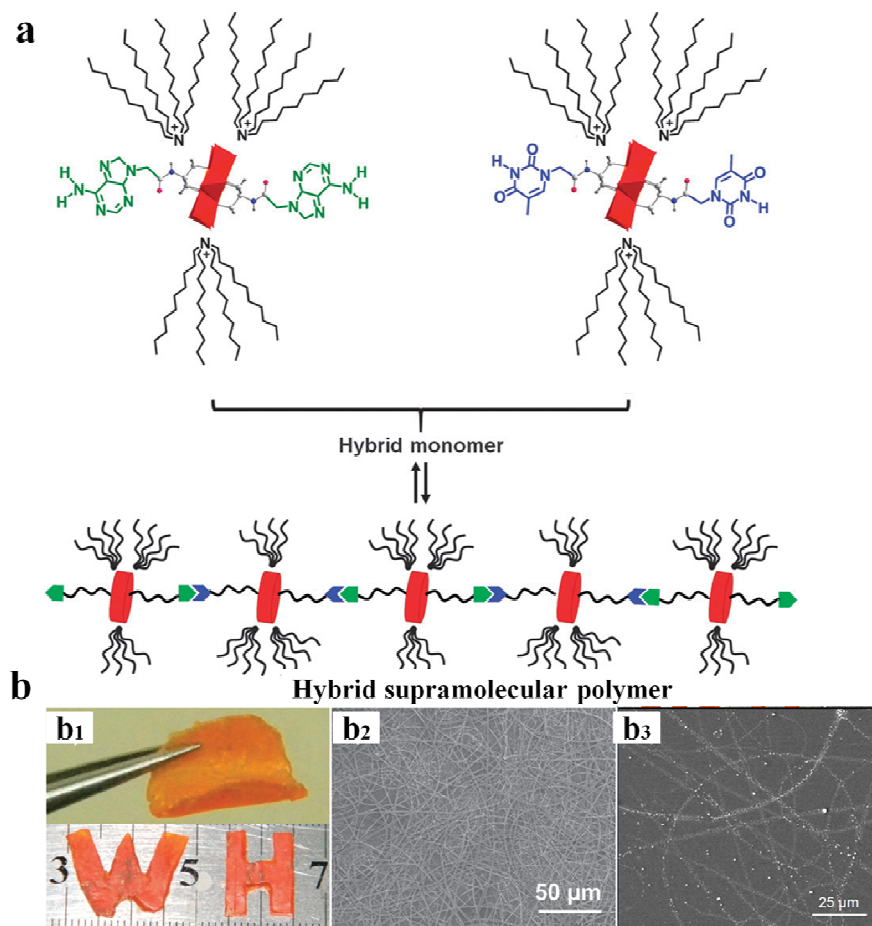


Fig. 14 (a) Schematic representation of hybrid supramolecularly engineered polymer based on complementary hydrogen bonding interaction. (b) The assemblies of hybrid supramolecularly engineered polymer: (b₁) Photos of different shaped monoliths of the hybrid supramolecularly engineered polymer prepared by mold casting; (b₂) SEM image of the hybrid supramolecularly engineered polymer fibers prepared by electrospinning; (b₃) SEM image of the retained fibrous assemblies after calcinations. Reproduced with permission from ref. 130. Copyright 2013, Royal Society of Chemistry.

3. Supramolecularly engineered polymer assemblies for biomedical applications

The former section has summarized the recent progress in the self-assembly of supramolecularly engineered polymers. It has been demonstrated that the controlled preparation of supramolecular assemblies from supramolecularly engineered polymers with different building units and their hybrids can be achieved. Since the intrinsic nature of the noncovalent interactions is reversible and dynamic, the morphologies, structures and properties of the supramolecularly engineered polymer assemblies are very easy to tune by changing the surrounding environments.

Correspondingly, the supramolecularly engineered polymer assemblies display unique sensitivity and responsiveness. The process of supramolecularly engineered polymer self-assembly is based on the ‘bottom-up’ strategy to construct highly ordered structures from building blocks, and the final assemblies integrate the functions from multiple components. These special features offer an excellent platform for the construction and application of smart materials in biomedical fields. In this section, we will discuss the biomedical applications of these supramolecularly engineered polymer assemblies, including bioimaging, drug delivery, gene transfection, protein delivery, regenerative medicine and tissue engineering.

3.1 Bioimaging

Bioimaging aims at utilizing bioimaging probes to visualize specific molecular pathways, which has become a hot topical research area.^{131,132} Over the past few decades, a wide range of imaging techniques including optical imaging, magnetic resonance imaging (MRI), nuclear imaging and ultrasound imaging, have been successfully applied in biomedical fields.^{133,134} In sharp contrast to small-molecule-based bioimaging probes used in clinical treatment, polymer-based bioimaging probes have greatly enhanced stability, reduced toxicity and improved target specificity, making them promising candidates for targeted bioimaging in near future.¹³⁵⁻¹³⁷ Especially, supramolecularly engineered polymer bioimaging probes have exhibited unique advantages in the diagnosis/treatment of cancers compared to conventional polymeric probes. Herein, we highlight the remarkable advances in supramolecularly engineered polymer assemblies for bioimaging application.

Due to their safety and sensitivity, optical imaging using fluorescent probes becomes the most widely used bioimaging technique in diagnosis and clinical studies. The optical imaging of biological systems shows several basic obstacles including autofluorescence, light scattering, and absorption by tissues.¹³⁸ A large number of supramolecular fluorescent probes have been extensively reported. In one example, we prepared a new class of supramolecular fluorescent nanoparticles by the self-assembly of β -CD-grafted hyperbranched polyethylenimine (PEI-CD), AD-functionalized calcein (CA-AD), AD-functionalized PEG derivative (PEG-AD), and AD-functionalized folate (FA-AD) based on host-guest interaction (Fig. 15).¹³⁹ In our system, the host-guest interaction remarkably suppressed fluorescence self-quenching of calcein fluorescent dyes, which provides a novel approach to prepare highly fluorescent materials. The introduction of the folate receptor endowed these supramolecular fluorescent nanoparticles with excellent bioimaging efficacy in HeLa cancer cells (a human cervical carcinoma cell line). This supramolecular

self-assembled system exhibited not only controllable size and excellent fluorescent properties, but also smart tumor-targeting ability. In addition, multifunctional supramolecular nanomaterials have been extensively developed for both therapeutic and diagnostic purposes in nanomedicine. For example, Wang and coworkers have reported the supramolecular dot-shaped nanoaggregates based on bis(pyrene) derivatives for lysosome-targeted cell imaging.¹⁴⁰ The J-type nanoaggregates with average diameters of 2-6 nm exhibited high pH-stability, photostability and low cytotoxicity in physiological condition and could be used as excellent fluorescence nanoprobes for lysosome-targeted imaging in living cells.

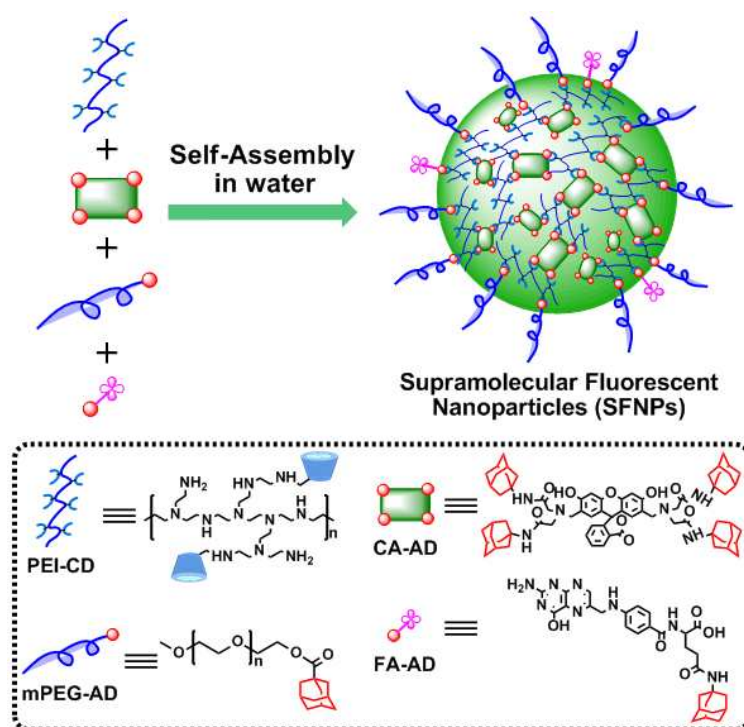


Fig. 15 Schematic representation of calcein-based supramolecular fluorescent nanoparticles assembled from PEI-CD, CA-AD, PEG-AD, and FA-AD via β -CD/AD host-guest interaction. Reproduced with permission from ref. 139. Copyright 2012, American Chemical Society.

Besides the aforementioned supramolecular optical probes, MRI imaging probes and nuclear imaging probes using supramolecularly engineered polymer assemblies with high sensitivity have also been widely used for bioimaging. MRI imaging shows a series of advantages including high spatial resolution, nonionizing radiation source as well as high soft-tissue resolution and discrimination.^{141,142} Up to date, a variety of supramolecular MRI contrast agents have been successfully prepared. For example, Tseng and coworkers reported a new class of supramolecular nanoparticle-based contrast agents formed by the self-assembly of Gd^{3+} -DOTA/CD-grafted PEI, AD-grafted poly(amidoamine) dendrimer, and AD-grafted PEG. The resulting Gd^{3+} -DOTA nanoparticles displayed significant improvement of sensitivity and

relaxivity.¹⁴³ Differently, Liu and coworkers reported a distinct MRI probe based on a Mn^{III}-porphyrin-based linear supramolecularly engineered polymer, which presented remarkably enhanced MR signal *in vitro* and *in vivo*.¹⁴⁴ Additionally, Tseng et al. further developed supramolecular nuclear probes with high sensitivity by using a flexible and modular synthetic approach.¹⁴⁵ In their design, size-controlled supramolecular nanoparticles were used for microPET/CT imaging to achieve the lymph node trafficking in mice. The results indicated that the size of these supramolecular nanoparticles greatly affected their *in vivo* characteristics.

3.2. Drug delivery

Supramolecularly engineered polymer assemblies have been widely used for drug delivery in recent years and show great potential for therapeutic purposes. Advantages of the noncovalent connected assemblies from supramolecularly engineered polymers include the ease of supramolecular precursor synthesis, excellent biocompatibility and biodegradability, responsive nature, and possibility to incorporate a multiple array of different functional units through intermixing of different building blocks. All of these features are of great important for designing and producing drug carriers.

The aim of developing drug delivery systems is for clinical treatment.¹⁴⁶ At present, most of drug carriers need tedious and sophisticated synthesis, which makes the potential pharmaceutical development more complex, especially in terms of the manufacturing process, reproducibility and quality control. Therefore, it is important to simplify the preparation process of drug carriers. From this point of view, the supramolecularly engineered polymer assemblies exhibit unique advantages. In contrast to conventional covalent bonded polymers, supramolecularly engineered polymers offer an alternative strategy to fabricate polymeric assemblies. First of all, the way to prepare supramolecularly engineered polymers usually only involves simple modification reactions and avoids the complicated synthesis and purification procedures, which are usually required for synthesizing the covalent bonded polymers. Secondly, in supramolecularly engineered polymers, the functional groups can be attached to the building blocks by noncovalent recognition, greatly speeding their construction. In addition, the building blocks for supramolecularly engineering polymers can also be either small molecules or polymers, which endow the assemblies with a vast compositional range, unusual structural diversity, and abundant functionalities in optics, electronics, magnetics, biomedicine, and so on.

As one example, our group developed a supramolecular drug delivery system by the self-assembly of a supramolecular amphiphilic polymer in which the hydrophilic PEGylated calix[4]arene (DC4-PEG) and hydrophobic drug photosensitizer chlorine e6 (Ce6) were coupled by the host-guest interaction (Fig. 16).¹⁴⁷ The star-like DC4-PEG was easily obtained by a two-step reaction. The resultant DC4-PEG with a

hydrophilic cavity could encapsulate Ce6 efficiently and further self-assembled into polymeric nanomicelles. These supramolecular micelles shielded the negative charges in the surface of Ce6 and thus improved cellular uptake. Thus, supramolecular DC4-PEG/Ce6 micelles exhibited more efficient photodynamic therapy efficacy than free Ce6. The synthetic hydrophilic hosts could be utilized for appropriate guests including various drugs. Moreover, the supramolecular drug delivery system possessed stimuli-responsive ability due to the host-guest interaction.

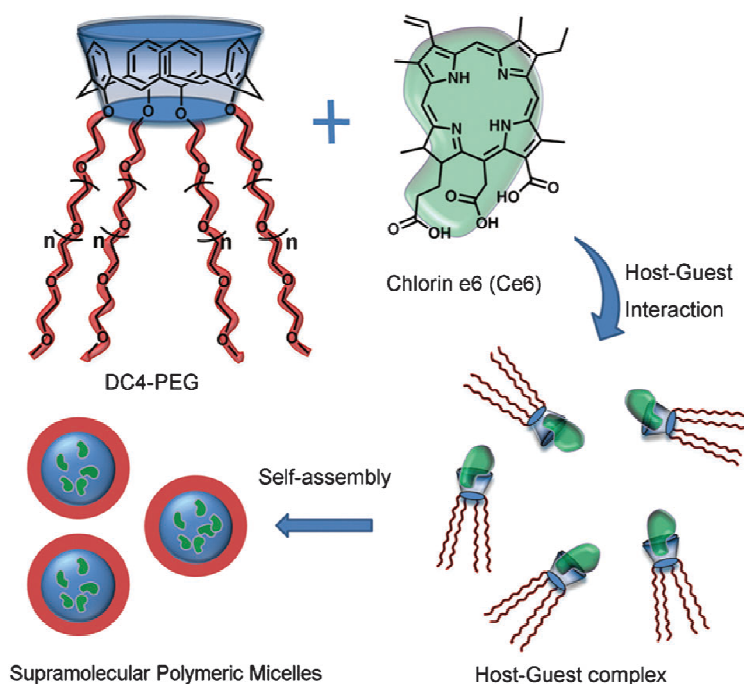


Fig. 16 Schematic representation of self-assembled polymeric micelles from SEPSM based on host-guest interaction for drug delivery. Reproduced with permission from ref. 147. Copyright 2011, Royal Society of Chemistry.

For the treatment of diseases using drug delivery systems, it is often required to accomplish rapid drug release after drug carriers arriving at the pathological sites, which may enhance the therapeutic efficacy as well as reduce probability of drug resistance. The use of stimuli-responsive carriers offers an interesting opportunity for drug delivery. So far, several kinds of molecular assemblies are employed as stimuli-responsive carriers for either passive or active targeting, including conventional polymeric assemblies, liposomes, supramolecularly engineered polymer assemblies and so on.^{148,149} Especially, the supramolecularly engineered polymer assemblies are more sensitive to external stimuli due to the weak noncovalent connection, which provides a significant advantage for them as drug vehicles. In the past decade, a great deal of researches has been carried out on stimuli-responsive supramolecular materials for drug delivery, especially concerning their design and application as nanocarriers. The stimuli-responsive supramolecular systems, including

pH-, thermal-, light-, enzyme-, and redox-responsive ones, have been designed and investigated for drug delivery.^{90,120,150-152} Compared to those of the covalent assemblies, the self-assembly and disassembly processes of supramolecularly engineered polymer assemblies are more easily to control due to the existence of noncovalent connection, which renders the supramolecular assemblies as an ideal vehicle for drug delivery. For example, Scherman and coworkers reported a triple stimuli-responsive supramolecular double hydrophilic block copolymer micelles for controlling drug release (Fig. 17).¹⁵³ Thermo-responsive PNIPAM and pH-responsive poly(dimethylaminoethylmethacrylate) (PDMAEMA) formed supramolecularly engineered polymer via the linkage of CB[8], which further formed supramolecular micelles above LCST of PNIPAM and loaded the anticancer drug DOX efficiently. The micelles would be disassembled by decreasing the temperature, lowering the pH or adding competitive guests, and then release the DOX in a controlled manner. Compared to the covalent connected micelles, these supramolecular micelles exhibited a faster release rate. Moreover, the DOX-loaded supramolecular micelles displayed a significant inhibition against HeLa cells, and the tumor cell inhibiting rate could be tuned by the use of the three stimuli. This triple stimuli-responsive supramolecularly engineered polymer micelle system may represent an evolution over conventional stimuli-responsive covalent copolymer systems.

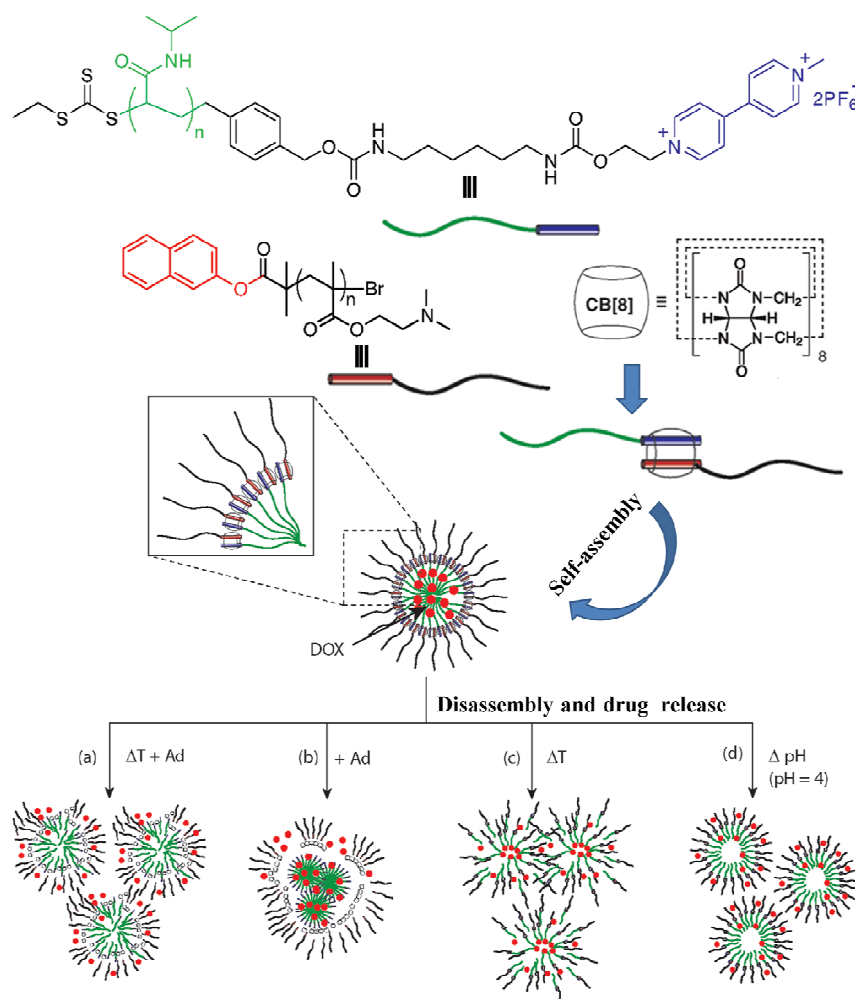


Fig. 17 Schematic representation of hierarchical self-assembly of the supramolecularly engineered polymer and its subsequent mode of drug release after being exposed to different triggers. Reproduced with permission from ref. 153. Copyright 2012, American Chemical Society.

Biodegradability and biocompatibility are the main concern for designing ideal biomedical polymeric vehicles. From this perspective, supramolecularly engineered polymer assemblies have become increasingly important in the biomedical fields due to the general ease of degradation and metabolization. For example, α -CD/PEG polyrotaxane is an interesting candidate and is made entirely of biocompatible components, by threading α -CD molecules with the PEG chain.¹⁵⁴ Thus, the supramolecular assemblies from polyrotaxane, such as films, capsules and gels, possess excellent biodegradability and biocompatibility since the degradation products, linear PEG chains and the relatively small α -CDs are both biocompatible, making them promising carriers for future drug delivery.¹⁵⁵⁻¹⁵⁹ Caruso and coworkers prepared biodegradable core-shell nanoparticles self-assembled from triblock polyrotaxanes.¹⁵⁸ The degradation of these polyrotaxane particles could be achieved under simulated intracellular reducing conditions through the cleavage of disulfide bonds between the blocking groups and the PEG backbone in the polyrotaxanes.

These supramolecular polyrotaxane nanoparticles exhibited the ability of loading and releasing small hydrophobic molecules, which demonstrated that they could be used in the manufacture of controlled drug delivery systems. In addition, Ji and coworkers reported the biocompatible supramolecularly engineered polymer vesicles based on the inclusion complexation between α -CDs and double-hydrophilic poly(ethylene oxide)-*block*-poly(2-methacryloyloxyethyl phosphorylcholine) (PEO-*b*-PMPC) in aqueous solution.¹⁵⁹ The biocompatible vesicles could encapsulate hydrophilic drug efficiently and release the drug into cancer cells, which are attractive as drug vehicles for biomedical applications.

Another apparent advantage of supramolecularly engineered polymer assemblies for drug delivery is easy to functionalize and construct the multifunctional structures. Such nature offers an excellent platform for the construction of multifunctional drug delivery systems in which two or more components are integrated smartly. For example, Li and coworkers reported a multifunctional bioreducible supramolecular self-assembly system for targeted and synergistic co-delivery of gene and drug.¹⁶⁰ The anticancer drug PTX was incorporated into the cavity of γ -CD and multiple OEI arms with FA via a disulfide linker. The supramolecularly engineered polymer, termed as γ -CD-OEI-SS-FA/PTX, was formed via the host-guest complexation of PTX and γ -CD. They formed polyplexes with pDNA to further self-assemble into positively charged nanoparticles with the average diameter ranging from 70 to 110 nm, giving the multifunctional supramolecular bioreducible targeted and synergistic co-delivery system. The multifunctional supramolecularly engineered polymer co-delivery system exhibited combined and synergistic effects of the PTX-enhanced gene transfection, the FA-targeted delivery, and the redox-sensitive folate receptor (FR) recycling, leading to the effective delivery of wild-type p53 gene into FR-overexpressed KB cancer cells (a human carcinoma cell line) at low N/P ratios to induce an efficient cell apoptosis. The multifunctional supramolecular self-assembly co-delivery system may represent a promising candidate for potential cancer therapy.

3.3 Gene transfection

Gene therapy has attracted tremendous attention as a new class of effective therapeutic methods for the treatment of various diseases.¹⁶¹ However, the *in vivo* transportation ability of genetic materials (free oligonucleotides, DNA and RNA) is insufficient due to the instability against enzymatic degradation, low uptake efficiency into the target cells and preferential liver and renal clearance. To circumvent these obstacles, it is indispensable to develop gene vectors to protect the genetic materials from degradation. In comparison with viruses and cationic lipids, the polycationic vectors exhibit several apparent advantages such as high stability, low host immunogenicity, ease of manufacture, low cost of synthesis and unrestricted

trans-gene size. Therefore, the self-assembly of cationic polymers and genetic materials has received more and more attention.^{162,163} Among different cationic polymers, cationic supramolecularly engineered polymers combine stability of polymers with dynamic tunability of noncovalent bonds and excellent biocompatibility together, which provides significant benefits for gene delivery.

Thompson and coworkers reported a novel siRNA delivery vector based on the self-assembly of supramolecularly engineered polymer consisting of cationic β -CD derivative host and cholesterol (Chol)-modified poly(ethylene glycol)-poly(vinyl alcohol) (PEG-PVA) guest whose Chol units were coupled with an acid-sensitive benzylidene acetal motif.¹⁶⁴ The self-assembled Chol-PEG-PVA/amino- β -CD pendant polymer complexes were capable of condensing the siRNA via multivalent electrostatic interaction, which formed stable nanoparticles less than 200 nm in size with a slightly negative zeta potential. *In vitro* experiments confirmed that the nanoparticles had 10^3 -fold lower cytotoxicities than 25 kDa PEI, while they showed high gene knockdown efficiencies that were comparable to 25 kDa PEI. Recently, we have reported a facile supramolecular method to prepare charge-tunable supramolecular dendritic polycations through the host-guest interaction between primary amine- or tertiary amine-modified β -CD host and AD-functionalized HPG (HPG-AD) guest.¹⁶⁵ A series of supramolecular dendritic polymers with different charge density could be obtained by altering the molar ratios of β -CD derivatives and HPG-AD. Correspondingly, the gene transfection efficiency of supramolecular dendritic polymers could be readily regulated and the size of compact polyplex particles was easy to optimize. This kind of supramolecular dendritic polymers showed efficient pDNA condensation ability and excellent *in vitro* gene transfection efficiency in COS-7 cells (a cell line derived from kidney cells of the African green monkey).

Up to now, almost all reported supramolecular gene delivery systems have been constructed through the host-guest complexation between macromolecules and small molecules. As far as we know, the assemblies from SEPS are more sensitive to external stimuli and it may be significant to design and prepare the SEPS as gene vectors. Very recently, we synthesized cationic SEPS via host-guest complexation between β -CD dimer (β -CD₂) and a positively charged ferrocene dimer (Fc₂).¹⁶⁶ The cationic SEPS exhibited very low *in vitro* cytotoxicity in contrast to those of commercially available 10 kDa PEI and was capable of condensing pDNA when the N/P ratio was at 20. The pDNA release from SEPS/pDNA polyplexes would be accelerated after adding H₂O₂ which induced the depolymerization of SEPS. Although the reported cationic SEPS showed weak capacity of condensing pDNA, it may open up a new strategy for designing efficient and safe gene vectors. SEPS with stronger host-guest interaction, higher molecular weight and higher surface charge density can be expected to form a more stable polyplex and improve

transfection efficiency.

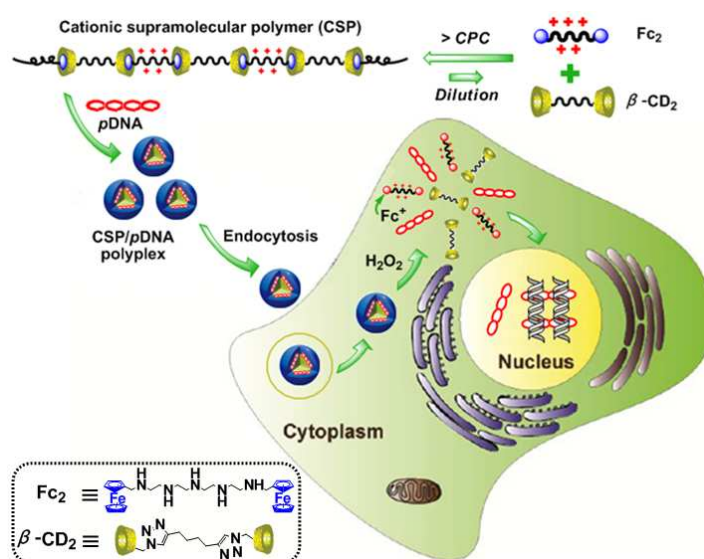


Fig. 18 Schematic representation of a cationic SEPS constructed via orthogonal host-guest interaction between $\beta\text{-CD}_2$ and Fc_2 as well as its H_2O_2 -induced pDNA release behavior. Reproduced with permission from ref. 166. Copyright 2013, Royal Society of Chemistry.

3.4 Protein delivery

In the past few years, protein-based therapeutics have emerged and developed rapidly for the treatment of a broad range of diseases, including autoimmune diseases, metabolic disorders and cancers.¹⁶⁷ Nevertheless, the therapeutic value of protein drugs is still limited due to low stability against proteases, poor cellular uptake, and rapid elimination from the body.¹⁶⁸ A major expectation for the protein therapeutic success is believed to be the development of effective carriers that can improve the protein stability and carry them to the pathogenic sites.¹⁶⁹ As mentioned in the above section, supramolecularly engineered polymer assemblies have been proved to be excellent drug delivery systems, thus they can also be used to deliver proteins.

Scherman and coworkers reported triply responsive supramolecular micelles from supramolecularly engineered double hydrophilic block copolymer for insulin delivery.¹⁷⁰ The supramolecularly engineered copolymer was composed of temperature- and glucose-responsive MV-terminated poly(*N*-isopropylacrylamide)-*r*-poly(*t*-butylacrylate)-*r*-poly(acrylic acid) and dibenzofuran-terminated poly(dimethylacrylamide) linked by CB[8], which further self-assembled into micelles in aqueous solution. The protein was incorporated into the hydrophobic micelle core via hydrophobic interaction. The release rate of insulin from micelles could be controlled using three external triggers, including changing glucose concentration, decreasing temperature or adding a competitive guest for CB[8]. This self-assembled supramolecular system offered good control over the

release of insulin under physiological conditions, which provides a new model for clinically relevant protein delivery. Except for the micelles or nanoparticles, vesicles are promising candidates for protein encapsulation due to their hydrophilic interior. Very recently, the same group prepared self-assembled vesicles from supramolecular peptide polymer for the delivery of basic fibroblast growth factor (bFGF).¹⁷¹ Pyrene-modified peptide and MV-terminated PNIPAM were held together by CB[8] ternary complexation to form a supramolecular peptide polymer, which subsequently self-assembled into double layer vesicles. The encapsulation of bFGF in the vesicles was carried out at 37 °C without using the excipients such as heparin, but effectively protected the protein against denaturation. The bFGF could be released in a controlled manner and its bioactivity could be sustained even over 5 days. Moreover, Meijer and coworkers reported supramolecular transient networks based on supramolecularly engineered polymers consisting of UPy-difunctionalized PEG for the delivery of bone morphogenetic protein 7 (BMP7).¹⁷² *In vivo* experiment confirmed that the BMP7 growth factor proteins could be released from the bioactive supramolecular assemblies and the activity of them was not influenced.

3.5 Regenerative medicine and tissue engineering

Regenerative medicine is a newly emerging area in which stem cells are used to regenerate biological tissues and improve tissue functions. Benefiting from stem cell-based therapy, regenerative medicine offers a possible alternative treatment of current clinical medicine.¹⁷³ To satisfy the needs of regenerative medicine and tissue engineering, the design of biomaterials is shifting away from the use of inert synthetic materials towards an increasing emphasis on bioactive scaffolds based on supramolecularly engineered polymers. These polymers can be random and entangled coils with the mechanical properties of plastics and elastomers, but with excellent processability and adjustability due to their reversibility. Moreover, these supramolecularly engineered polymers can further self-assemble into various morphologies, resulting in shape-persistent and highly ordered structures. The use of strong and directional noncovalent interactions among different building blocks has exhibited obvious advantages. It not only enriches dynamic behavior but also possesses high degrees of internal order differing from conventional covalent bonded polymers. These prominent properties are well suitable for the construction of the new scaffold. As a result, supramolecularly engineered polymers play an increasingly important role in regenerative medicine and especially tissue engineering. Nowadays, we have witnessed more and more fruitful work in this field.

Stupp and coworkers developed the concept of self-assembly for functional bulk materials using designed molecules.^{31,174} They reported a class of peptide amphiphiles (PAs) and subsequently constructed diverse supramolecular assemblies from one

dimension to three dimensions based on PAs. These assemblies showed excellent *in vivo* efficacy in different models, including spinal cord injury, cartilage regeneration, bone regeneration, myocardial infarction, peripheral vascular disease, and peripheral nerve regeneration. For instance, they utilized the branched PAs as self-assembling coatings for tissue engineering scaffolds. This strategy of molecular design and coating may have potential application in bladder tissue regeneration.¹⁷⁵ Meijer and coworkers made outstanding achievements by developing a series of supramolecular systems based on hydrogen-bonded polymers for renal regenerative medicine.¹⁷⁶ For example, they proposed a modular and supramolecular approach to construct bioactive scaffolds for tissue engineering via simply mixing ureido-pyrimidinone (UPy) functionalized polymers with UPy-modified biomolecules.¹⁷⁷ The reversible nature of the hydrogen bonds allowed for a modular approach to gaining control over cellular behavior and activity both *in vitro* and *in vivo*. Another supramolecularly engineered polymer system was presented in which relatively short trimethylene carbonate (TMC) prepolymers were linked via reversible quadruple hydrogen bonding UPy moieties. By mixing different trifunctional UPy-TMC with bifunctional UPy-TMC polymers, both mechanical and thermal properties could be readily adjusted. Since the UPy-TMC polymers had good biocompatible, fibroblasts could proliferate very well on UPy-TMC film. Thus, these supramolecularly engineered polymers are very promising biomaterials for applications such as tissue engineering.¹⁷⁸ They also constructed the hydrogels comprising a hydrophilic PEG matrix combined with nanoscopic hydrophobic compartments with associative strength amplified by hydrogen-bonded UPy motifs.¹⁷⁹ The resulting hydrogels exhibited high strength and resilience upon deformation, which showed great potential in the field of regenerative medicine and tissue engineering. Zhang and his group designed a variety of peptides to self-assemble into novel supramolecular biomaterials after serendipitously discovering a self-assembled peptide, EAK16, which self-organized into ordered nanofibers and further into scaffolds.¹⁸⁰⁻¹⁸² One example was the use of peptide scaffolds to support neurite growth and differentiation, neural stem cell differentiation, cardiac myocytes, and bone and cartilage cell cultures. The peptide scaffolds from RADA16-I and RADA16-II formed nanofiber scaffolds in physiological solutions that stimulated extensive rat neurite outgrowth and active synapse formation on the peptide scaffold.

4. Conclusions and perspectives

During the past two decades, supramolecularly engineered polymers have demonstrated great potential to be excellent candidates for macromolecular self-assembly, and a vast variety of delicate supramolecular structures have been

reported. The supramolecularly engineered polymer assemblies from different topological features exhibit distinct morphologies, unique architectures and specific functions, which further provides a new platform for designing and developing smart supramolecular materials and functional supramolecular devices. The special dynamic tunable nature of supramolecularly engineered polymers provides unique advantages in supramolecular self-assembly when compared with the conventional covalent bonded polymers, which stimulates the continuously growing interest in this research field. In addition, these self-assembled supramolecular structures have exhibited apparent advantages in biomedical areas including bioimaging, drug delivery, gene transfection, protein delivery, regenerative medicine and tissue engineering.

Despite of great progress, the self-assembly of supramolecularly engineered polymers is still an emerging field, and a lot of work still needs to be done to get a clear structure-function correlation and gain better understanding and control over the parameters governing the self-assembly and nanostructure formation. Up to now, the supramolecular structures obtained from supramolecularly engineered polymers are still limited, especially for macroscopic self-assemblies. One highly demanding area is designing 'smart' supramolecular structures, which respond to external stimuli and then change shape, dimension, size, properties or adapt to their environment. Another exciting area is the self-assemble processes of supramolecularly engineered polymers that can mimic the formation of functional structures in nature, such as DNA, protein and cell membrane. In addition, one important area that may demand much research is the specific applications of the obtained supramolecular structures self-assembled from supramolecularly engineered polymers. For example, current work on drug delivery systems is mainly centered on conventional micelles, other assemblies, like supramolecular vesicles, nanofibers, nanotubes, films, have seldom been involved. For gene delivery, only a small number of supramolecular structures from SEPSM and SEPM have been reported, and a lot of assemblies from supramolecularly engineered polymers have not been explored. By integrating multiple noncovalent interactions, which respond to very subtle changes in the surrounding environment, such as temperature, light, chemical stimuli, and pH, into supramolecularly engineered polymer systems, the self-assembled supramolecular structures may hold great promise in many fields.

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