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Supramolecular Assembly and Stimuli-Responsive Behavior of Multielement Hybrid Copolymers

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Abstract

Toward the organic polymer, hybrid elements can be defined as those beyond C, H, O, and N. Polymers comprising hybrid elements, such as Si, P, B, or metal ions have attracted great attention in the design of high performance or smart materials. Introduction of hybrid elements into a polymeric network may also lead to the formation of new intermolecular interactions, thus promote the self-organization of polymer chains to form controllable structures and morphologies. In this chapter, we introduce some of the recent important development in the design and self-assembly of hybrid amphiphilic copolymers. Specific attention was paid on the hybrid amphiphilic copolymers containing POSS, boronic acid, or boronate functional moieties. We introduce the design, synthesis, self-assembly behavior, and properties of these hybrid amphiphilic copolymers in detail. Also, the advantages and drawbacks of these polymers and their corresponding nanoassemblies are discussed.

Keywords: hybrid polymer, self-assembly, stimuli-response, nanostructure, functionality

1. Introduction

The development of copolymer self-assembly depends not only on the exploration of reliable driving forces but also on the creation of new building blocks. Conventional organic copolymers composed of C, H, O, and N elements generally self-assemble through Van der Waals interactions. The highly dynamic and weak strength features of this intermolecular interaction usually bring a great challenge to the controllable self-assembly of copolymers. Recently, introduction of hybrid elements (such as Si, B, P, and metal ions) onto the polymer chains

has become a favorable pathway to achieve novel properties. Notably, hybrid elements are of high capability to change the interaction among polymer chains. For example, the stacking ability of polyhedral oligomeric silsesquioxanes (POSS) units has discovered to be an effective driven force for the self-assembly of polymer chains. Also, intermolecular coordination created by B-N dative bond and organic-metal chelating can organize polymer chains into ordered three-dimensional structures because of their bonding directionality.

In this chapter, we focus on some of the recent development in design, synthesis, property, and potential applications of the nanoassemblies derived from multielement amphiphilic copolymers, especially those containing POSS, boronic acid, or boronate moieties. As the smallest organic/inorganic hybrid unit, POSS has gained great attention due to its well-defined structure, high thermal stability, easy functionalization, and so on [1–4]. Synergy between the inorganic core and the organic side groups renders POSS with excellent solubility in many solvents and high compatibility with various polymeric matrices. Thus, POSS and POSS-based polymers have been widely used in the modification of polymer resin to construct high performance organic/inorganic hybrid materials [5]. Herein, we pay particular attention to the POSS-based amphiphilic copolymers and their self-assembly behavior in solutions. Boronic acid moiety has a high binding affinity to saccharide, glycol, and catechol derivatives, and the as-formed boronate group is cleavable in response to glucose and acidic pH. Therefore, amphiphilic copolymers containing boronic acid or boronate moieties are of particular interest in the fabrication of smart nanoassemblies.

2. Design, self-assembly of multielement hybrid copolymers

2.1. Self-assembly of POSS-based amphiphilic copolymers

POSS cages are generally hydrophobic and have a larger diameter ranging from 1 to 3 nm. Amphiphilicity can be achieved even only one POSS cage is incorporated onto a hydrophilic polymer chain. The aggregation and ordered stacking of POSS cages have powerful strength to promote the solution self-assembly of POSS-based amphiphiles. This is particularly important for the realization of kinetic and thermodynamic equilibrium of self-assembly behavior, thus leading to the formation of well-defined assemblies. Chemical modification of POSS cages and polymerization of POSS cages with carbon-carbon double bond are the most used methods to create POSS-based amphiphilic copolymers [6–8]. The former method can easily generate one POSS-capped amphiphiles, whereas the second method usually results in the incorporation of multiple POSS cages onto one polymer chain.

2.1.1. POSS end-capped amphiphiles

POSS cages can be designed with functional groups that are reactive to hydrophilic polymer chains thus creating POSS end-capped amphiphiles. Among numerous POSS derivatives, primary amine functionalized POSS is usually used to prepare POSS end-capped amphiphiles because of their easy synthesis and the highly reactive primary amine group. For example,

starting from aminopropylisooctyl-POSS, we have designed and synthesized a hybrid amphiphile that contains a hydrophobic POSS head and a hydrophilic PEG tail functionalized with a bidentate ligand through amidation and esterification reactions [9]. Self-assembly of this amphiphile in water solution affords uniform assemblies, and their morphologies can be adjusted by Zn^{2+} , therefore endowing the assemblies with unique metal ion sensitivity (**Figure 1**).

POSS cages attached with a primary amine group could also be incorporated onto the end of a hydrophilic polymer chain through atom transfer radical polymerization (ATRP). Li et al. [10] constructed a aminopropylisooctyl-POSS end-capped amphiphilic copolymer poly(2-(2-methoxyethoxy) ethyl methacrylate)-co-oligo(ethylene glycol) methacrylate) (POSS-P(MEO₂MA-co-OEGMA)) using POSS-Br as ATRP initiator (**Figure 2**). This polymer could self-assemble into spherical micelles comprising POSS core and P(MEO₂MA-co-OEGMA) corona in aqueous solution (**Figure 3**). The LCST and CP values of the thermoresponsive

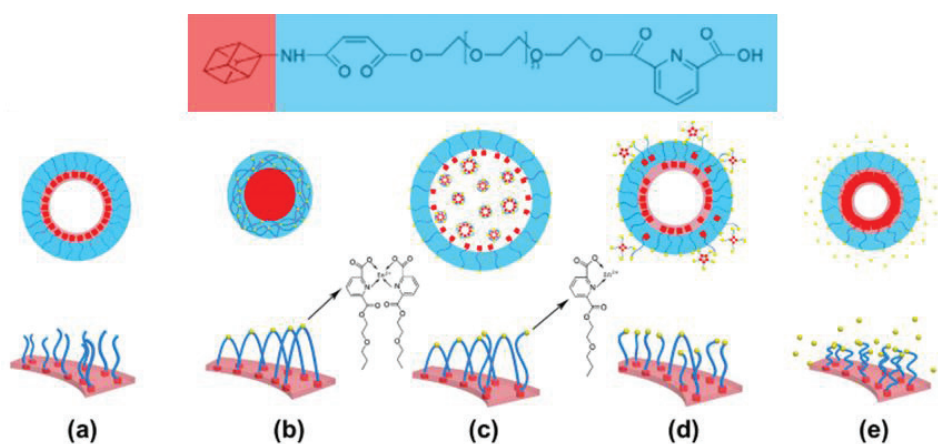


Figure 1. Proposed self-assembly model of Zn^{2+} /POSS-MA-PEG-DPA by metal coordination modulation.

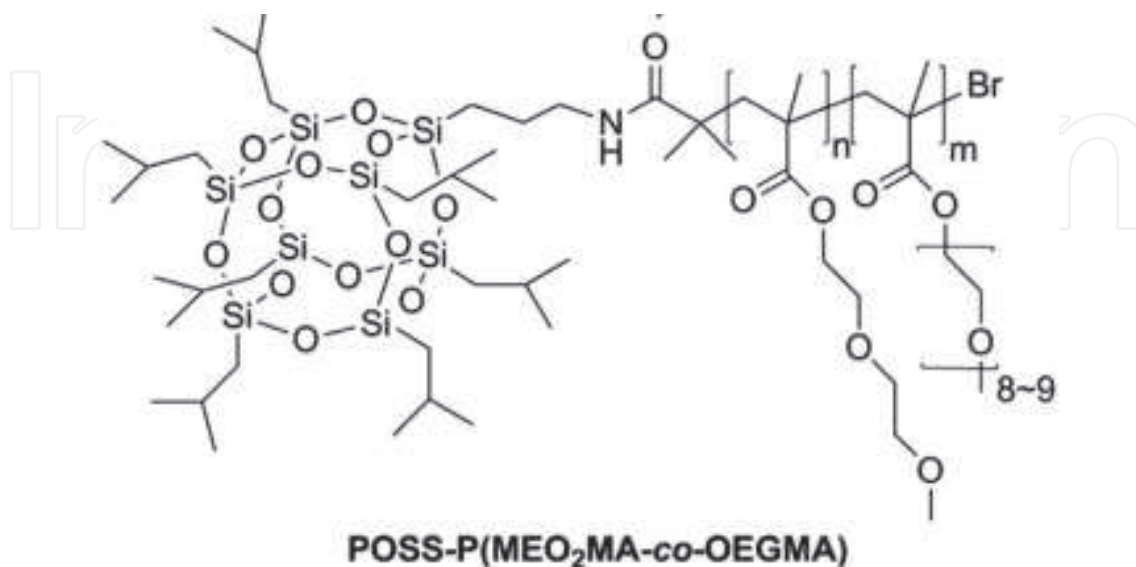


Figure 2. The chemical structure of POSS-P(MEO₂MA-co-OEGMA).

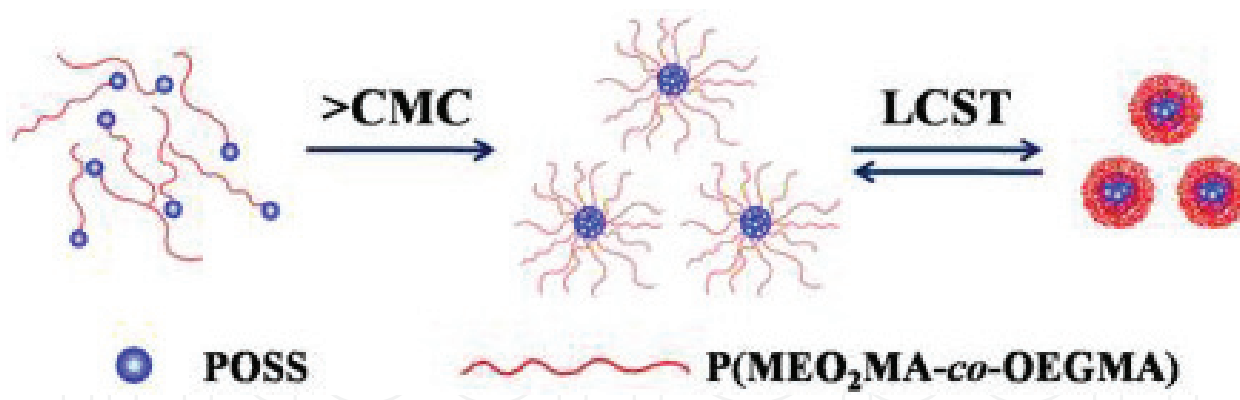


Figure 3. The schematic self-assembly process of the POSS-P(MEO₂MA-co-OEGMA) in water response to temperature.

polymers were increased with higher OEGMA content and could be well controlled by varying the ratio of MEO₂MA and OEGMA. Core-shell micelles and large aggregates were formed at temperatures below and above the LCST, respectively. Synthesis of aminopropylisooctyl-POSS end-capped amphiphilic POSS-poly (*N,N*-dimethylaminoethyl methacrylate)-block-poly (methyl methacrylate) (POSS-b-PDMAEMA-b-PMMA) (**Figure 4**) has also been reported by Wu et al. [11]. They found that POSS-b-PDMAEMA-b-PMMA could self-assemble into polymeric micelles with different shapes such as spherical, rod, and necklace morphology in different solutions. These micelles could encapsulate tetraphenylethene (TPE) and influence its fluorescent intensity. The introduction of POSS to polymer micelles could increase the fluorescence intensity of TPE, and spherical micelles could more tightly pack TPE to restrict intramolecular rotation of TPE to increase the fluorescent intensity compared with rod-like and necklace-like micelles. However, rod-like structure had a large specific surface area to interact with cell surface receptors, which enhanced its propensity to be internalized. Thus, the encapsulation of TPE aggregates in polymeric micelles not only facilitated the dispersion of TPE aggregates in biological environments but also enhanced the intracellular uptake of probes.

Yusa et al. [12] prepared a POSS end-capped amphiphiles using incompletely condensed (IC) and completely condensed (CC) POSS tethered with hydrophilic PEG chains (**Figure 5**). The association behavior of these amphiphiles in water solution was controlled based on

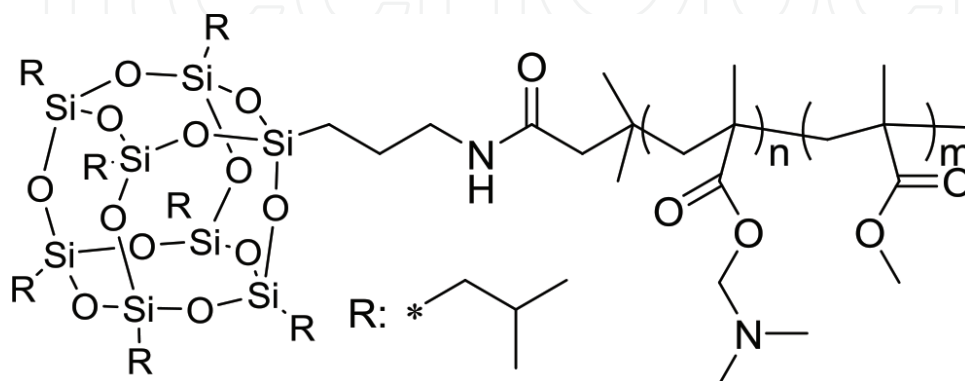


Figure 4. The chemical structure of POSS-b-PDMAEMA-b-PMMA.

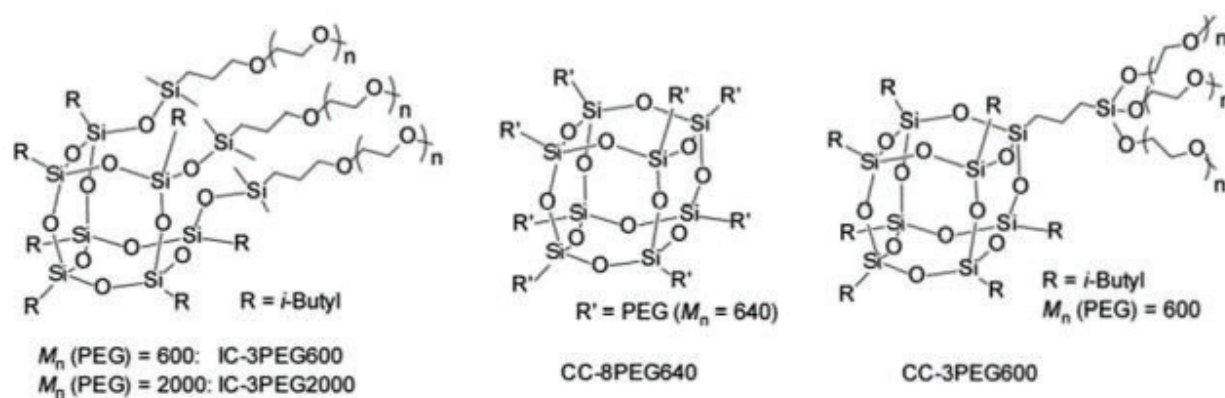


Figure 5. The chemical structures of amphiphilic POSS derivatives.

their chemical structure (**Figure 6**). The eight PEG chains-containing CC-POSS was hydrophilic and could be molecularly dissolved in water. Spherical micelles could be formed from IC-POSS in water solution as it contained three PEG chains with a molecular weight of 2000. Polydispersed worm-shaped micelles were formed by IC-POSS with three PEG chains of 600 molecular weight. Amphiphilic CC-POSS containing branched PEG chains with a molecular weight of 600 formed vesicle structures. These results indicated that the length of PEG chain and the shape of the POSS head group played a crucial role in determining the self-assembly structures.

2.1.2. POSS containing amphiphilic block/random copolymers

Copolymerization of carbon-carbon double bond bearing POSS cages with other water-soluble monomers was generally used to create amphiphilic block or random copolymers. Because of the larger diameter of POSS cage, the evident steric effect brings great difficult to the homo- and copolymerization of POSS monomers. This limitation was particularly evident in the chain extension of POSS macromolecular chain transfer agent during reversible

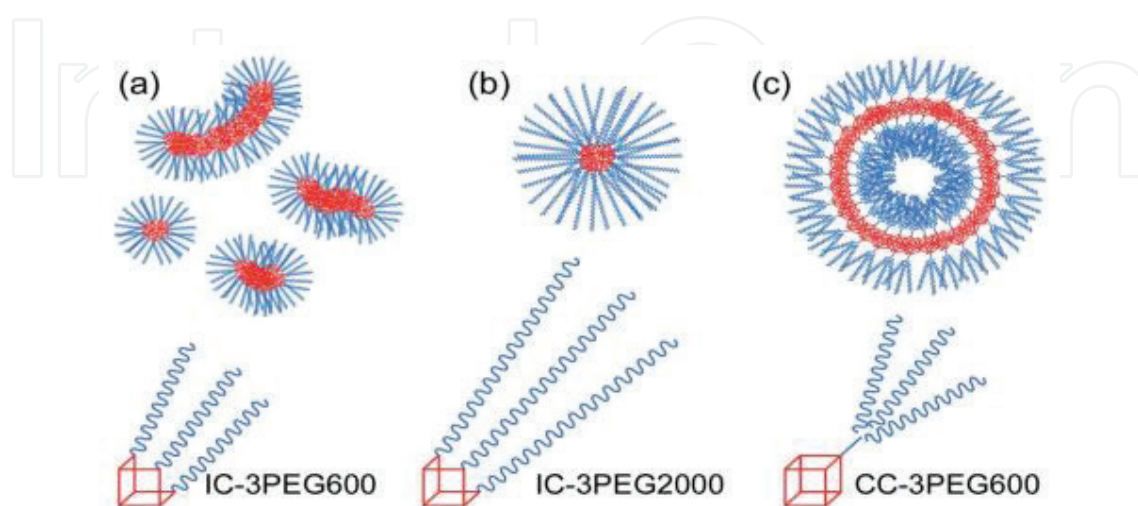


Figure 6. Schematic of the aggregates formed from (a) IC-3PEG600, (b) IC-3PEG2000, and (c) CC-3PEG600 in pure water.

addition-fragmentation chain transfer polymerization (RAFT). Therefore, great efforts have been focused on improving copolymerization activity of POSS monomers. For example, we have found that a trace amount of styrene (St) monomer can easily promote the chain extension of POSS macromolecular chain transfer agent for many monomers such as methyl methacrylate (MMA), acrylic acid (AA), 4-vinylpyridine (4VP), and *N*-isopropylacrylamide (NIPAm) [13]. This method is of great interest for the design and synthesis of POSS-based amphiphilic copolymers. Phase separation could be easily achieved during the self-assembly of POSS-based amphiphilic copolymers in water solution. We have synthesized a PMAPOSS-*b*-P(AA-co-St) block copolymer through RAFT polymerization and selective hydrolysis [14]. In a water solution, PMAPOSS-*b*-P(AA-co-St) with phase-separation patterns as core and hydrophilic segments as corona in aqueous media were obtained (**Figure 7**).

Xu et al. [15] reported a POSS-based hybrid pH-sensitive block copolymers poly(methacryl-isobutyl-POSS)-*b*-poly(4-vinylpyridine) (PMAiBuPOSS-*b*-P4VP) through RAFT polymerization. The size of aggregates in aqueous solution initially decreased and later increased as the pH value increased (**Figure 8**). It was supposed that this behavior was caused by the pH sensitivity of the P4VP block of the hybrid. Copolymerization of POSS monomers with more than one water-soluble monomers has also been demonstrated to be useful to create multicomponent hybrid amphiphilic copolymers. Xu et al. [16–18] also reported the synthesis of multicomponent organic/inorganic hybrid amphiphilic copolymers such as poly(methacrylate

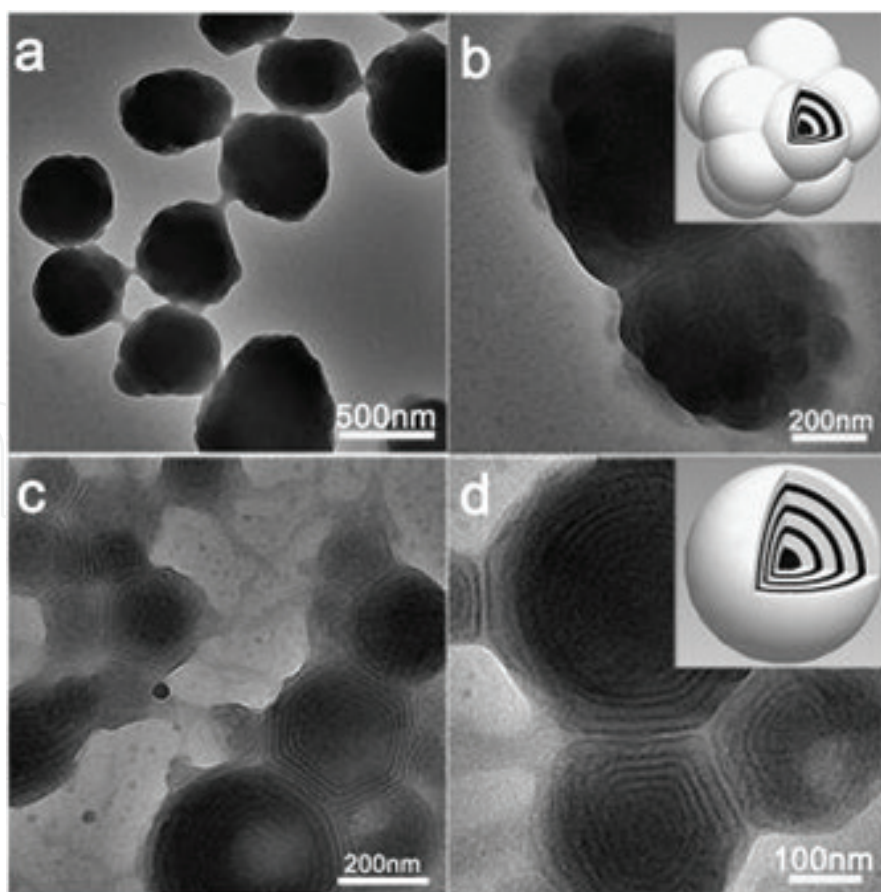


Figure 7. Morphologies of obtained BCPs aggregates in aqueous solutions.

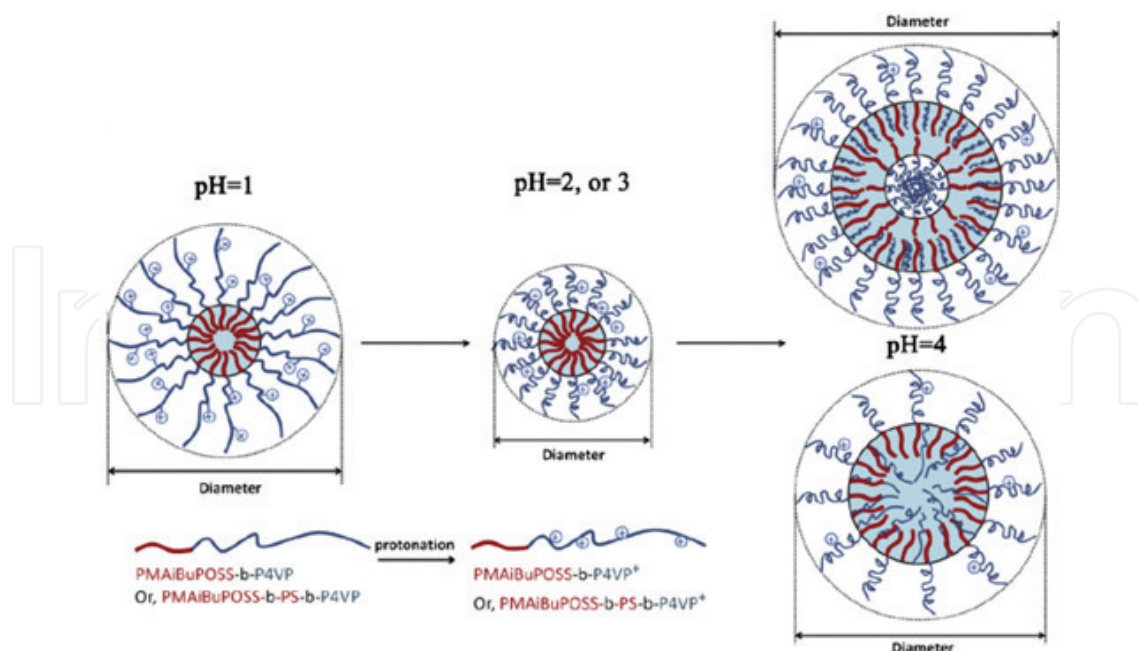


Figure 8. Schematic representation of the variation in aggregate size as a function of pH.

isobutyl POSS)-b-poly(*N*-isopropylacrylamide-co-oligo(ethylene glycol) methyl ether methacrylate) (PMAPOSS-b-P(NIPAM-co-OEGMA)) and poly(methacrylate isobutyl POSS-co-*N*-isopropylacrylamide-co-oligo(ethylene glycol) methyl ether methacrylate-co-2-vinylpyridine) P(MAPOSS-co-NIPAM-co-OEGMA-co-2VP) through RAFT polymerization. These random copolymers could self-assemble into spherical aggregates in water solution and show interesting stimuli-responsive behavior to pH, Zn²⁺, or temperature (**Figures 9** and **10**). These hybrid assemblies could be potentially used in biological and medical fields, especially in drug nanocarriers for targeted therapy.

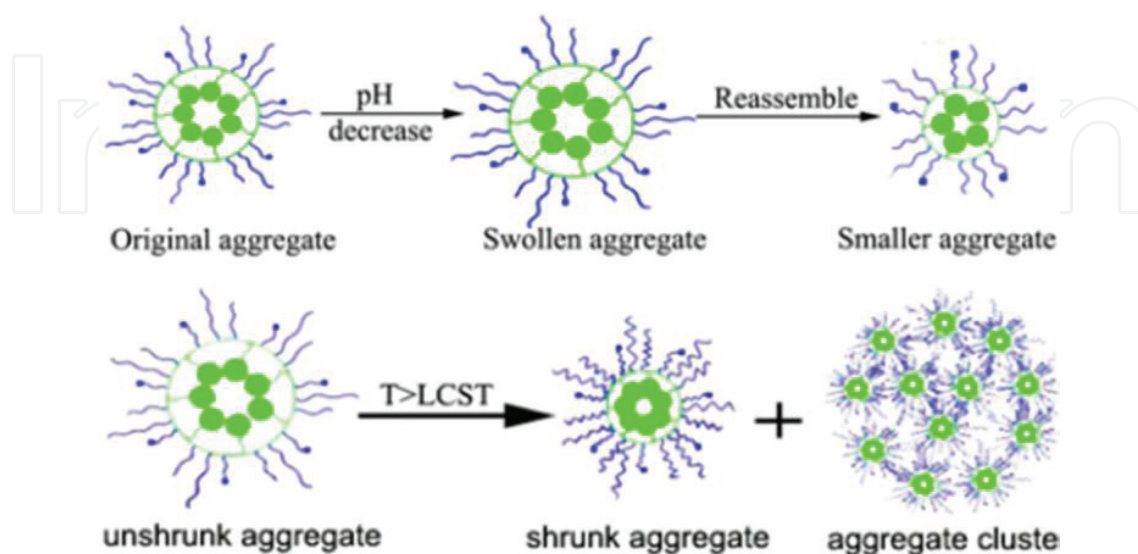


Figure 9. Schematic representation for the change in size of poly(MAPOSS₂₅-co-NIPAM₈₀-co-OEGMA₂₀₂VP₄₀) aggregates responding to pH and temperature.

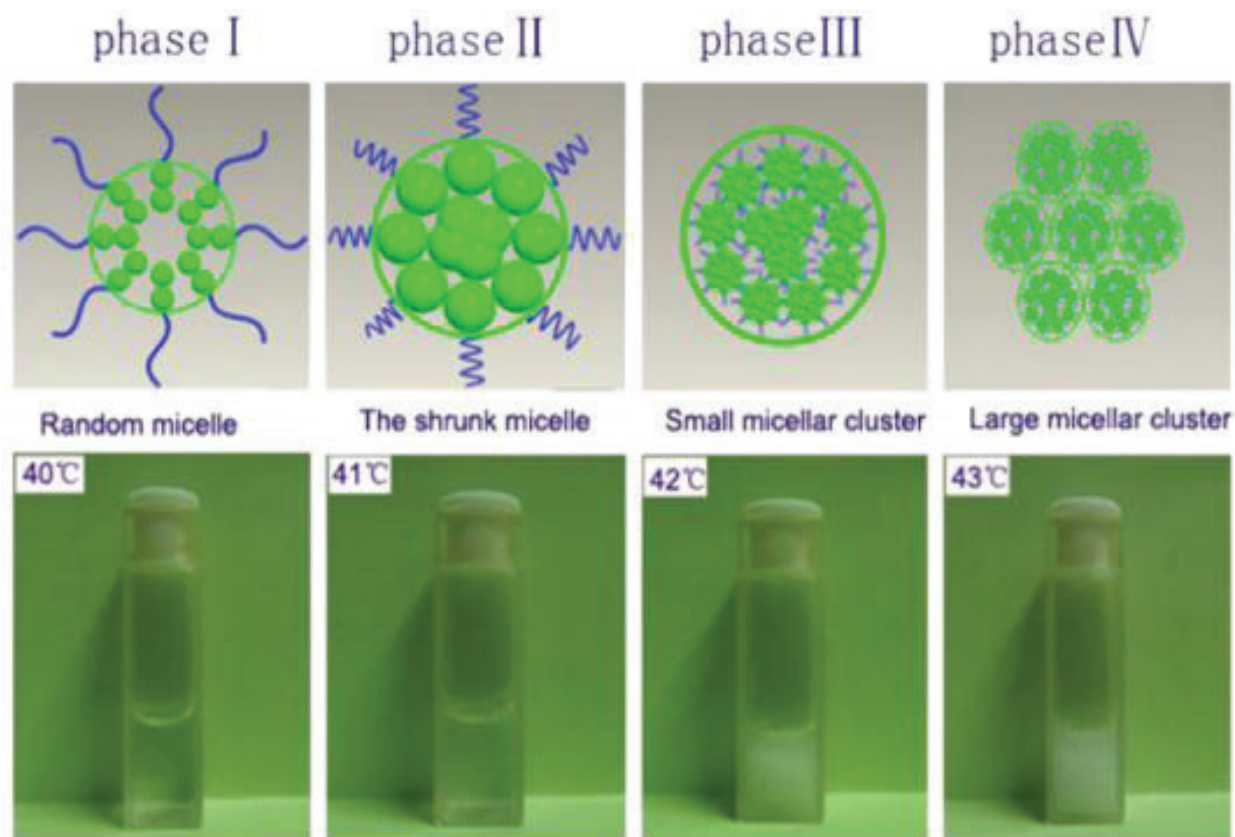


Figure 10. Schematic representation of the phase changes for PMAPOSS-b-P(NIPAM-co-OEGMA) micelle with the solution heating and the macroscopic phase transition of PMAPOSS₉-b-P(NIPAM₁₈₀-co-OEGMA₁₅) solution with the temperature ranging from 40 to 43°C.

Zeng et al. [19] synthesized a hybrid diblock copolymer consisting of bidentate ligand-functionalized chains by combining click reaction and RAFT polymerization. This copolymer was utilized to construct metal-containing polymer micelle by the metal-ligand coordination and electrostatic interaction. It was interesting to note that in common chloroform solvent, both the positively charged Zn^{2+} and negatively charged AuCl_4^- could induce the formation of inverted micelles with a PVBT core and a PMAPOSS shell (**Figure 11**). Besides, the micelle could aggregate together to produce larger aggregates upon the addition of metal ions.

Matejka et al. [20] prepared a P(MMA-co-GMA)-b-PMAPOSS block copolymer by ATRP (**Figure 12**). In selective solvents, this polymer self-assembled to form ordered micellar-like structures. Spherical, cylindrical, or vesicle-like morphologies were produced by tuning the polymer and solvent composition. Cross-linking of the polymer by the reaction of the glycidyl group in the P(MMA-co-GMA) block of the micelle shell with a diamine results in a long-range structure ordering. The hexagonally packed cylindrical arrangement of the polymeric network was revealed by SAXS and TEM. The assemblies exhibited short-range structural order in solution and showed an order-disorder transition that is dependent on the solvent composition. Crosslinking the copolymers to form polymeric networks leads to stable long-range ordering.

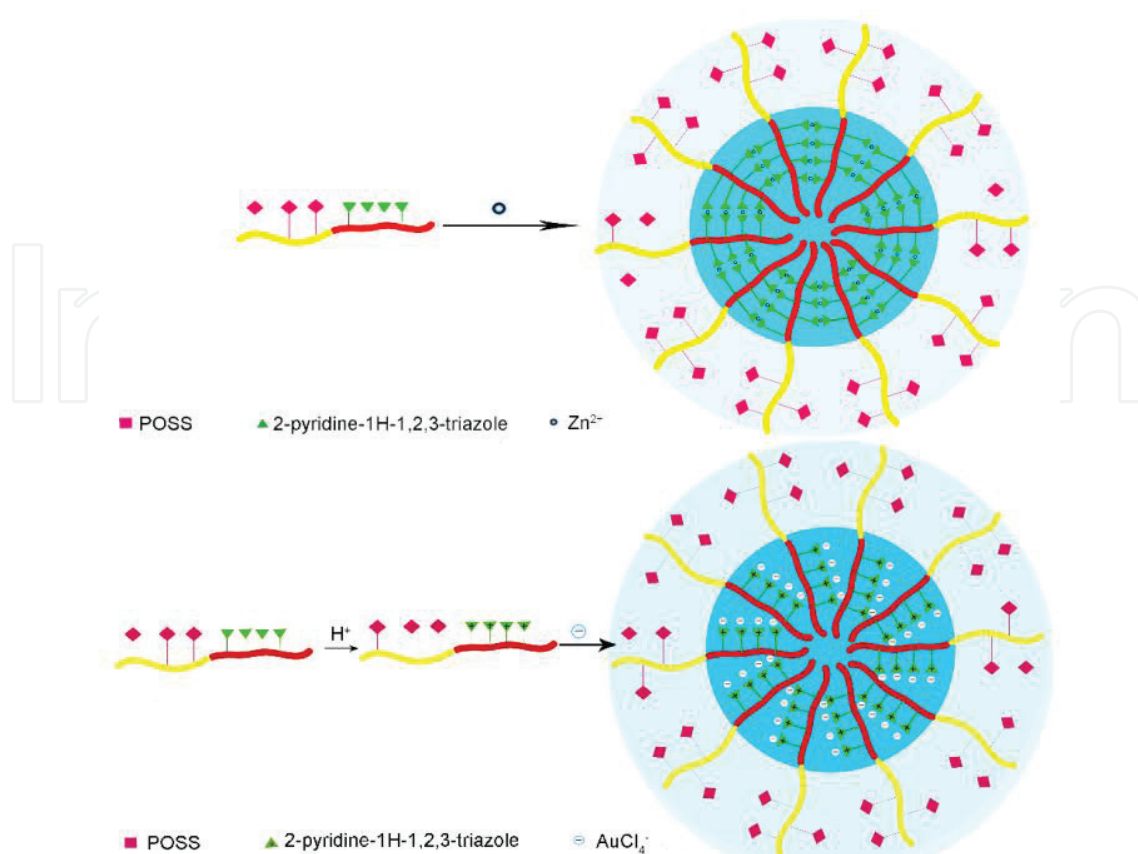


Figure 11. Schematic illustration of the Zn^{2+} -PMAPOSS₁₈-b-PVBPT₈₄ system and $\text{H[AuCl}_4\text{]}$ -PMAPOSS₁₈-b-PVBPT₈₄ system.

Zhang et al. [21] reported a poly(maleimide isobutyl POSS-alt-vinylbenzyl polyethylene glycol) (P(MIPOSS-alt-VBPEG)) amphiphilic copolymer brushes with a sequence of alternating MIPOSS and PEG side chains through ordinary radical polymerization and RAFT polymerization (**Figure 13**). These alternating copolymer brushes had a low polydispersity index of less than 1.25. The DSC results showed that the crystallization behavior of PEG segments was greatly suppressed by the POSS moieties in copolymers. TGA results indicated that the thermal stability

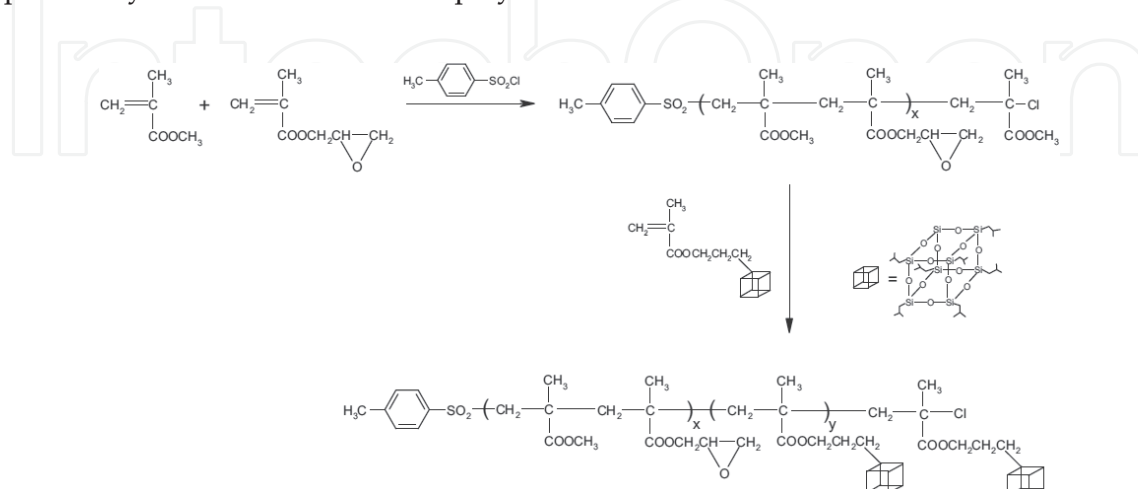


Figure 12. Synthesis of P(MMA-co-GMA)-b-PMAPOSS block copolymer.

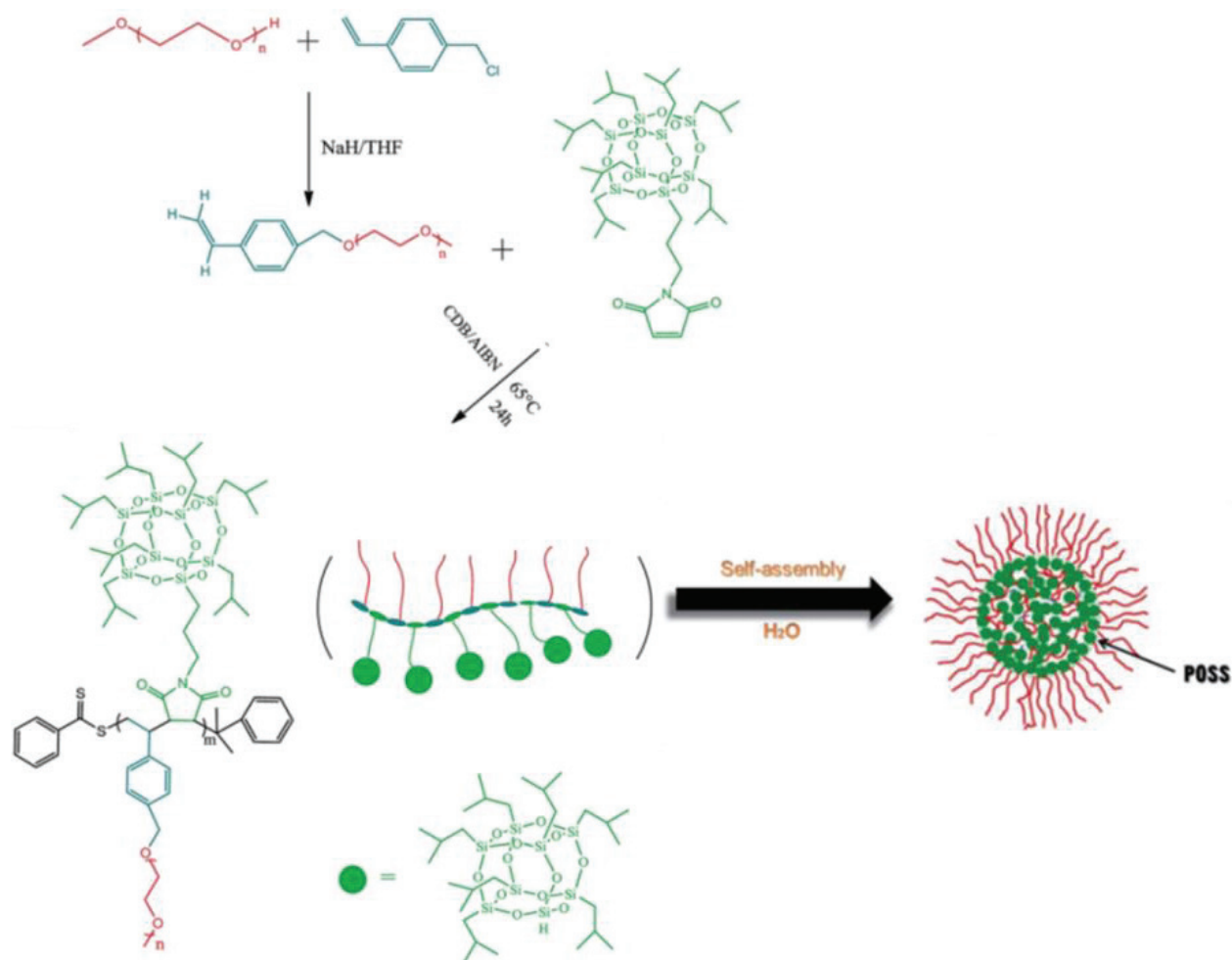


Figure 13. Synthetic route of P(MIPOSS-alt-VBPEG) and its self-assembly behavior in water solution.

of the P(MIPOSS-alt-VBPEG) could be enhanced by the incorporation of MIPOSS. These alternating copolymer brushes could form spherical aggregates in water. Moreover, the size of the aggregates increased on decreasing the chain length of the PEG monomer.

Hong et al. [22] also linked a POSS cage on a methacrylate monomer to afford a polymerizable POSS monomer (HEMAPOSS), which could efficiently decrease the steric hindrance of POSS cage in free-radical polymerization. Through a RAFT polymerization, PHEMAPOSS macro-chain transfer agent with a higher polymerization degree could be easily synthesized. Subsequently, *N,N*-dimethylaminoethyl methacrylate (DMAEMA) was adopted to achieve a chain extension of PHEMAPOSS to create a series of amphiphilic copolymers PHEMAPOSS-*b*-PDMAEMA. By simply varying the length of PDMAEMA block, these polymers could form assemblies with morphologies ranging from irregular aggregates, core-shell spheres, complex spheres (pearl-necklace-like structure) to large compound vesicles (**Figure 14**). Also, the assembly morphologies could transform reversibly from spherical micelles to complex micelles when cycling the solution from acidic to basic pH.

Wei et al. [23] reported a series of organic/inorganic random copolymers that were synthesized from methacrylate-terminated poly(ethylene oxide) (MAPEO) and 3-methacryloxypropylheptaphenyl POSS (MAPOSS) macromers through RAFT polymerization with

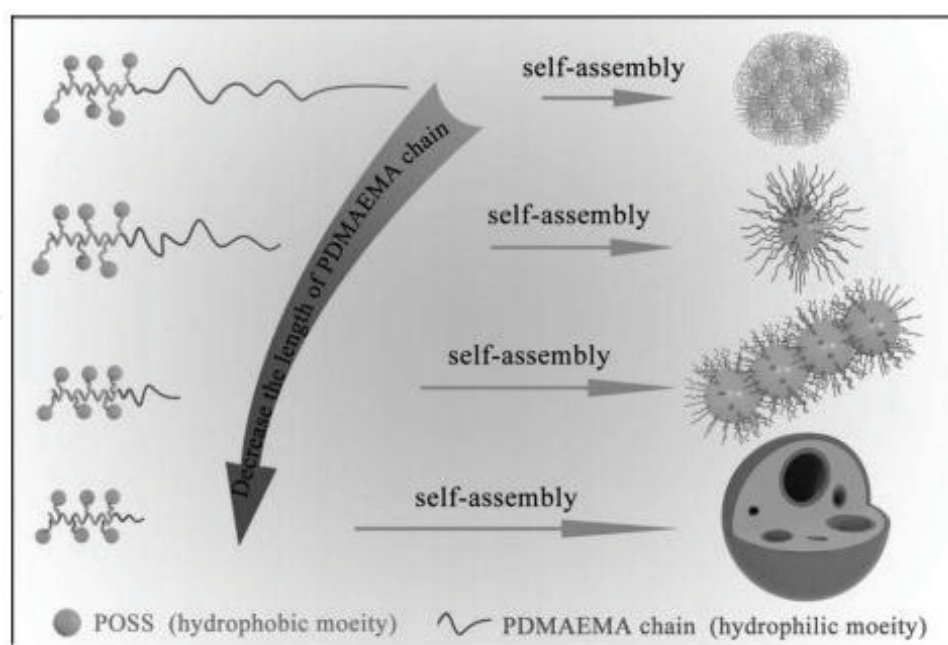


Figure 14. Self-assembly of PHEMAPOSS-b-PDMAEMA in water with the decreasing length of hydrophilic PDMAEMA chain.

4-cyano-4-(thiobenzoylthio) valeric acid as the chain transfer agent. The organic-inorganic random copolymers in bulk were microphase-separated and the POSS microdomains were formed through POSS-POSS interactions. In aqueous solutions, the organic-inorganic random copolymers were capable of self-assembling into spherical nanoobjects. The self-assembly behavior of the organic-inorganic random copolymers was also found to occur in the mixtures with the precursors of epoxy (**Figure 15**). The nanostructures were further fixed through subsequent curing reaction, and thus the organic-inorganic nanocomposites were obtained. In the organic-inorganic nanocomposites, the inorganic segments had a tendency to enrich at

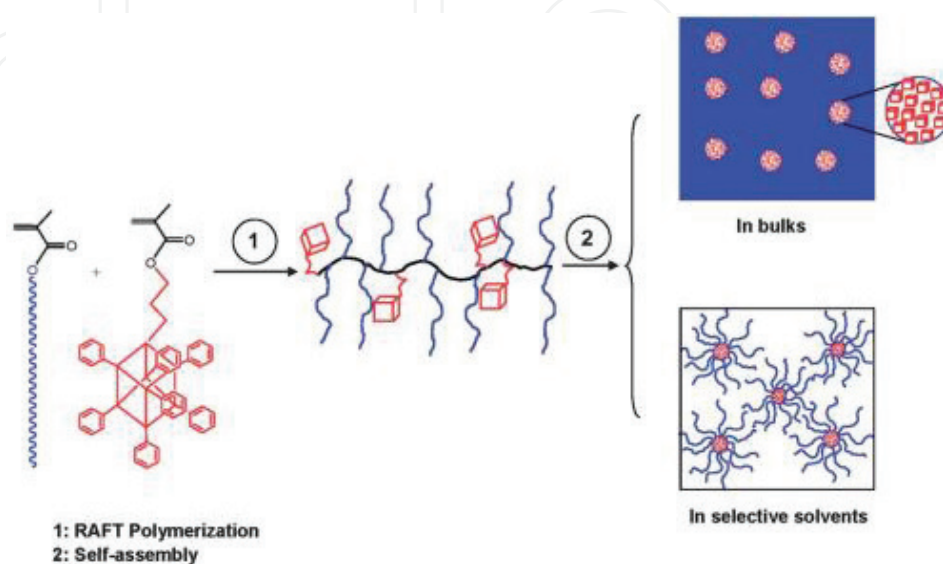


Figure 15. Self-assembly of P(MAPOSS-r-MAPEO) random copolymers.

the surface of the materials and the dewettability of surface for the organic-inorganic nanocomposites was improved.

2.1.3. POSS-containing star-shaped amphiphilic polymers

POSS cages generally have several organic moieties (at most eight). These organic moieties can be designed with reaction activity, and thus it can be used to create star-shaped amphiphilic polymers. For example, Yuan et al. [24] prepared a series of novel star-shaped hybrid P(2-(2-methoxyethoxy) ethylmethacrylate)-co-oligo(ethylene glycol) methacrylate (P(MEO₂MA-co-OEGMA)) polymers with a POSS core named (POSS-(P(MEO₂MA-co-OEGMA))₈) through ATRP (**Figure 17**). The obtained inorganic/organic hybrid polymers could self-assemble into micelles in aqueous solution owing to the amphiphilic property resulting from the hydrophobic inorganic POSS core and the hydrophilic P(MEO₂MA-co-OEGMA) segments. The tunable thermoresponse of the micelle solutions was achieved by varying the molar ratio of MEO₂MA and OEGMA (**Figure 16**). These amphiphilic hybrid polymers have potential applications in nanocarrier, nanoreactor, smart materials, and biomedical areas.

Li et al. [25] prepared a series of well-defined thermoresponsive amphiphilic star-shaped POSS-based inorganic/organic hybrid block copolymers of poly (ε-caprolactone)-poly(2-(2-methoxyethoxy)-ethyl methacrylate)-co-poly(ethylene glycol) methacrylate (POSS-(PCL-P(MEO₂MA-co-PEGMA))₁₆) through click chemistry, ring opening polymerization (ROP), and

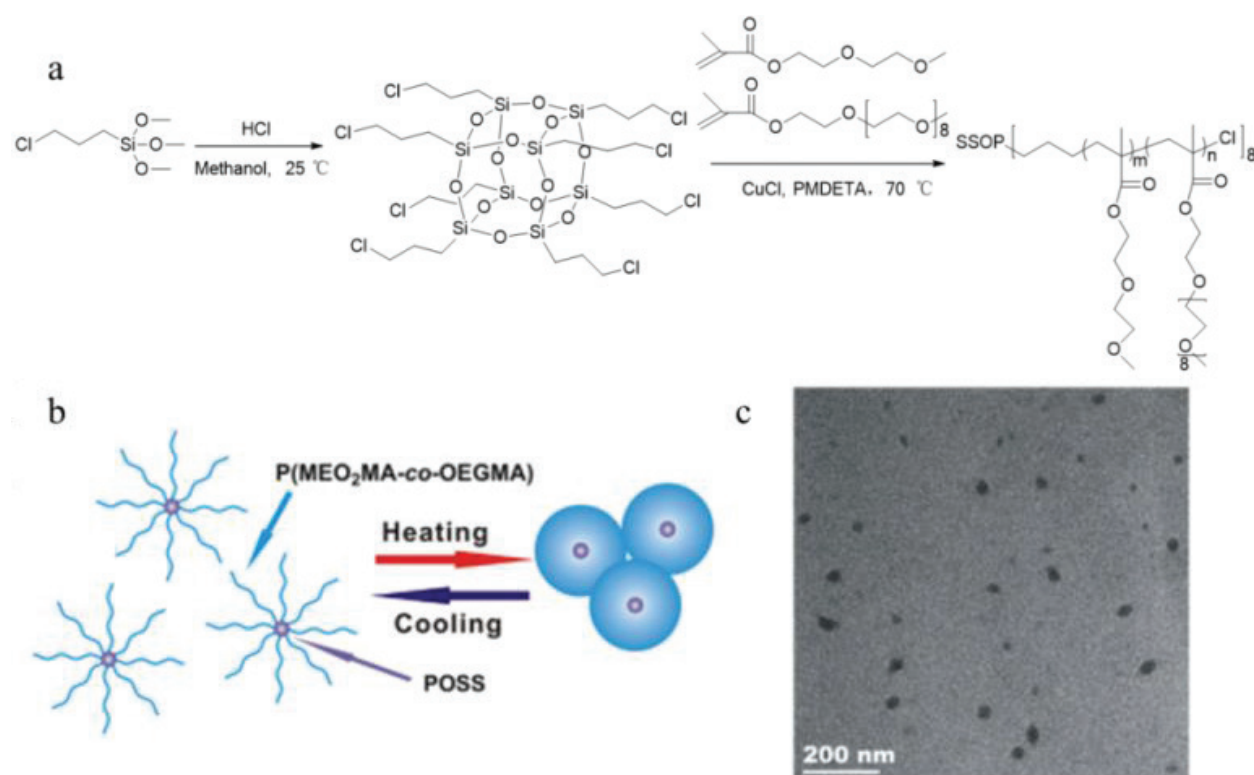
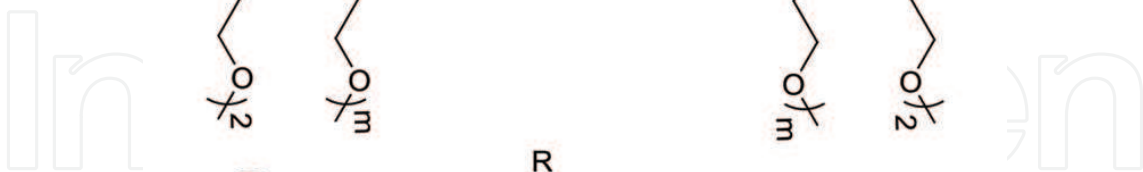


Figure 16. Synthesis of POSS-(P(MEO₂MA-co-OEGMA))₈ (a), schematic process of micelle aggregation with the increase of temperature (b), and TEM image of micelles at 25 °C (c).



ATRP. By combining hydrophobic POS and PCL components with hydrophilic P(MEO₂MA-co-PEGMA) segments together, these copolymers could self-assemble into ellipsoidal aggregates with a moderately uniform size. Thermal-responsive behavior was observed to these organic/inorganic hybrid polymeric micelles. The critical phase transition temperature of these micelles in water solution could be finely tuned by changing the feed ratios of PEGMA and MEO₂MA. By increasing the content of PEGMA, the lowest critical solution temperature (LCST) of star-shaped POSS-(PCL-P(MEO₂MA-co-PEGMA))₁₆ increased from 34 to 57°C. At temperature higher than the corresponding LCSTs, the micelles aggregated to form spherical nanoparticles (**Figures 17 and 18**).

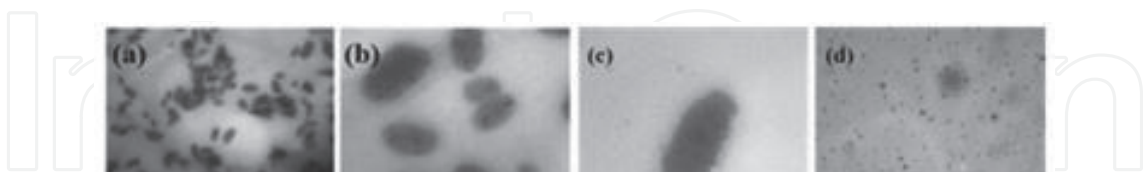


Figure 18. TEM images of POSS-(PCL-P(MEO₂MA-co-PEGMA))₁₆ micelles at 30°C (a-d) and at 50°C (e-h).

Li et al. [26] also prepared a well-defined pH-responsive amphiphilic POSS-containing star-shaped inorganic/organic hybrid block copolymers (BCPs), POSS-(PCL-P(MMAEMA-co-PEGMA))₁₆, through thiol-ene click reaction, ROP, and ATRP (**Figure 19**). These BCPs self-assembled into micelles in aqueous solution with a diameter about 175 nm. The stimuli-responsive behavior of these assemblies to solution pH and the controlled release of doxorubicin (DOX) were investigated. It was found that weakly acidic pH could cause the effective release of DOX up to 82 wt% (w/w). The low cytotoxicity, good biocompatibility, and excellent biodegradability make these micelles applicable in drug delivery. The DOX-loaded micelles could easily enter the cells and produce the desired pharmacological action, and minimize the side effect of free DOX (**Figure 20**).

2.2. Boron-containing amphiphilic copolymers

The development in organic chemistry have provided various routes to synthesize small molecules with boronic acid or boronate moieties, which are of great interest in the fabrication of polymers and functional materials containing boron element. There have been two general routes to create boronic acid or boronate polymers: (1) polymerization of boronic acid molecules with a carbon-carbon double bond; and (2) condensation reaction between multifunctional boronic acid molecules and catechol molecules. Because of the excellent response to biologies and pH, assemblies derived from boronic acid or boronate amphiphilic polymers have been widely used in biomedical applications.

2.2.1. Boronic acid-containing amphiphilic copolymers

Molecules with a boronic acid group attached on a benzene ring can be easily designed and synthesized. Carbon-carbon double bond can be further decorated onto the benzene ring to create polymerizable monomers. For example, Roy et al. [27] reported the synthesis of a low pK_a boronic acid monomer, which was decorated with an electron withdrawing amide carbonyl on the phenylboronic acid moiety, and prepared an amphiphilic block copolymer

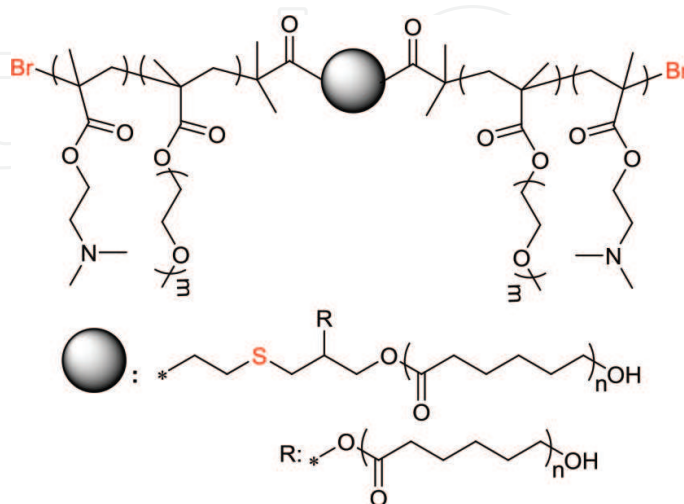


Figure 19. The chemical structure of POSS-(PCL-P(DMAEMA-co-PEGMA)).

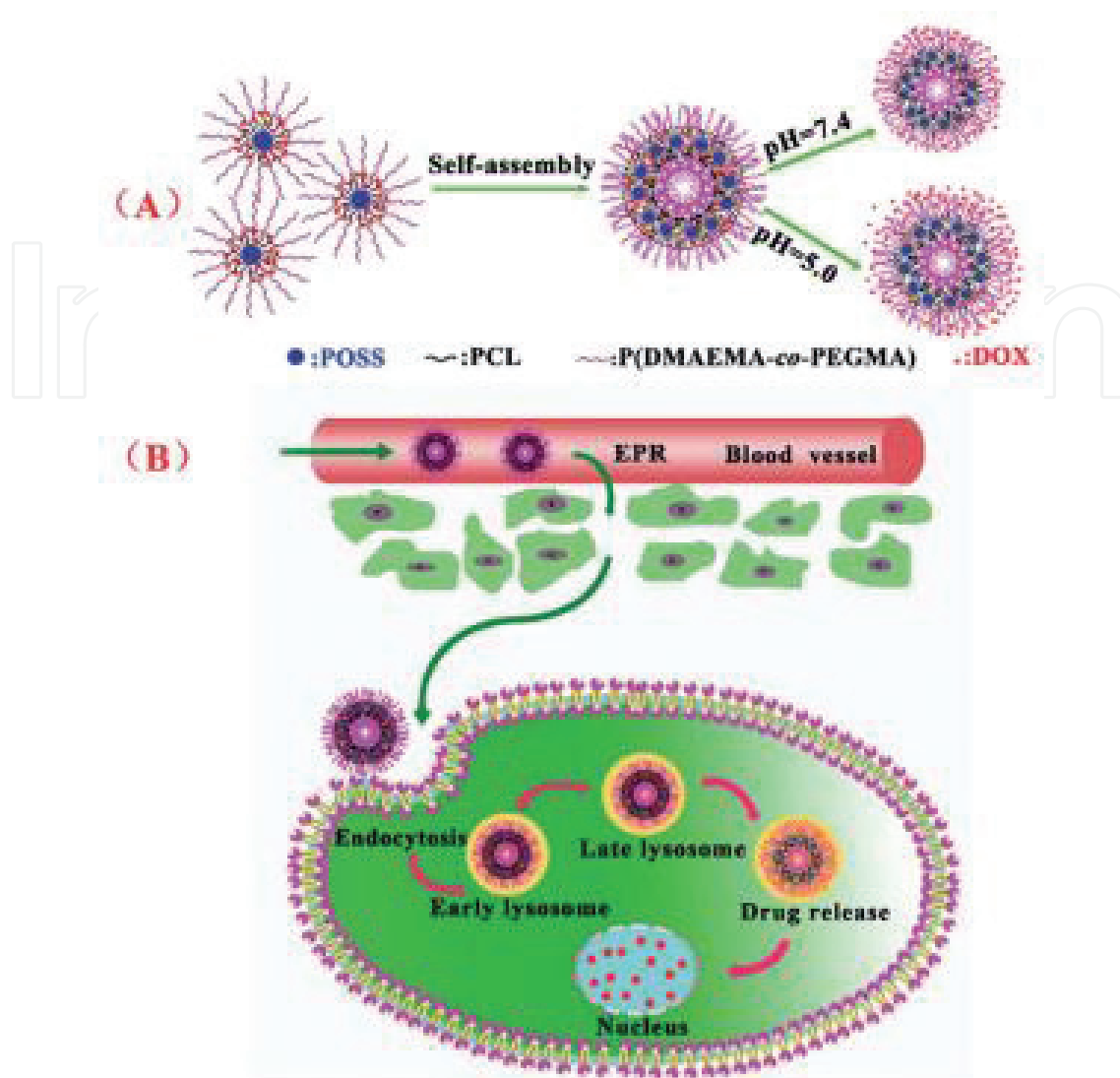


Figure 20. Illustration of pH-responsive self-assembly of the amphiphilic copolymer of POSS-(PCL-P(DMAEMA-co-PEGMA)) for the efficient intracellular release of anticancer drugs.

named PDMA-b-PAEBB via RAFT polymerization (**Figure 21**). This polymer could self-assemble into micelles composed of a hydrophilic PDMA corona and a hydrophobic PAEBB core. With the addition of sugar or the pH of aqueous media exceeding the pK_a of the block copolymers, the micelles dissociate, thus holding promise application in the areas of saccharide-sensing and self-regulated sugar-induced delivery.

Yuan et al. [28] developed a triply responsive amphiphilic copolymer by linking poly(ethylene oxide) (PEO) and poly(3-acrylamidophenylboronic acid) (PAPBA) with a disulfide bond. Micelles constructed with a PEO shell and a PAPBA core could be formed by the self-assembly of this copolymer. A simple adjustment of the solution pH led to the formation-dissociation of the micelles. Around the pK_a of PAPBA segments, these micelles exhibited an interesting glucose response behavior by completely disassembling into copolymer solution. Moreover, these micelles could also dissociate through the breakage of disulfide bonds

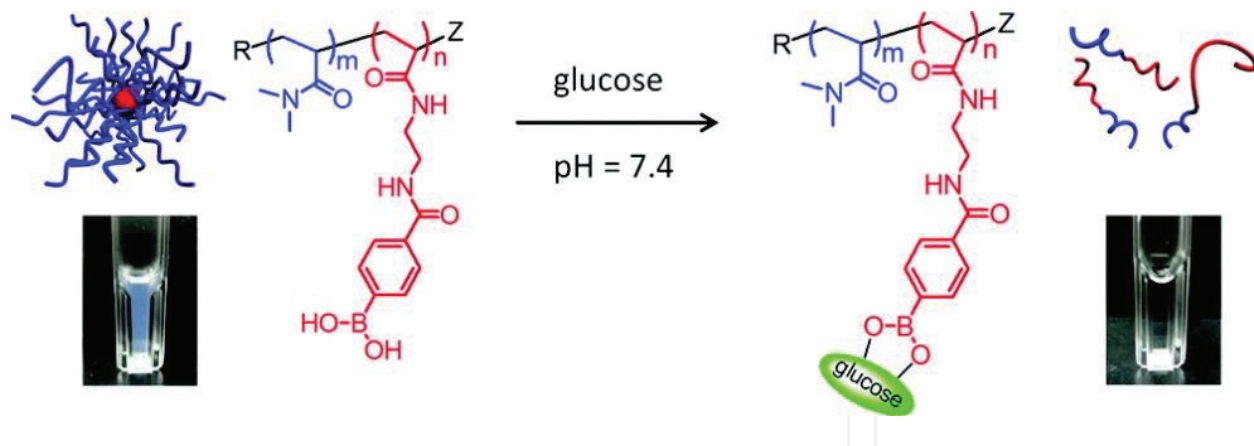


Figure 21. Schematic representation of the self-assembly of PDMA-b-PAEBB and their glucose-responsive behavior at pH = 7.4.

with the present of GSH. As a result, controllable release of insulin could be realized under the stimuli of glucose or GSH (**Figure 22**). Similar triply responsive amphiphilic copolymer assemblies were also described by Roy and coworkers [29]. They created a block copolymer through the RAFT copolymerization of a boronic acid acrylamido monomer and NIPAM and described the preliminary solution characterization of the resulting block copolymer. The boronic acid-containing copolymer displayed triply responsive behavior owing to the thermoresponsive nature of PNIPAM with the pH- and diol-responsive solubility of boronic acid-containing block.

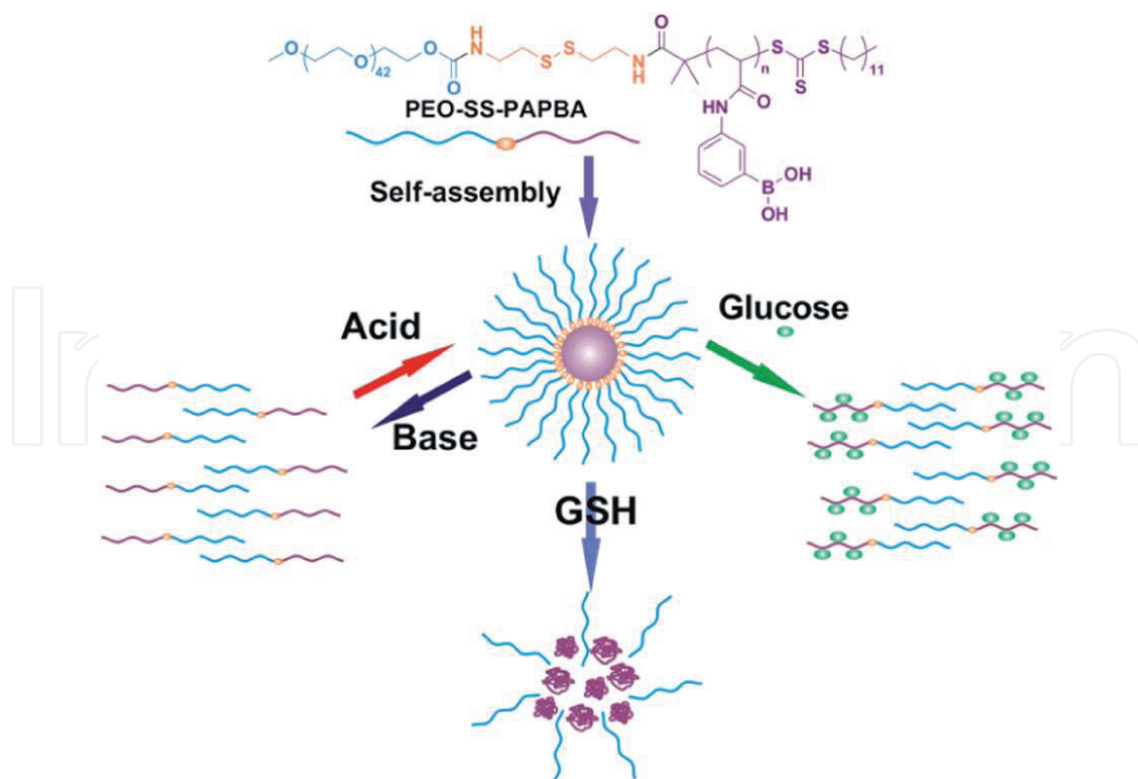


Figure 22. Self-assembly of the PEG-SS-PAPBA copolymer and glucose, pH, and redox triple responses.

Due to the reactivity of boronic acid group, monomers with a boronic acid moiety are hard to be polymerized through an ATRP method. Generally, the boronic acid group should be protected before ATRP. Kim and coworkers [30] synthesized a boronic acid polymer through ATRP route by employing a PEG macroinitiator to initiate polymerization with a pinacol-protected styrene boronic acid monomer. Then, deprotection of the pinacol-derived block copolymer afforded a boronic acid-containing PEG-PSBA block copolymer. Assemblies formed by this polymer were of great interest in smart reactors (**Figure 23**). Owing to the reversible hydrophilic-hydrophobic transition behavior of PSBA block, the use of stimuli-responsive block copolymers to construct nanoreactors with PSBA block as pore-generating components allowing the guest molecules to reach the enzyme residing inside the nanoreactors. In detail, they mixed PEG-PS and PEG-PSBA for the preparation of permeable polymersomes based on using an optimal amount of PEG-*b*-PSBA as a minor component; phase-separated PSBA domains would be dispersed throughout the PS matrix in the membrane of the polymersome, and these domains would be readily extracted from the matrix. They observed that when mixed in ratios of $W_{\text{PSBA}} = 30 \text{ wt\%}$ and lower, the two block copolymers could coexist as a mixture in the membrane of the polymersome without experiencing complete phase separation, and the optimal mixing ratio is at $\sim W_{\text{PSBA}} = 10 \text{ wt\%}$. They also found that the polymersomes did not suffer from structural damages

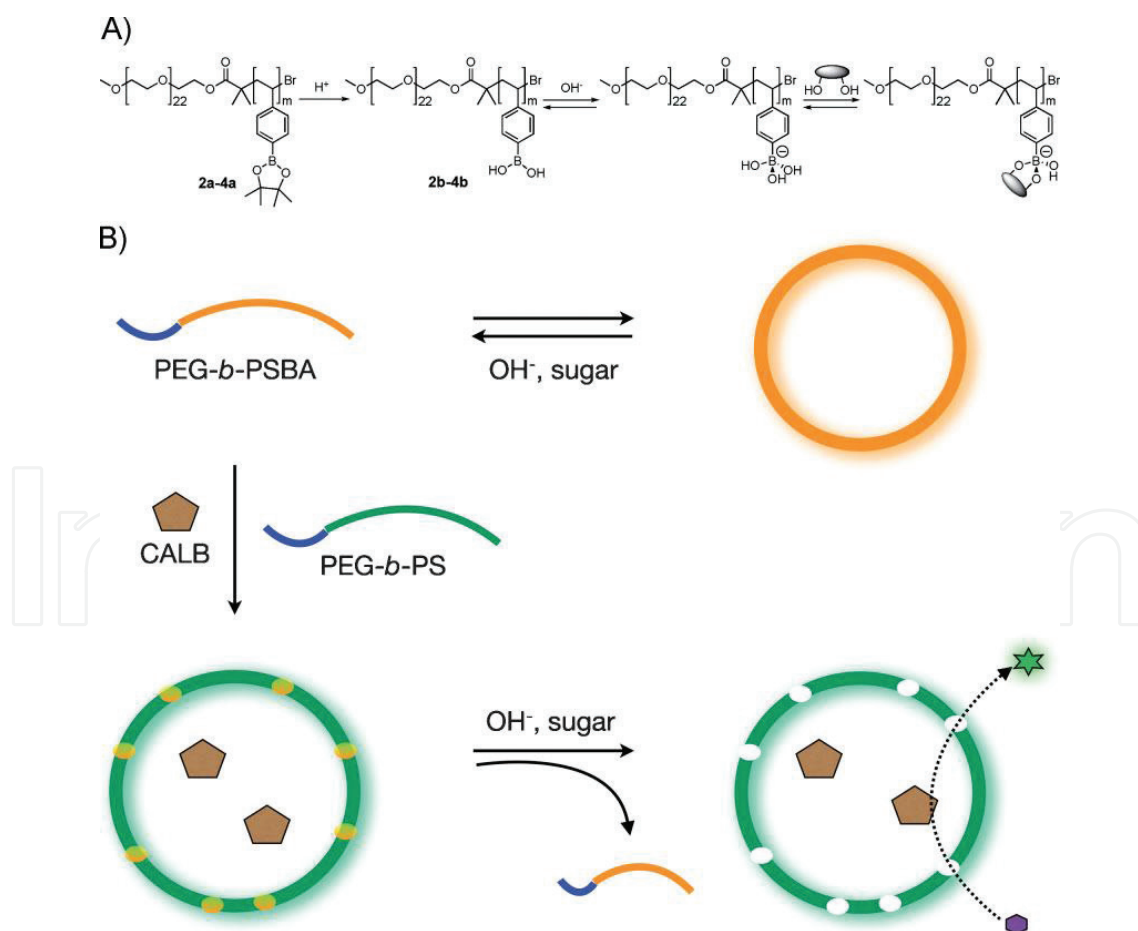


Figure 23. Synthesis of PEG-*b*-PSBA and schematic representation of the formation of bioreactors with a permeable membrane.

upon disassembly of the stimuli-responsive block copolymers observed by TEM. And the study of catalytic activity suggested that the differences in reactivity of bioreactors come from the difference in permeability of the polymersomes, which could be proportional to the area occupied by the phase-separated domains of PBSA block in the membrane.

To overcome the problem that boronic acid group brings to ATRP, thus acquiring boronic acid terminated polymers, Xu et al. [31] first synthesized alkyne-terminated PNIPAm using the BMP initiator and then conjugated the clickable boronic acid (APBA) with the obtained PNIPAm through the terminal alkyne via click reaction to get boronic acid terminated PNIPAm (**Figure 24**). The LCST of PNIPAm and BA-PNIPAm are 28.2 and 27.9°C, respectively. The CP of PNIPAm and BA-PNIPAm are 32.4 and 32.2°C, respectively. Owing to the excellent binding performance of BA-PNIPAm for saccharides and the LCST property of BA-PNIPAm, the author took advantage of the BA-PNIPAm to separate saccharides such as fructose from aqueous solution. Besides, they found that the fluorescence characteristic of APBA remained even after the terminal azide group is converted into triazole after an alkyne-azide click reaction, and the intensity of fluorescence emission of BA-PNIPAm increased with the increasing fructose concentration because of the fluorescence emission of APBA was a result of possible B-N bond formed between the boron and one of the nitrogen atoms in the terminal azide.

Besides RAFT or ATRP routes, there are also some special methods to prepare amphiphilic copolymers with boronic acid groups. Aguirre-Chagala et al. [32] first reported a biodegradable derivatives of organoboron polymers (PPBC) synthesized by ring-opening polymerization (ROP) using a boronic acid-installed cyclic carbonates, catalyzed by 1,8-diazabicycloundec-7-ene (DBU) from a poly(ethylene glycol) macroinitiator (**Figure 25**). They used two types of monomers to synthesize a pinacol-protected or an acetonide-protected polymer, PPBC. And they found that deprotection of the acetonide-protected derivative could be achieved

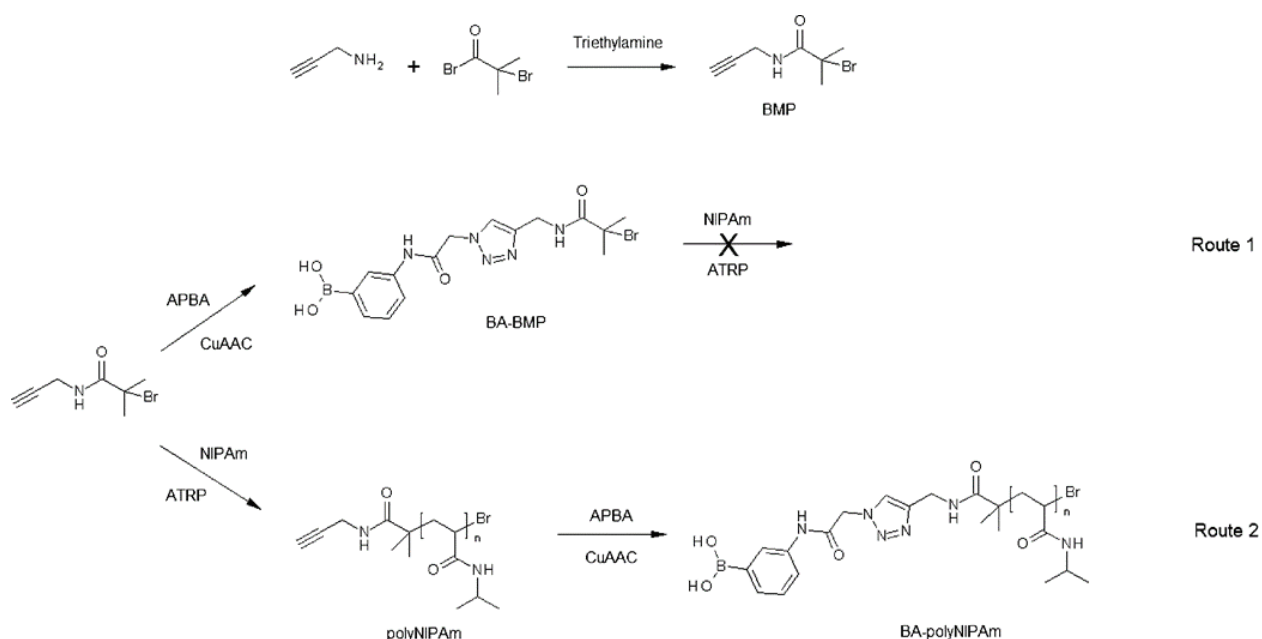


Figure 24. Synthesis of boronic acid terminated PNIPAm.

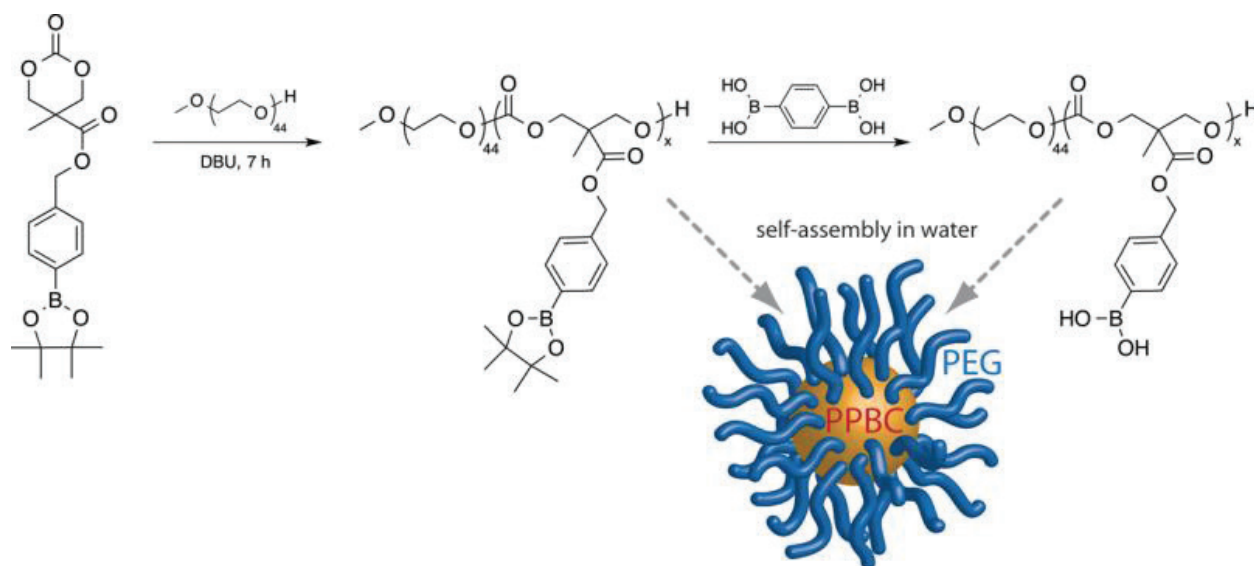


Figure 25. Synthesis and self-assembly of phenylboronic acid carbonate-based amphiphiles.

under more tractable conditions than the pinacol-protected polymer, by simply using an ion-exchange resin at room temperature. To study the self-assembly behavior of the PEG-*b*-PPBC copolymers, a multi-inlet vortex mixer (MIVM) was used to form aggregates by a rapid change in solvent quality. According to the results of TEM and static light scattering measurements, smaller, spherical aggregates were formed from amphiphiles with shorter PPBC lengths, while vesicle-like aggregates were observed for the copolymer with the longest PPBC block.

Since phenylboronic acid can form reversible covalent esters with 1,2- or 1,3-*cis*-diols including a ribose ring, small interfering RNA (siRNA) can be easily conjugated to the phenylboronic acid group. Naito and coworkers [33] synthesized a boronic acid-functionalized cationic polymer through modification of poly(ethylene glycol)-block-poly(L-lysine) (PEG-*b*-PLys) with 3-fluoro-4-carboxyphenylboronic acid (FPBA). They utilized the cationic polymer self-assembly into a micelle with siRNA as a cross-linker to stabilizing the polyion complex (PIC) and spontaneously delivering siRNA to targeted place, thus avoiding the leakage of the siRNA. They demonstrated that the PBA-assisted PIC micelles can be tailored to exhibit a dramatic disruption accompanied by the release of siRNAs in response to a change in the ribose concentration, which parallels events in the intracellular environment (**Figure 26**).

2.2.2. Boronate-containing amphiphilic copolymers

In comparison with boronic acid moiety, the boronate group is featured by its dynamic character, which is of great advantage in the construction of smart nanomaterials. Coumes et al. [34] designed a cleavable covalent block copolymer using boronate ester as a linker. They first synthesized two chain transfer agents terminated with a nitrodopamine or a boronic acid group, which were subjected to RAFT polymerizations with numerous monomers such as NIPAM, dimethylacrylamide (DMAc), *n*-butyl acrylate (nBuA), *tert*-butyl acrylate (tBuA), and St. Then, the coupling reaction between nitrocatechol- and boronic acid-terminated polymers was achieved via the nanoprecipitation method at room temperature, allowing the formation

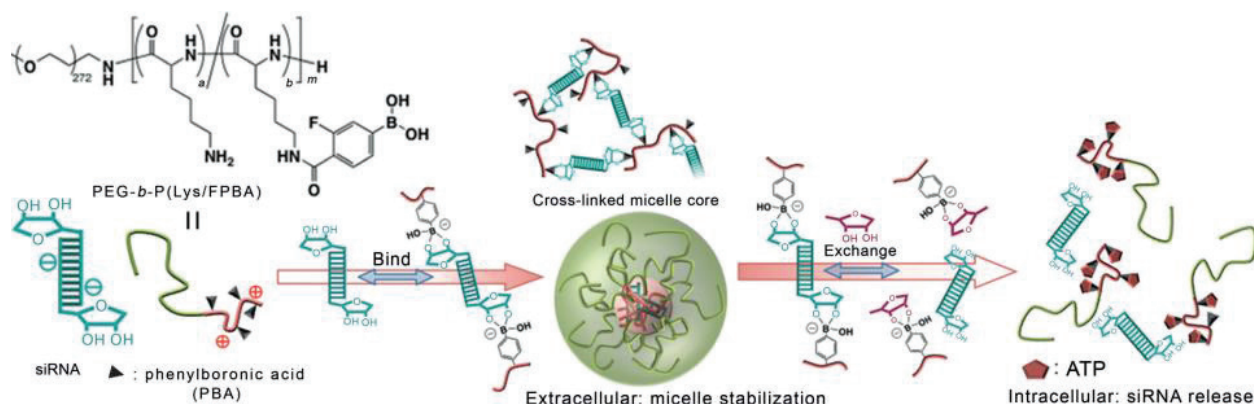


Figure 26. Schematic representation of the phenylboronic acid-based strategy for siRNA delivery.

of amphiphilic block copolymers. As the boronic esters are dynamic covalent structures, the amphiphilic copolymer can be cleaved at weakly acidic pH media or in the presence of sugars. Besides, the nitrocatechol derivatives can be chemical debonded by UV irradiation and cause the disassembly of the aggregates (**Figure 27**).

The formation of boronate could be also used to covalently attach functionality to the end of a polymer chain. De and coworkers [35] designed and synthesized a boronic acid-functionalized CTA by reacting 3-bromomethylphenylboronic acid with DMP and then prepared homopolymers and block copolymers with boronic acid functional end groups prepared by RAFT polymerization (**Figure 28**). They subsequently investigated their self-assembly behavior in aqueous or organic media.

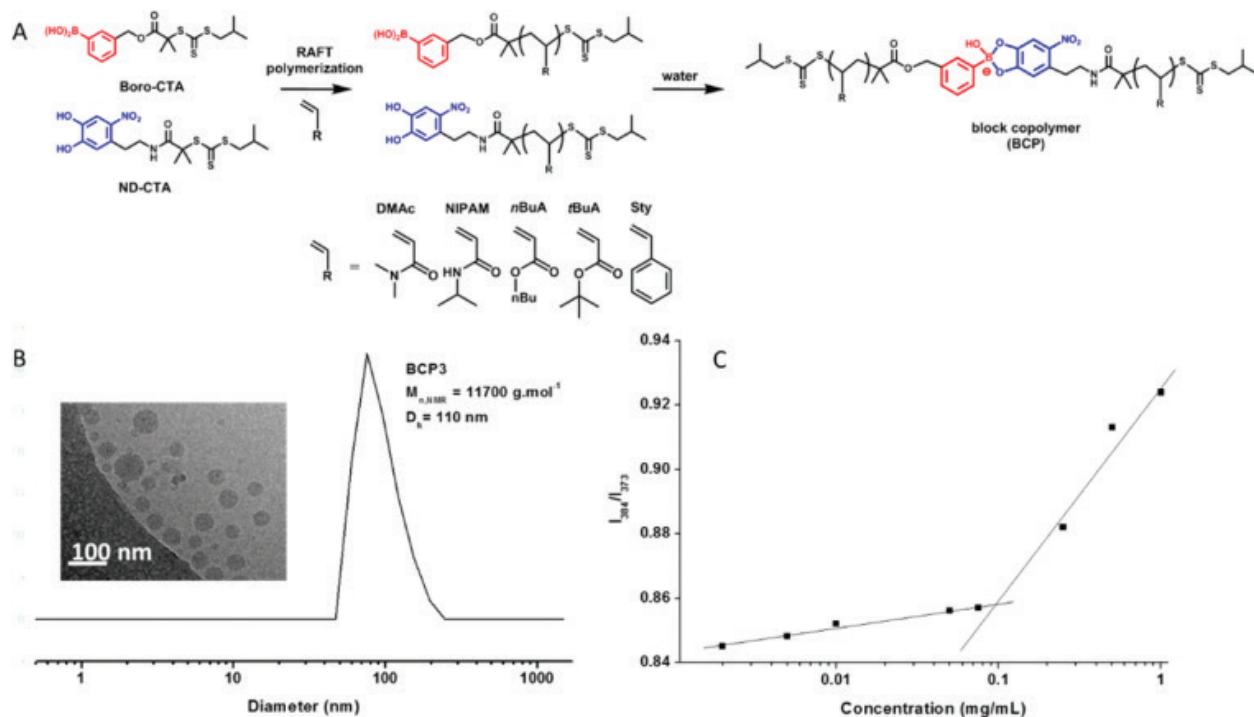


Figure 27. Synthesis and characterization of block copolymers (BCP) from nitrodopamine (ND-CTA)- and boronic acid (Boro-CTA)-functionalized CTAs.

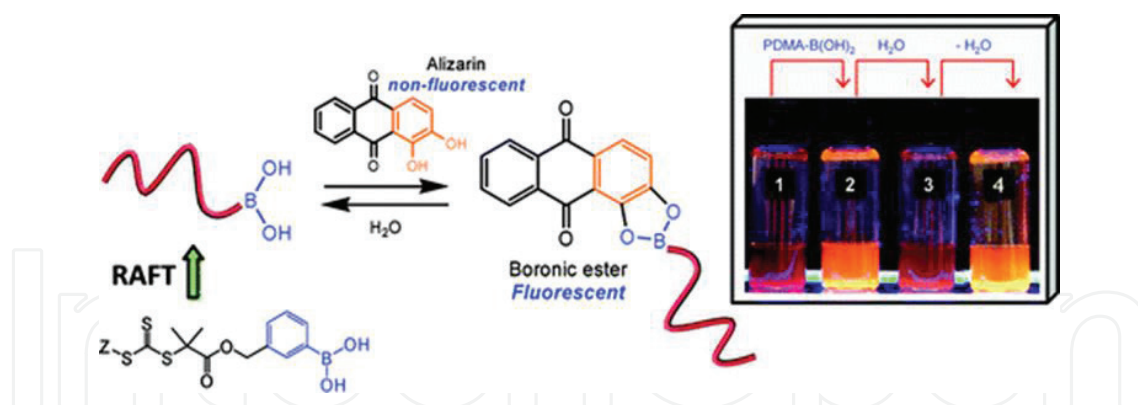


Figure 28. Proposed boronic ester formation between alizarin and boronic acid-terminated polymer.

It is well known that saccharide molecules having higher affinities with boronic acid groups than acyclic diols. The competition between saccharide molecules and acyclic diols to boronic acid groups may be useful in designing novel sugar-responsive materials. Yao and coworkers [36] designed and synthesized a new type of amphiphilic block copolymer with phenylboronate ester as a leaving group by ATRP. The block copolymer was amphiphilic because of the pinacol boronate ester units generated by the phenylboronic acid-acyclic diol complexation. With the presence of sugar molecules, boronic acid groups were prone to combine with sugar molecules; therefore, the pinacol phenylboronate moieties detaching from polymer and triggering the polarity transfer of the polymer from amphiphile to double hydrophilic. As a result, the polymer nanoaggregates disassembled, thus causing the release of the loaded guest molecules (**Figure 29**).

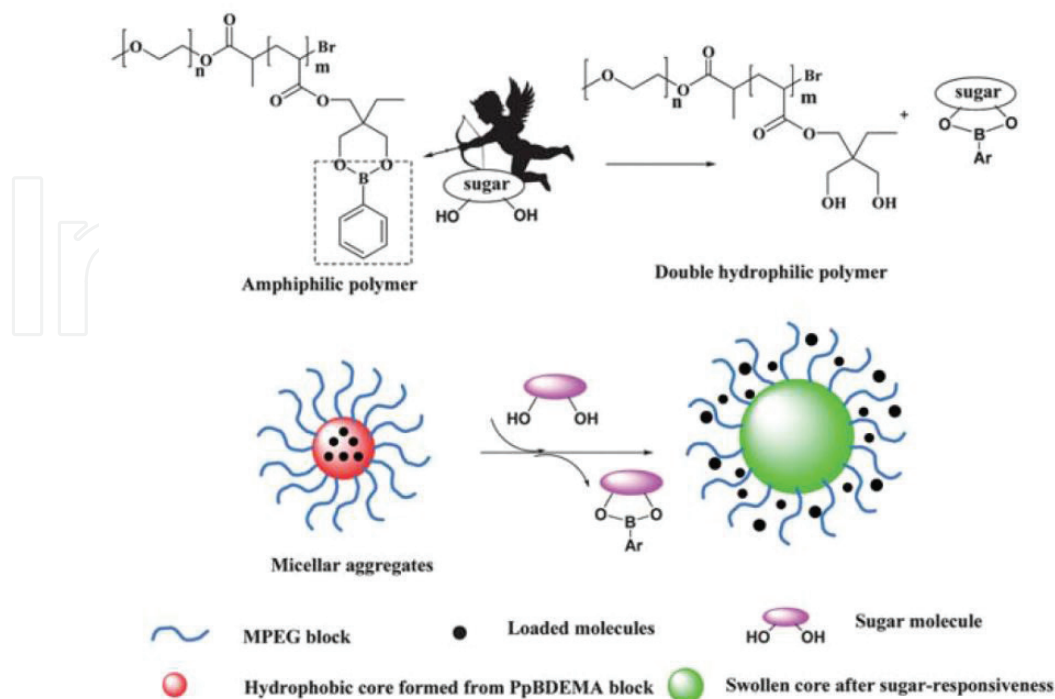


Figure 29. Schematic diagram for sugar-responsive behavior.

2.2.3. Supramolecular assembly derived by dative B-N bond

Boronate esters are Lewis acidic compounds, which can form B-N dative bond with N-donor ligands. Sheepwash and coworkers [37] utilized this B-N interaction for the creation of crystalline organic networks and organogel by connecting triboronate esters with bipyridyl linkers. They used two kinds of triboronic acid along with 4-tert-butylcatechol and 4,4'-bipyridine or 1,2-di(4-pyridyl)ethylene as the model molecules. The triboronic acid undergo a triple condensation reaction with the catechol to give a triboronate ester in organic solvents such as chloroform or toluene, which were then linked by the bipyridyl linker to form a polymer precipitated upon cooling. Polymers can be crystallized by slow cooling of toluene solutions or by vapor diffusion of pentane into toluene solutions. They also found that condensation reactions implemented between the extended triboronic acid, which was obtained from 1,3,5-tris(4'-bromobiphenyl)benzene, with 4-tert-butylcatechol and 4,4'-bipyridine in toluene resulted in the formation of an orange gel. The gel formation can also be reversed by increasing the temperature.

In order to investigate the factors that govern the binding strengths of dioxaboroles, Sheepwash and coworkers [38] utilized ^1H NMR spectroscopic titration experiments to study the binding constants of K_a between Lewis-acidic arylboronate esters and nitrogen-donor ligands with different electron effect substituents. The use of appropriate molecular components with both an electron withdrawing substituent on the dioxabole segment and an electron donating group on the pyridyl ligands has led to a significant improvement in the K_a values. This finding provided a new way to create main-chain supramolecular polymers with dative B-N bonds. Therefore, they designed and synthesized three monomers by condensation of the 4-(6-(methyl(pyridin-4-yl)amino)hexyl)benzene-1,2-diol with different arylboronic acids. Indeed, these monomers self-assembled into aggregates through the formation of B-N dative bond (**Figure 30**). This study turn out that main-chain supramolecular polymers could be achieved based on dative B-N bonds, and the B-N binding motif can also be used for the formation of branched or cross-linked supramolecular polymers.

Li et al. [39] have developed a cooperative polymerization strategy to prepare nanospheres using B-N dative bond as the driving force. Two monomers incorporated with boronic acid and catechol groups were prepared (**Figure 31**). When the methanol solutions of these two monomers were mixed together, boronate ester polymers were formed through sequential boronate esterification. Simultaneously, B-N dative bond formed between imine and boronate moieties in the polymer chains led to the formation of uniform nanospheres. It was found that the formation of the nanospheres adopted a N-E polymerization process, and the size of the nanospheres could be well controlled (**Figure 32**). This was the first example for the cooperative polymerization using B-N dative bond as a driving force.

We have also found that intermolecular B-N dative bond can be formed among small molecules [40]. A planar boronate ester (BCe), containing two imine moieties, a boronate ester group and two polymerizable carbon-carbon double bonds, has been created by the condensation reaction between a boronic acid molecule (BM) and a catechol molecule (CM) (**Figure 33**). In a methanol solution, B-N dative bond occurs among BCe molecules, thus leading to the formation assemblies with different morphologies. These assemblies can be further stabilized

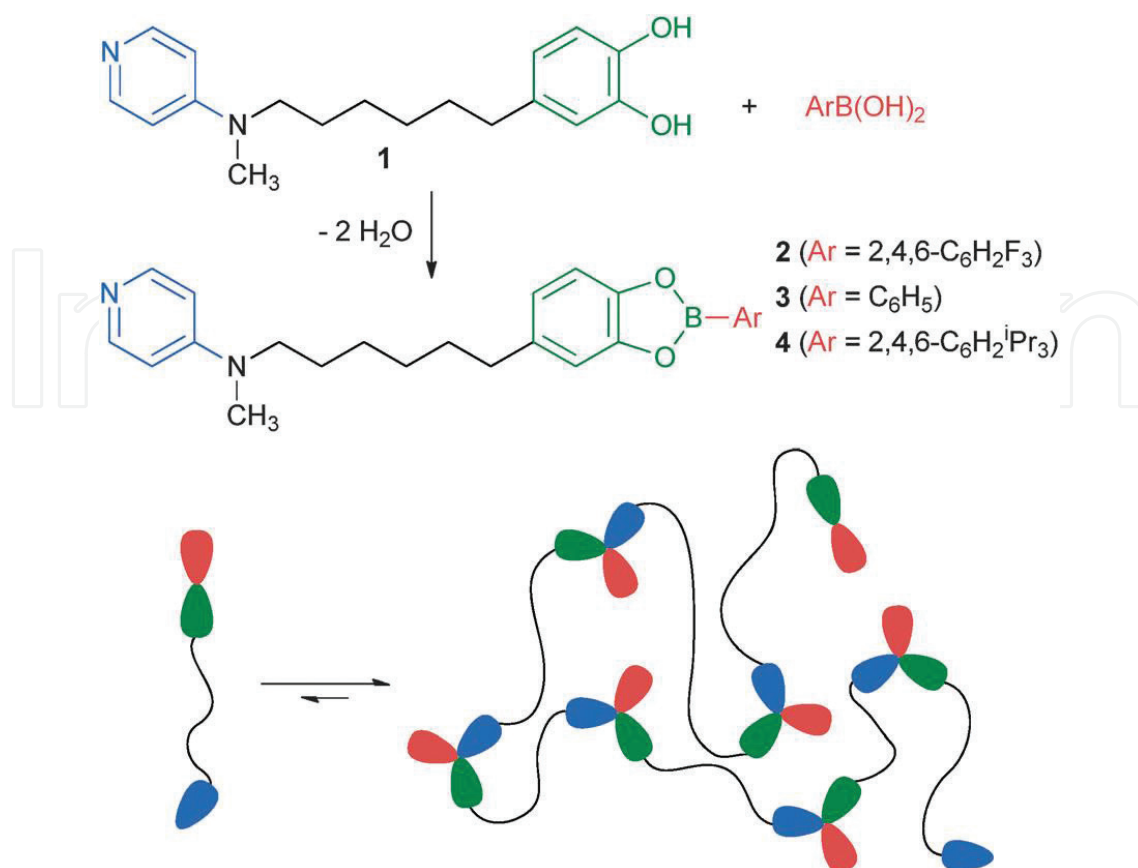


Figure 30. Synthesis of the heteroditopic monomers and aggregation through B–N dative bonds.

through the polymerization of carbon-carbon double bonds. Dramatic fluorescence intensity evolution has been observed along with the degradation of these assemblies under the stimuli of pH or D-glucose. Importantly, the reformation of B–N dative bond endows the assemblies with excellent self-healing property.

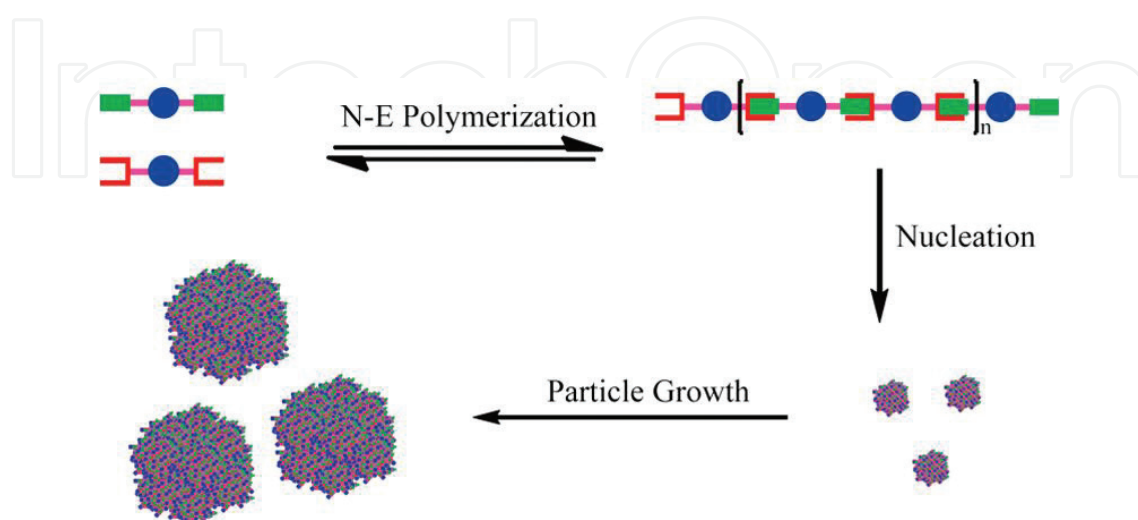


Figure 31. Schematic representation of the B–N dative bond derived boronate nanospheres.

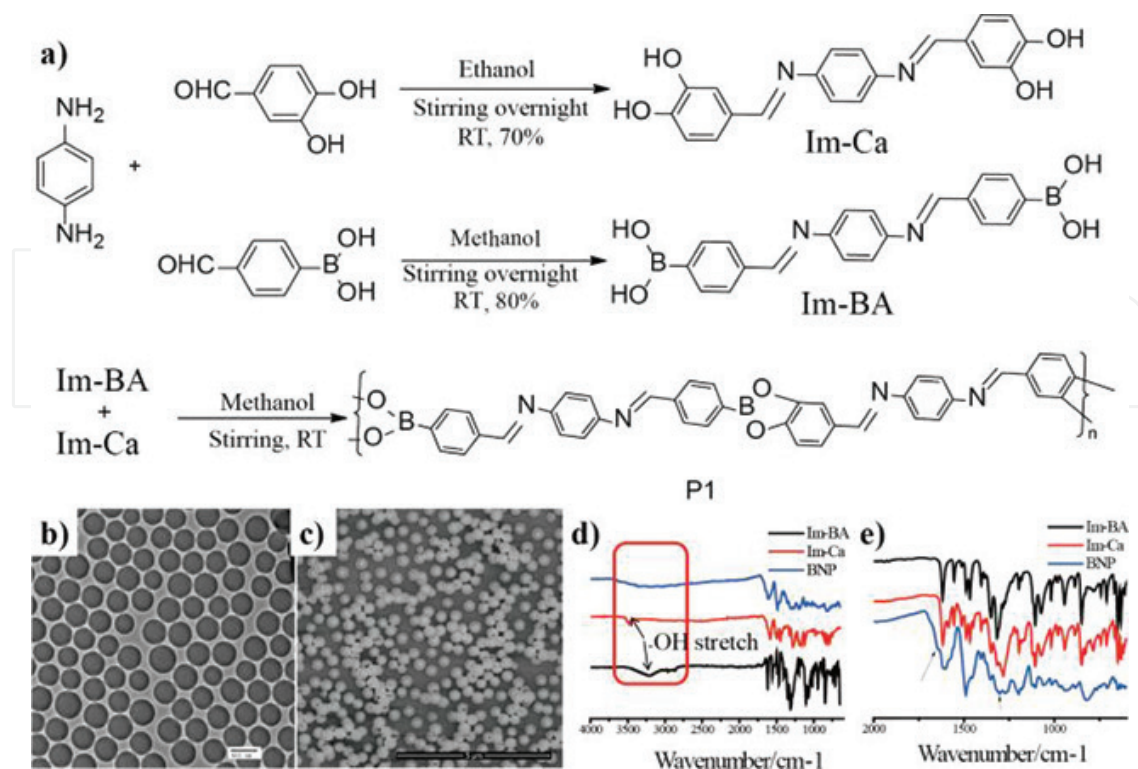


Figure 32. Synthesis and characterization of boronate nanospheres.

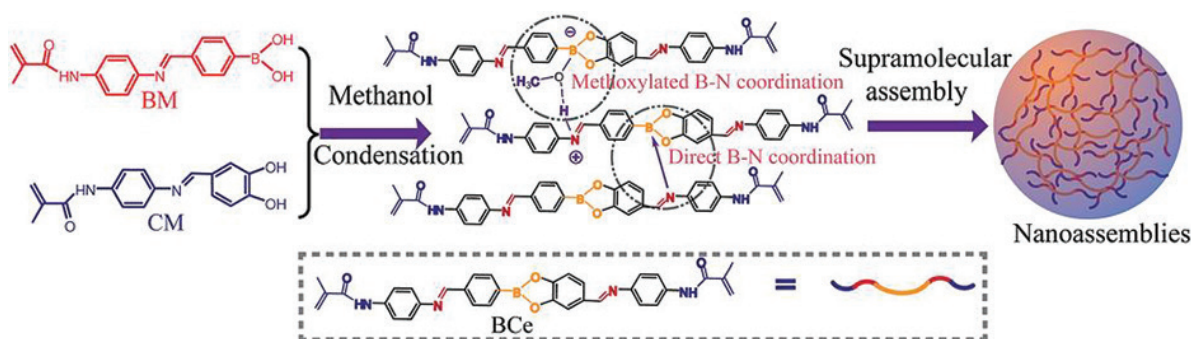


Figure 33. Synthesis and supramolecular assembly of BCe.

3. Conclusion

Polymer chemistry has provided numerous methods to design and synthesize polymers with various compositions and structures. This is the fundamental support for the explosion of high performance or functional materials. Up to now, polymers comprising only C, H, O, and N elements have been extensively investigated and the limitations of these materials have been well understood. Introduction of hybrid elements such as Si, P, As, B, or even metal ions into polymer chains have gained great interest in developing new polymeric materials with enhanced or new properties. In addition, new intermolecular interactions among polymer chains may emerge in polymers containing hybrid elements. This is particularly important for the self-assembly of polymers to form novel structures and morphologies.

However, great challenge has been encountered in the synthesis of hybrid polymers: (1) synthesis of monomers containing hybrid elements is usually difficult; (2) many hybrid monomers have a low polymerization activity; (3) purification and processing of hybrid polymers normally need complicated procedures. Fortunately, the development of organic and polymer chemistry has provides great opportunities for the design of new polymers comprising POSS, boronic acid, or boronate moieties. As demonstrated by the above minireview, amphiphilic copolymers possessing POSS, boronic acid, or boronate moieties are of high capability to self-assembly in solution systems, because new driving forces such as POSS stacking or B-N dative bond emerge. These hybrid nanoassemblies generally have controllable morphologies, diameters, properties, and shown potential applications in sensor and biomedical areas.

Notably, we should also concern the shortcomings of the nanoassemblies derived from amphiphilic polymers containing POSS, boronic acid, or boronate moieties. (1) POSS cage itself is usually inert and has no evident advantage to endow POSS-based polymers with smart properties; (2) the polymerization degree of POSS monomer is still much lower than normal monomers; (3) boronic acid or boronate moieties incorporated into the main chain of polymers have not been well developed; (4) polymerizable monomers with boronic acid or boronate moieties are rare. Future development directions in this area might focus on the design of novel hybrid polymerizable monomers and explosion of new self-assembly driving forces. For example, new POSS structures with dynamic bond incorporated in the POSS cages may endow POSS-based polymers with smart properties; novel monomers with boronic acid or boronate moieties may endow the polymers with new intermolecular interactions to promote the self-assembly of polymeric networks.

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