

Strategies for Constructing Polymeric Micelles and Hollow Spheres in Solution via Specific Intermolecular Interactions

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ABSTRACT

We succeeded recently in developing a series of new pathways to polymeric micelles and hollow spheres via intermolecular specific interactions. A new micellization mechanism of block copolymers was realized by using the specific interaction between a low molecular weight compound and one of the blocks in low-polarity solvents. Many more successes have been achieved by our “block copolymer-free” strategies. We are now able to use homopolymers, random copolymers, oligomers, etc. as building blocks to construct noncovalently connected micelles (NCCM), in which the core and shell are connected by hydrogen bonding. Some of such NCCMs are readily converted further into hollow spheres by cross-linking the shell and then switching the medium to one that dissolves the core. Rigid polymer chains and their complementary homopolymers can directly assemble into large hollow spheres thanks to the propensity to parallel packing of the rigid chains. In addition, some of the NCCMs show perfect stimuli-responsive properties. pH-dependent micellization and pH-dependent micelle–hollow-sphere transition are realized in water-soluble graft copolymers driven by complexation and decomplexation between the main chain and grafts.

Introduction

Specific interactions, including hydrogen bonding and ion–ion interaction have long been extensively studied to understand the mechanism of life, to mimic the life processes, as well as to construct new materials with desirable functions and properties.¹ In the past decades, great progress has been made in the use of specific interactions as the main driving forces to construct linear supramolecular polymeric chains and a variety of assemblies with two- or three-dimensional regularities.^{2,3} In most cases, the building blocks are small molecules or oligomers. In the field of polymer science, the introduction of the specific interactions into multicomponent polymers has been proven to be an efficient way of improving miscibility and forming interpolymer complexes.⁴ How-

ever, because of the inherent flexible and long-chain nature of most synthetic polymers, the specific interactions between complementary polymers usually occur in an uncontrollable way and consequently lead to irregular structures.⁴ Thus, it has been a great challenge to construct regular supramolecular structures by means of specific interactions from polymeric building blocks in solutions.

Polymeric micelles and hollow spheres are the most extensively studied polymeric nano-objects with a simple structural regularity. The micellization of block copolymers, in which different polymer chains are connected covalently, in selective solvents, which dissolve only one of the blocks, is the most common way to produce such assemblies.^{5–7} Recently, some procedures using inorganic or organic templates have been reported for the preparation of polymeric hollow spheres.⁸ However, these methods usually lead to the hollow spheres with a size beyond micrometers, which limits somewhat their range of application. On the basis of our long-term research on interpolymer complexation via hydrogen bonding, over the past years, we have focused on developing new routes to polymeric micelles and hollow spheres, using intermolecular-specific interactions as the major driving forces. In this Account, we recount the strategic discoveries along this line in two major areas of research: the assembly of systems composed of small molecules and block copolymers and the “block copolymer-free strategies” in which complementary polymer pairs are used as the building blocks.

Self-Assembly of the Complexes of Block Copolymer/Small Molecules in Low-Polarity Media

In this section, we concentrate on our new approaches to micellization of block copolymers based on the specific interactions between one kind of blocks and small organic molecules (SM) having an interacting head and a nonpolar tail. The complexation between block copolymers and SM and the behavior of the resultant complexes in solid state were studied in the literature.⁹ In *aqueous media*, because of the association of the hydrophobic tails of SM, the complexes of SM and a block copolymer may result either in vesicles alone,¹⁰ in micellar clusters, or in precipitation.¹¹ However, in a low-polarity solvent, because the tails of SM are soluble, the SM/block copolymer complexes are often molecularly dispersed without micelle formation.¹² For example, in the mixtures of polystyrene-*b*-poly(4-vinyl pyridine) (PS-*b*-P4VP) and a linear aliphatic acid in a nonpolar solvent, the complexation takes place between the headgroup of the SM and the pyridine units. Although the junction point of a high polarity tends to aggregate, the solvation of both the nonpolar tails of SM and the PS blocks in the medium is strong enough to keep the complex molecularly dissolved. Therefore, we believe that, for realizing micellization of SM/block copolymer systems

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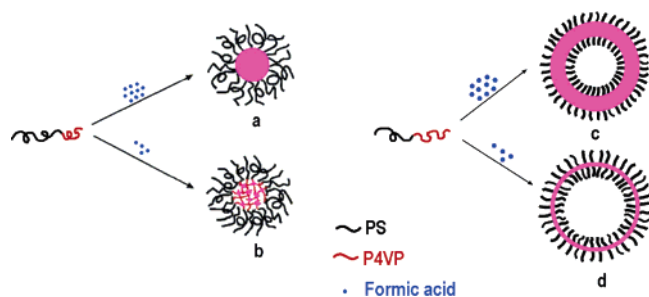


FIGURE 1. Schematic representation of the formation of micelles with different morphologies from formic acid/PS-*b*-P4VP. When the block length ratio of PS to P4VP is ca. 2:1, micelles are formed (a and b) with a solid core when $MR \geq 2.3$ (a) and a low-density core when $MR < 1.2$. When the length ratio is ca. 1:1, vesicles are formed with the wall thickness increasing with MR (c and d).

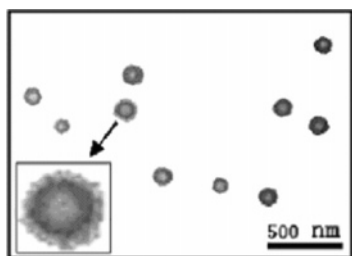


FIGURE 2. TEM graphs of the vesicles resulting from the complexation between formic acid and PS-*b*-P4VP (molecular weights: PS, 33 000; P4VP, 29 000) in CHCl_3 . The molar ratio of formic acid to pyridine unit $MR = 1.3$.¹³

in nonpolar solvent, the key point is shortening the tails of SM to reduce its role of solubilization.

We studied the stoichiometric complexes of PS-*b*-P4VP with a series of linear aliphatic acids.^{13,14} All of the complexes of the block copolymer with stearic acid, decanoic acid, and acetic acid at low concentrations, respectively, could be molecularly dispersed in chloroform. However, formic acid, the acid without a hydrocarbon tail, can self-assemble with the block copolymer into ordinary micelles or vesicles. As schematically represented in Figure 1, the morphology of the aggregates varies with the structural parameters of the block copolymer and the molar ratio of formic acid to the pyridine units of the P4VP block (MR). A typical TEM image of the resultant vesicles is shown in Figure 2.

When perfluorooctanoic acid (PFOA) was used to replace hydrocarbon SM, different results were obtained. Although PFOA has an 8-carbon chain, it can induce the micellization of PS-*b*-P4VP in their common solvent instead of forming a soluble complex.¹⁵ Vesicles form (Figure 3) instantaneously when stoichiometric PFOA and the copolymer are mixed in chloroform at low concentrations. When PFOA is in excess, i.e., $MR = 2$, the morphology changes from typical vesicles to micelle-like aggregates (inset in Figure 3).

Similar to the micellization of block copolymers in selective solvents, the micellization of SM/block copolymer in the solvent is always conducted at a concentration no higher than 5.0 mg/mL; otherwise, an irregular aggregate or precipitant is obtained. Therefore, the preparation efficiency is quite low. In our previous studies, we

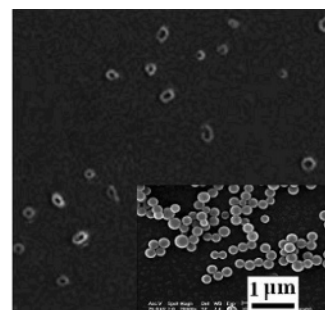


FIGURE 3. Morphologies of discrete aggregates at $MR = 1$ and $MR = 2$ (inset) of PFOA/PS-*b*-P4VP observed by SEM.¹⁵

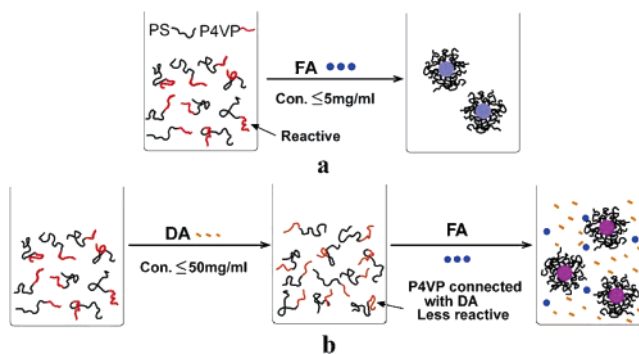


FIGURE 4. Schematic description of the micellization of the complex of PS-*b*-P4VP/formic acid (FA) (a) without and (b) with the premixing of PS-*b*-P4VP with decanoic acid (DA).¹⁷

succeeded in preparing narrow size distributed core-shell micelles of PS-*b*-P4VP at a concentration as high as 20% (w/v) in its common solvent by selectively cross-linking P4VP.¹⁶ Here, we believe that the aggregation of the cross-linked blocks can proceed very slowly by controlling the speed of the cross-linking reaction. Therefore, even at a high concentration, there is enough time for the soluble PS block chains to disentangle, stretch out, and surround the aggregated block, thereby playing a role as a shield to protect the aggregates. This suggests that slowing down aggregation of the insoluble block may be helpful to carry out the micellization at high concentrations. On the basis of this conclusion, we designed a new way of controlling the micellization as follows.¹⁷

First, we prepared the stoichiometric complex of PS-*b*-P4VP/decanoic acid, which can be molecularly dispersed in chloroform. Then, a stoichiometric amount of formic acid was introduced into the PS-*b*-P4VP/decanoic acid solution. Obviously, the pyridine/decanoic acid units can be replaced wholly or partially by the pyridine/formic acid units and the latter self-associate. The pre-existing pyridine/decanoic acid units will retard the complexation of the copolymer with formic acid and the resultant micellization. As a result, the micellization can be conducted at concentrations of PS-*b*-P4VP up to 50.0 mg/mL, resulting in regular micelles. The process and mechanism are sketched in Figure 4.

Taking advantages of the versatility of the interaction of SM and a block copolymer, we are even able to produce "short life" micelles.¹⁸ As shown in Figure 5, micellization of PEO-*b*-PAA is caused by the PAA block reacting with ETC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide me-

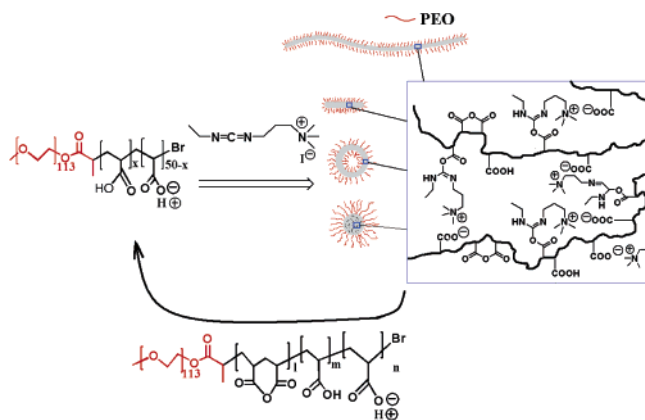


FIGURE 5. Schematic description of the reaction of the PAA block of PEO-*b*-PAA with ETC (1-(3-dimethylaminopropyl)-3-ethylcarbodiimide methiodide) leading to the formation and dissociation of the nanoaggregates.¹⁸

thiodide) forming the ion–ion complexes.¹⁹ Thanks to the instability of the intermediates of the reaction, acylisourea returns to the acrylic acid functionalities after a certain period; therefore, the micelles start to dissociate. Because of this cycle, the polymeric nanoaggregates exist in the aqueous solutions for only 1–3 weeks.

Noncovalently Connected Micelles (NCCM)

Self-Assembly of Hydrogen-Bonding Graft Copolymers.

We shall now describe our work on block–copolymer-free strategies. A polymer pair bound together by a specific interaction, e.g., hydrogen bonding, can lead to interpolymer complexes. In most cases, the complex aggregate is ill-defined and precipitates in solution because a proton-donating polymer chain can react with many proton-accepting polymer chains and vice versa. Only a few exceptions based on interpolymer complexes resulting in structured assemblies have been reported in the literature.^{20,21}

In our approach to polymeric assemblies with a micelle-like structure, a polymer pair was applied composed of an oligomer (A) with a single interacting site on one of the ends and a polymer (B) with many interacting sites.^{22–24} Because of a specific interaction between B and the end of A, a graft-like soluble complex forms with main-chain B and grafts A in the common solvent. Then, the soluble complex may assemble into a core–shell structure after the common solvent is switched to a selective one (Figure 6).

We first studied complexation of poly(4-vinyl pyridine) (P4VP, MW 140 000) as a proton-accepting polymer and low-molecular-weight carboxyl-end polystyrene (CPS) as a proton-donating polymer.²² Mixing CPS and P4VP in chloroform led to the formation of a soluble complex. The soluble complex of P4VP/CPS in chloroform self-assembled into stable micelles when toluene, a selective solvent for CPS, was added.^{23,24} This case obviously differs from the micelles of block copolymers; here, the CPS shell and the P4VP core are linked by hydrogen bonding instead of covalent bonding, hence our appellation, “noncovalently connected micelles” (NCCM). For the NCCMs of

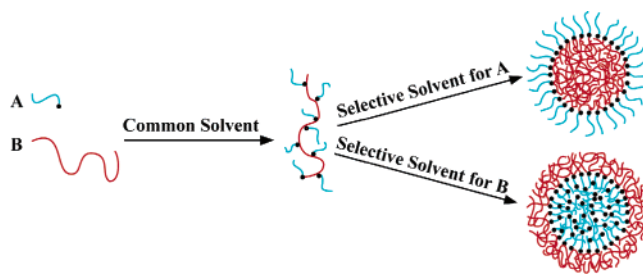


FIGURE 6. Schematic representation of the formation of hydrogen-bonding grafting polymers and their assembly in selective solvents.

(P4VP)-CPS (In this Account, (A)-B stands for micelles with A core and B shell), it was found that the micellar size increases markedly with an increase in the molar mass of CPS. This means that the higher the CPS molar mass, the weaker the stabilization ability and, consequently, the larger the micelles formed. When the MW of CPS increased to 23 400, macroscopic precipitation took place instead of NCCM formation.

The above procedure was also successfully used for producing NCCMs composed of carboxyl-ended polybutadiene (CPB) and P4VP.²⁵ Hydrogen-bonding graft copolymers were first formed in their common solvent chloroform, and then their micellization was realized by adding *n*-hexane or nitromethane into the solutions, the respective precipitants for P4VP and CPB. Stable micelles of (P4VP)-CPB and (CPB)-P4VP were respectively formed. The average hydrodynamic diameters ($\langle D_h \rangle$) of the micelles were mostly in the range from 100 to 300 nm depending on the solvent composition, polymer concentration, the chain number ratio of CPB to P4VP, etc.

Pispas et al.²⁶ of Athens University succeeded in producing NCCMs via hydrogen-bonding complexation. They used poly(2-vinyl pyridine) (P2VP) and polyisoprene with a sulfonic acid end (suPI) and obtained NCCMs of (P2VP)-SuPI in THF/decane. Because the building blocks were monodispersed, they were able to work out sufficient characterization of the resultant complexes and assemblies.

Assembly of Polymer Pairs in Solvent/Precipitant.

In the approach to NCCM just mentioned, we emphasized the importance of restricting one kind of interaction sites to the end of polymer chain. In fact, this restriction can be relaxed when we use a different mixing procedure as follows.²⁷ Suppose that we have polymers A and B having complementary interacting sites, which exist in either each repeating unit or randomly along the chains. We first prepare solutions A and B with different solvents. The solvent for B has to be a precipitant for A. Therefore, when solution A is added into solution B, the chains of A aggregate into nano- or submicrometer size particles, but their macroscopic precipitation is prevented by the B chains gathered around the A aggregates through the interpolymer hydrogen bonding between A and B. Thus, micelle-like particles are formed with a compact A core surrounded by a B shell. Using this approach, several NCCMs have been realized from polymer pairs including slightly sulfonated polystyrene/P4VP,^{28,29} poly(styrene-*co*-methacrylic acid)/poly(vinyl pyrrolidone),³⁰ hydroxyl-

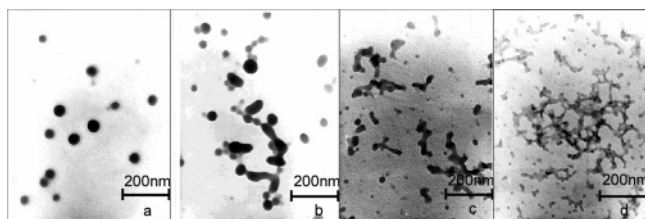


FIGURE 7. TEM micrographs of NCCM of (PSOH- x)-P4VP (x , the molar content of hydroxyl-containing units in PSOH) showing morphological change with hydrogen-bonding density, (a) PSOH-2/P4VP, (b) PSOH-20/P4VP, (c) PSOH-27/P4VP, and (d) PSOH-42/P4VP.³¹

containing polystyrene (PSOH)/P4VP,³¹ CPB/poly(vinyl alcohol),³² poly(ϵ -caprolactone) (PCL)/poly(acrylic acid),³³ etc.

We now discuss the assembly of PSOH/P4VP in more details.³¹ PSOHs are random copolymers of styrene and hydroxyl-containing monomer *p*-(1,1,1,3,3,3-hexafluoro-2-hydroxypropyl)- α -methylstyrene. Chloroform is a good solvent for both, while nitromethane is a good solvent for P4VP but a nonsolvent for PSOH. When a dilute solution of PSOH in CHCl_3 was added into nitromethane containing P4VP, NCCM of (PSOH)-P4VP formed because of the hydrogen bonding between the pyridine ring and hydroxyl in PSOH. As shown in Figure 7, the interaction density between the components, which can be adjusted by altering the hydroxyl molar content in PSOH, exerts a strong effect on the morphologies of the NCCMs.

Hydrophilic NCCMs with biodegradable PCL as the core and a water-soluble graft copolymer of MAF as the shell were attained.³⁴ MAF having a hydrophilic backbone and short PCL branches was produced by copolymerization of methacrylic acid (MAA), methyl methacrylate (MMA), and macromonomer [$\text{CH}_2=\text{HCOOCH}_2-\text{CH}_2(\text{OCOCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2)_3\text{OH}$]. Note that the macromonomer has PCL repeating units. When the dilute blend solution of MAF/PCL in DMF was added into water, the PCL did not precipitate but formed a micellar core that was stabilized by the shell of hydrophilic main chains of MAF with the PCL branches anchored to the aggregate. After the composition of MAF and the weight ratio of MAF to PCL in the initial solutions were changed, the size of the resultant micelles of (PCL)-MAF could be adjusted. As shown in Figure 8a, the micelles have a three-layer structure. The gray outer shell is composed of the hydrophilic main chains of MAF. The inner shell shows a much lower chain density, which can be attributed mainly to the short PCL branches. These morphological results illustrate the role of the PCL branches acting as glue between the outer shell and core.

NCCMs Produced via *In Situ* Polymerization. Recently, we developed an entirely new route to NCCMs in which the polymerization of the shell component accompanies the process of self-assembly.³⁵ An example is the NCCM of (PCL)-PNIPAM, where the shell is cross-linked thermosensitive poly(*N*-isopropyl acrylamide). As shown in Figure 9, PCL solution in DMF containing initiator AIBN is added dropwise into water, leading to PCL nanoparticles. NIPAM monomer and cross-linker of

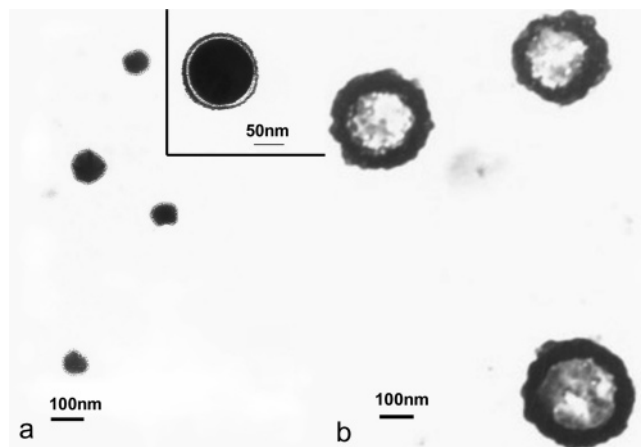


FIGURE 8. TEM images of MAF/PCL (1:1, w/w) nanoparticles before (A) and after (B) biodegradation.³⁴

methylene bisacrylamide are then introduced to the PCL dispersion followed by increasing the temperature to 76 °C to initiate the polymerization. The polymerization is expected to take place at the periphery of the PCL nanoparticles because the initiator tends to reside in the hydrophobic PCL particles, while the monomer and cross-linker exist mainly in water. Once the cross-linked PNIPAM chains are formed, they would collapse and adhere to the PCL particles because of their hydrophobicity at a temperature higher than its LCST (32 °C). The first PNIPAM layer formed would further trap the monomer and the cross-linker from the water phase so that the polymerization continues and the shell grows. The diameter of the resultant spheres can be adjusted over a range between 100 to 400 nm by changing the reaction parameters.

Hollow Spheres Obtained from NCCMs

Over the past years, polymeric hollow spheres have received special attention because they are expected to have much higher efficiency of encapsulation, particularly for large-size molecules. When block copolymers are used as precursors to produce hollow spheres, a sequence of steps has to be followed: synthesis of a block copolymer composed of a cross-linkable block and a degradable block, micellization, cross-linking the shell block, and finally, removing the core block by degradation chemically or biologically.^{36–39} Recently, we succeeded in obtaining hollow spheres by using NCCM as precursors. This procedure could avoid the possible difficulties in the synthesis of the block copolymers containing a degradable block and a cross-linkable block. Thus, a broad range of common polymers can be used. In addition, the size and thickness of the hollow spheres can be easily adjusted over a certain range by altering the conditions of preparation such as the shell–core weight ratio.

For the NCCMs of (PSOH)-P4VP mentioned above, the shell was locked in by the P4VP reacting with 1,4-dibromobutane under mild conditions. Further cavitation of the spherical micelles was realized by simply switching the solvent into DMF, which not only could solubilize PSOH but also could cause dissociation of the interpoly-

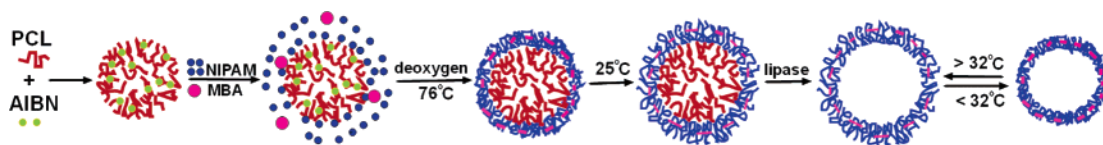


FIGURE 9. Schematic illustration of the preparation route to thermosensitive hollow spheres of cross-linked PNIPAM.³⁵

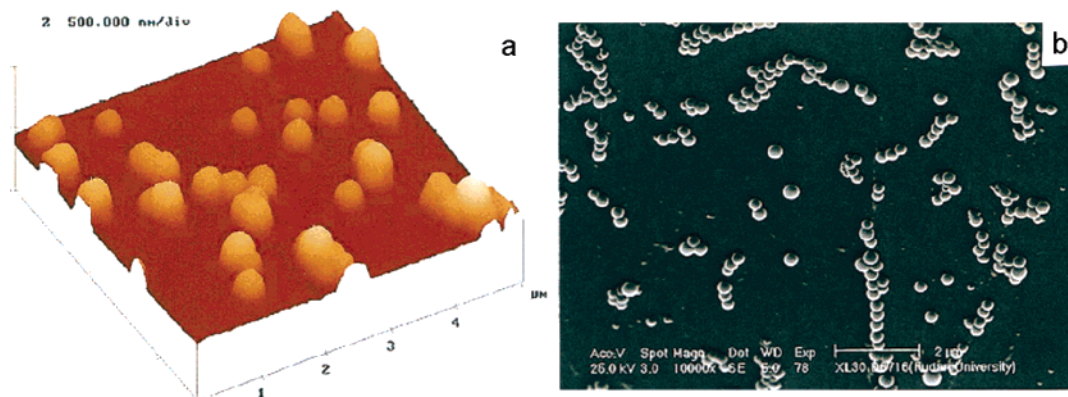


FIGURE 10. Micrographs of hollow spheres made of PSOH-2 by (a) AFM and (b) SEM.³¹

mer hydrogen bonding leading to decomplexation. The hollow structure was confirmed by $\langle R_g \rangle / \langle R_h \rangle$ measurements.⁴⁰ As clearly shown in Figure 10, most of the hollow spheres are standing on the substrate with good integrity persistence.

NCCM of (PCL)-MAF³⁴ was then used as a precursor for producing hydrophilic hollow spheres. After the hydrophilic shell was cross-linked,³⁸ the PCL core was hydrolyzed by adding enzyme lipolase. In this process, the micellar diameter increases from 100 to 350 nm, while the mass of the particles decreased by one-half. This expansion happens because the restriction imposed by the insoluble blocks on the solvated blocks in the shell is relaxed. After core degradation, a hollow structure is clearly displayed in Figure 8b. In comparison with the particles shown in Figure 8a, both the overall size and the shell thickness are significantly greater.

Similarly, hydrophilic hollow spheres based on poly(vinyl alcohol) (PVA) were obtained from its precursor of shell-cross-linked NCCM of (CPB)-PVA by simply dissolving the CPB core in THF.³²

Thermoresponsive nanocages based on PNIPAM were produced from NCCM of (PCL)-PNIPAM³⁵ by removing the PCL core through biodegradation. The process was traced by dynamic light scattering (DLS), which showed that the intensity of scattering light (I_s , which is proportional to the particle mass) and the average hydrodynamic diameter $\langle D_h \rangle$ follow the opposite trends (Figure 11). The gradual decrease of the light intensity reflecting the degradation of the core is accompanied by an increase in size. This volume expansion is believed to be caused by relaxation of the restriction imposed by the core component on the hydrophilic shell.

Our major concern regarding these PNIPAM-based hollow spheres is their thermal sensitivity. As shown in Figure 12, the PNIPAM nanocage can shrink or swell over a wider range of volume with temperature. As the temperature increases from 20 to 45 °C, the diameter of the

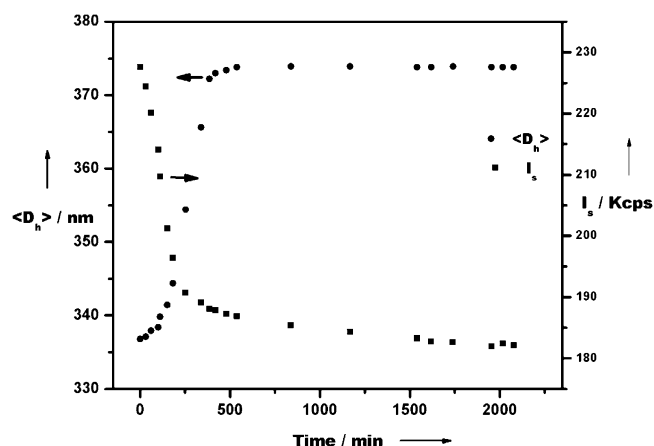


FIGURE 11. $\langle D_h \rangle$ and scattering intensity I_s of spheres (PCL)-PNIPAM as a function of the core degradation time.³⁵

hollow spheres decreases from 432 to 223 nm, corresponding to the “open” and “close” states, respectively. More importantly, the thermoresponsive properties of the nanocage are reversible as the heating curve coincides completely with the cooling curve.

Complexation-Induced Micellization and Micelle–Hollow-Sphere Transition

Encouraged by the success of our strategies in constructing NCCMs based on interpolymer-specific interactions of polymer pairs, we have extended our concept to cases in which the complementary polymer chains are linked together in a copolymer. Thus, we studied the self-assembly of the graft copolymer (HEC-g-PAA) prepared by free-radical graft polymerization of acrylic acid from hydroxyethyl cellulose (HEC) main chains.⁴¹ Note that HEC has plenty of proton-accepting groups and PAA is a pH-dependent proton-donating polymer.

Graft-copolymer samples with a low degree of grafting, i.e., on average 1–3 grafts per main chain, were used. The $\langle R_h \rangle$ of the copolymers in aqueous media did not change

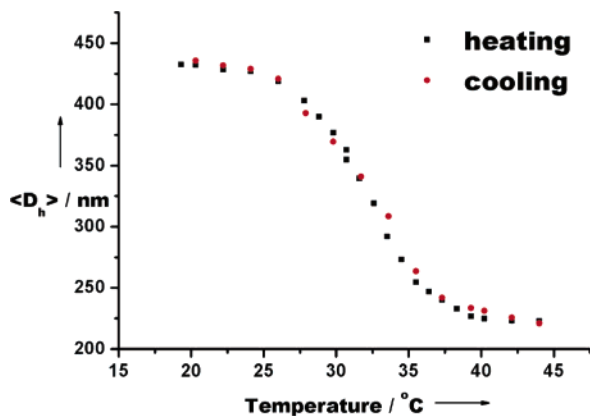


FIGURE 12. Average hydrodynamic diameters of the hollow spheres based on PNIPAM as a function of the temperature.³⁵

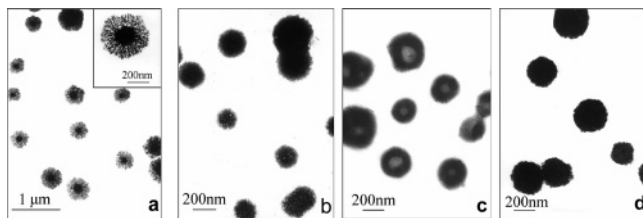


FIGURE 13. TEM image for (a) the micelles of sample 1 of FEC-*g*-PAA formed at pH 1.3 and that at a high magnification (insert), (b) the micelles of sample 2 formed at pH 1.3, (c) the hollow spheres of sample 2 after cross-linking and dialysis, and (d) the micelles of sample 2 obtained by adjusting the acidity to pH 1.3.⁴¹

over a broad range of pH between 13.5 and 4. However, as the pH value decreases to less than 4, the value of $\langle R_h \rangle$ jumped to some value in the range of 250–330 nm, reflecting the transition from individual molecules to aggregates. In addition, the transition was found to be reversible with pH.

Typical images of the aggregates shown in Figure 13a clearly display a micellar structure with a distinct boundary between a higher chain-density core and a lower density shell. The formation of the micelles can be rationalized as follows. PAA chains become sufficiently protonated at $\text{pH} < 4$; thus, they are able to form a complex with HEC and form small aggregates. Because of the small average degree of grafting of the copolymers, there are HEC chains with little or no PAA segments, which may still remain solvated and thus stabilize the complex aggregates. This is pH-dependent complexation-induced micellization.

The PAA chains of the micelles were then chemically cross-linked at room temperature. Dialysis against water was then performed to remove all impurities accompanied by an increase in the pH value to 7. Remarkable changes occurred in the micelles after cross-linking and dialysis took place; i.e., the micellar size was substantially increased and the core-shell structure was transformed to hollow spheres (Figure 13c). It is noteworthy that this cavitation was caused by neither degradation nor dissolution of the core; a change in the pH value is exclusively responsible for the transition. In our understanding, when the pH increases from acidic to neutral values, decom-

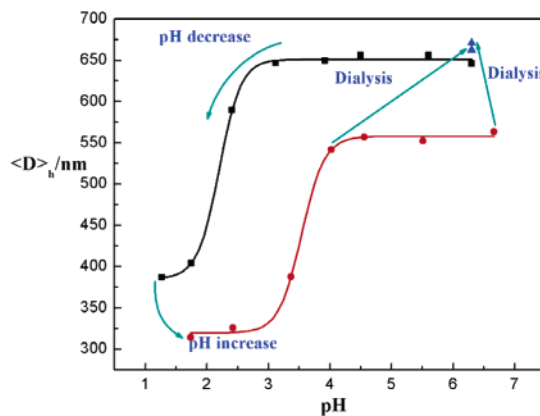


FIGURE 14. Average hydrodynamic diameter $\langle D_h \rangle$ of sample 2 of cross-linked HEC-*g*-PAA aggregates as a function of pH showing reversible transition between the micelle to hollow sphere.⁴¹

plexation between HEC and PAA occurs, which causes disintegration of the micellar core, but the cross-linked shell keeps its integrity. This pH-dependent cavitation of the micelles was also found to be reversible. Figure 14 presents a $\langle D_h \rangle$ cycle corresponding to a change from the hollow sphere to the micelle and then back to the hollow spheres when pH decreases from 6.3 to 1.3 and then goes back to 6.3. Such a reversible pH-dependent transition between micelles and hollow spheres is induced by the reversible complexation between the unlike chains in the graft copolymer (Figure 15).

Self-Assembly of Polymer Pairs Containing Rigid Chains

In all of the new assembly strategies discussed above, coil polymer chains were exclusively used as building blocks. Jenekhe and Chen⁷ reported that rod-coil block copolymers could self-assemble to large hollow spheres directly in selective solvents. This result aroused our interest in using rigid-coil homopolymer pairs to construct NCCMs. The first example in this approach was composed of a rigid oligomer polyimide (PI-1, MW 4600) (Scheme 1) with two carboxyl end groups and coil-like P4VP.^{42,43} Our expectation was that hydrogen-bonding “graft copolymers” might form when the two polymers were mixed in their common solvent. However, mixing dilute solutions of PI-1 and P4VP in chloroform unexpectedly led to the formation of particles with $\langle R_h \rangle$ in the range of 238 to 384 nm. Furthermore, the particles were found to be hollow spheres by DLS, TEM, and AFM observations.

Our understanding for the formation of the hollow spheres of the rigid-coil pair in their common solvent is as follows. Because of the hydrogen bonding between the end groups of PI and the pyridine unit in P4VP, a P4VP chain may carry many (up to 10^2 – 10^3) rigid PI chains. Therefore, the local concentration of PI chains surrounding a P4VP chain is much higher than the average, and consequently, the requirement of effective packing of such crowded rigid chains provides the driving force for forming large hollow spheres (Figure 16a).

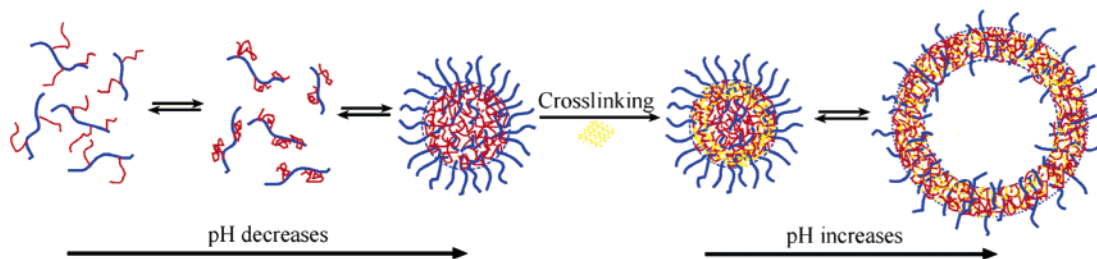
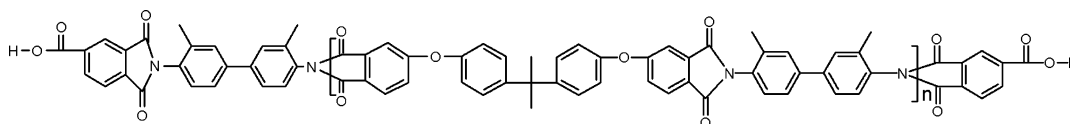
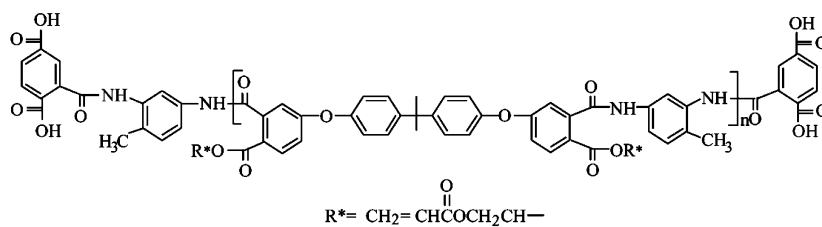


FIGURE 15. Proposed scheme of the pH-dependent micellization and transition from the micelle to hollow sphere of HEC-*g*-PAA. Blue and red chains are for HEC and PAA, respectively.⁴¹

Scheme 1. Chemical Structures of Poly(amic acid) Ester (PAE) and Polyimide



Polyimide-1 (PI-1)



Poly(amic acid) Ester (PAE)

To fix the assembled structure, we used a cross-linkable rigid polymer, i.e., photosensitive and carboxyl-terminated poly(amic acid) ester (PAE, MW 7450, Scheme 1), to replace PI-1.⁴⁴ The resultant hollow structure of the assemblies was then locked in by UV in THF. When the medium is switched to THF/DMF (1:1), the size of the cross-linked sphere was significantly decreased as a result of the outer shell of P4VP disappearing because of the dissociation of the hydrogen bonding between the PAE and P4VP (Figure 16b). As shown by SEM (Figure 17), most of the cross-linked hollow spheres of PAE maintain their integrity. The characteristically large cavity of the spheres can be clearly seen for the aggregates before cross-linking (inset of Figure 17).

Rigid Chain-Assisted Self-Assembly of Block Copolymers

Having reported our results on block-copolymer-free strategies for constructing polymeric micelles, we now return to self-assembly of block copolymers. Although in recently years, many new approaches to micelles of block copolymers have been proposed,⁴⁵ the basic driving force for the assembly is still the solubility difference between the component blocks. Aided by our experience in the assembly of rigid-coil polymer pairs, we have been thinking of a new mechanism of micellization of block copolymers in the presence of rigid chains.

Mixing the PS-*b*-P2VP and PAE solutions in their common solvent THF led to the formation of particles

with a radius of about 60 nm (Figure 18). The results clearly demonstrated that self-assembly of the block copolymers in the common solvent could be realized by grafting rigid oligomers onto one block via hydrogen bonding.⁴⁶ This rigid chain-assisted micellization of the block copolymers is associated with a new mechanism: the interaction between PAE (PI) and the pyridine units leads to the PAE gathering around P2VP, and then the tendency of parallel packing of the grafted PAE promotes the assembly of the block copolymers forming the shell of the hollow spheres.

On the basis of the fact that the P2VP block can be chemically cross-linked and PAE is easily photocross-linked, two approaches to stabilize the hollow particles of PAE/PS-*b*-P2VP are possible. We added equivolume DMF to the P2VP-cross-linked micelles resulting in dissociation of the interpolymer hydrogen bonding. Thus, nanocages of the block copolymer with PAE uniformly distributed inside were obtained. Alternatively, we could photocross-link the PAE layer of the PAE/PS-*b*-P2VP aggregates followed by adding equivolume DMF in the THF solution. In this case, the size of the cross-linked spheres in THF/DMF is substantially decreased as a result of the removal of the outer shell of the block copolymers from the aggregate because of the dissociation. Thus, nanocages based on PI alone were obtained. As schematically shown in Figure 19, when different parts of the hollow spheres of PAE/PS-*b*-P2VP were cross-linked, we

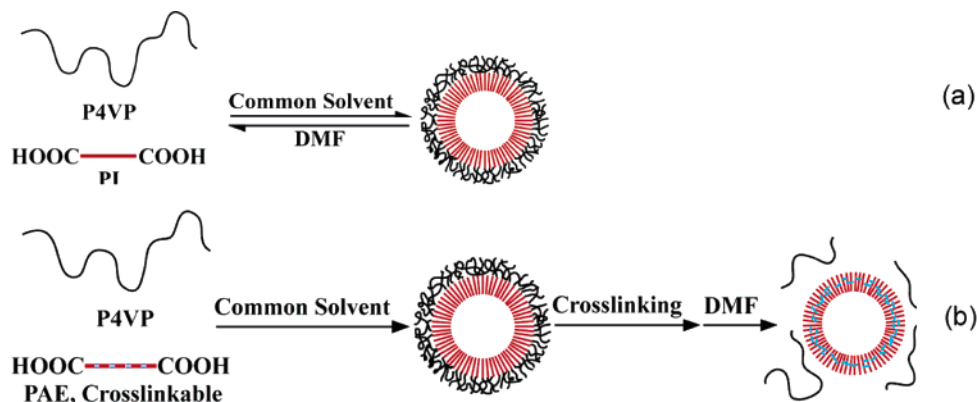


FIGURE 16. Schematic representation of the formation of hollow spheres of P4VP and PI (a) and of P4VP and PAE and cross-linking of the PAE layer (b).

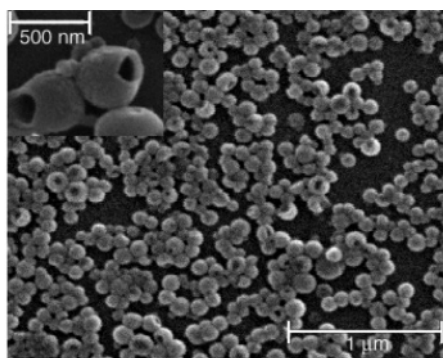


FIGURE 17. Morphologies of discrete cross-linked hollow spheres of PAE/P4VP observed by SEM. The inset is for the hollow spheres before cross-linking.⁴⁴

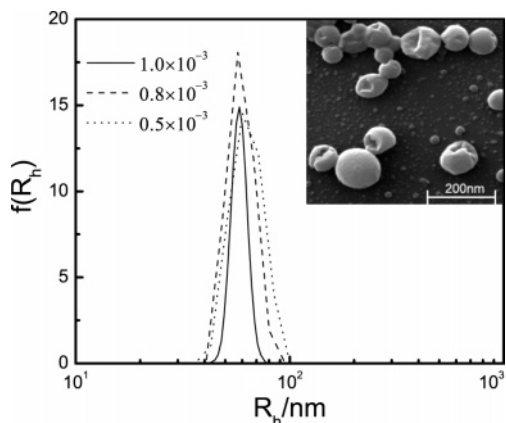


FIGURE 18. R_h distribution of the PAE/PS-*b*-P2VP hollow particles. In the final solution, $C_{PS-b-P2VP} = 1.0 \times 10^{-4}$ g/mL. C_{PAE} is shown in the legend. The inset is a typical SEM image of the particles.⁴⁶

are able to produce two kinds of nanocages differing totally in chemistry.

Concluding Remarks

Our recent achievements, which are briefly summarized in this Account, have demonstrated that, besides block copolymers, we can probably use, as building blocks to construct polymeric micelle-like and hollow structures, small molecules with suitable functionalities, oligomers, ionomers, homopolymers, random copolymers, graft copolymers, etc., provided that intermolecular specific in-

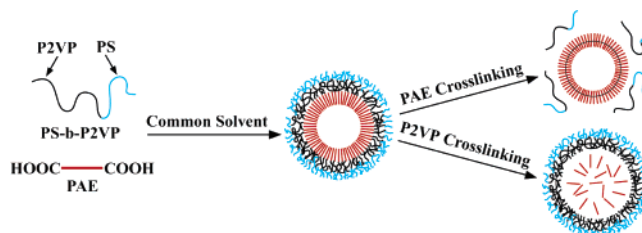


FIGURE 19. Schematic illustration of chemical and photocross-linking of PAE/PS-*b*-P2VP aggregates leading to nanocages based on PAE and the block copolymer, respectively.

teractions are properly utilized. These new strategies for self-assembly are characterized by simplicity of the preparing process and broadness of the available materials. These advantages open up further intriguing prospects for studies. Theoretical investigations are needed to explore the mechanisms and the chemistry of the assembly processes at a fundamental level. Meanwhile, various applications of these new assemblies such as capsules for active materials, catalyst, and drugs are expected to be actively pursued in the coming days. We believe that the future of these new assembled materials holds a good potential in life science as well, because some of these assembled materials are biocompatible and stimuli-responsive and it is also possible to incorporate biomolecules into the assemblies such as NCCMs based on synthetic or natural polymers.

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