Linear coupling of spherical block copolymer micelles induced by gradually depositing an insoluble component onto the core–shell interface†

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As an emerging cutting-edge area, the anisotropic assembly of isotropic nanoparticles provides not only a unique but also a convenient pathway for constructing materials with novel structures and functions. However, examples of the anisotropic assembly of isotropic nanoparticles are still limited. In particular, methods that can delicately control the assembly of isotropic nanoparticles for the preparation of regularly ordered superstructures are seldom reported. Here, we report that, in a suspension of block copolymer micelles, gradually depositing an insoluble component to the core–shell interface of the micelles can increase the size of the insoluble core, leading to core–core coupling. When a certain amount of a common solvent is added into the suspension to make the core flexible, the core–core coupling can lead to the linear coupling of the micelles. In this case, only the two opposite ends of the core can be coupled; each micelle behaves like a monomer with two functionalities. Furthermore, the deposition can result in the “branched polymerization” of the same micelles and the “copolymerization” of different micelles. The redistribution of the shell-forming chains during the core–core coupling enhanced the protection of the uncoupled surface of the core, resulting in an anisotropic interaction between the micelles.

1. Introduction

The self-assembly of nanoparticles is attracting increasing interest in research fields including materials, biological science, physics and chemistry. Usually, nanoparticle self-assembly forms superstructures with complexities and functionalities that are different from molecular assemblies. Besides, it uses mesosopically-sized building blocks, potentially bridging the gap between microscopic and macroscopic scales. In principle, except for templated assembly and colloidal crystallization which require uniformity in the size and shape of the particles, nanoparticle self-assembly is driven by anisotropic interactions between primary nanoparticles. Recent years have witnessed a great effort devoted to the preparation of anisotropic nanoparticles such as Janus particles and patchy particles. Anisotropic nanoparticles, especially those with sufficient flexibility, have shown great potential as the building blocks to construct regular superstructures, and various intriguing assemblies of anisotropic nanoparticles have been reported. Recent studies demonstrated that isotropic nanoparticles with great flexibility can also self-assemble anisotropically into regular superstructures; the anisotropic self-assembly of isotropic nanoparticles is actually also driven by anisotropic interactions. It is significant that, compared with anisotropic nanoparticles, isotropic nanoparticles are much easier to prepare. However, reported examples of isotropic nanoparticle self-assemblies are still limited, and involve complicated mechanisms and processes that are difficult to control. New methods, especially those with simple mechanisms and good controllability for isotropic nanoparticle self-assembly are desired.

Theoretically, for the anisotropic self-assembly of isotropic nanoparticles, both attractive and repulsive interactions between the nanoparticles are required. In a system where the primary nanoparticles are individually dispersed, the attractive and repulsive interactions are balanced. It is imaginable that increasing the attractive interaction sufficiently will break the balance; the particles will tend to aggregate. By selecting the system to let the aggregation be accompanied with a decrease in the attractive interaction and/or an increase in the repulsive interaction, we can build the balance again. This concept was confirmed in the present study by linear self-assembly of block copolymer micelles in water resulting from gradually depositing a hydrophobic component at the core–shell interface. The deposition increased the size of the attractive core, leading to the core–core coupling of the primary micelles. Endowed with certain flexibility, during the core–core coupling, the shell-forming block chains of the micelles can escape from the coupling area to redistribute nearby. The core–core coupling
decreased the total surface area of the core as well as the attractive interaction in the system, and meanwhile increased the shell–shell repulsive interaction since the redistribution results in densification of the shell-forming chains on the uncoupled surface of the core. Specifically, the redistribution of the shell-forming chains enhances the protection of the uncoupled area near the coupled area, leading to the linear or branched assembly of the micelles.

2. Experimental section

2.1 Synthesis of PEG110-b-P4VP90

PEG110-b-P4VP90 (poly(ethylene glycol)-b-poly(4-vinylpyridine), the subscripts represent the degrees of polymerization) was synthesized by atom transfer radical polymerization of 4-vinylpyridine using modified PEG-Br as the macroinitiator. The polydispersity index of the block copolymer is 1.1 (the procedures for the block copolymer preparation and characterization are described in ref. 31).

2.2 Preparation of the micelles encapsulating the hydrophobic radical initiator AIBN within the core

8.0 mg AIBN (azodisobutryonitrile) and 50.0 mg PEG110-b-P4VP90 were mixed in 5.0 mL methanol, the common solvent of PEG-b-P4VP. Then 45.0 mL water was added dropwise into the stirred solution using a syringe pump at a speed of 2.0 mL h\(^{-1}\). In the final solution, the concentration of the block copolymer was 1.0 mg mL\(^{-1}\).

2.3 Copolymerization of NIPAM and MBA in the presence of PEG-b-P4VP micelles and the characterization of the aggregates in the system

40.0 mg of the hydrophilic monomer \(\text{N-isopropyl acrylamide (NIPAM)}\) and 9.0 mg of the hydrophobic cross-linker methylene bisacrylamide (MBA) were added into 10 mL of the micelle solution at a concentration of the block copolymer of 1.0 mg mL\(^{-1}\). The mixture was stirred for 12 h. Then, under the protection of argon, the temperature of the system was increased to 65 °C. The polymerization lasted for 4 hours. The resultant suspension was a little more turbid than the precursor micelle suspension but no precipitation was observed. Aggregates formed in the system at different polymerization times were withdrawn from the polymerization system and characterized by dynamic light scattering (DLS), transmission electron microscopy (TEM) and \(^1\)H-NMR. \(^1\)H-NMR measurements were performed on a Bruker DMX500 spectrometer. DLS measurements were carried out using a modified commercial light scattering spectrometer (ALV/SP-125) equipped with an ALV-5000 multi-t digital time correlator and ADLAS DPY-425 solid-state laser (output power = 22 mW at \(i = 632.8 \text{ nm}\)). All the DLS measurements were performed at 90° and 25 °C. TEM observations were conducted on a Philips CM120 electron microscope at an acceleration voltage of 80 kV. Samples for TEM observations were prepared by depositing a drop of the aqueous suspensions onto a carbon-coated copper grid. Excess solution was absorbed immediately using filter paper to avoid further aggregation of particles on the grid during the drying the samples.

3. Results and discussion

Both PEG\(110\)-b-P4VP\(90\) and AIBN can be molecularly dispersed in methanol. The addition of water into the methanol solution of PEG-b-P4VP–AIBN to the water–methanol volume ratio of 9 : 1 resulted in PEG-b-P4VP micelles with PEG as the shell and P4VP as the core (the respective concentrations of the block copolymer and AIBN in the final micellar suspension were 1.0 mg mL\(^{-1}\) and 0.16 mg mL\(^{-1}\)). The average hydrodynamic radius \((R_h)\) of the micelles measured by DLS was 32 nm, and the polydispersity index was 0.07 (Fig. 1a). TEM observation revealed that the micelles were spherical and had a very narrow size distribution, which is consistent with the DLS result, as indicated in Fig. 1b.

Subsequently, the hydrophilic monomer NIPAM and the hydrophobic cross-linker MBA were introduced into the mixture (the weight ratios of NIPAM–PEG-b-P4VP and MBA–PEG-b-P4VP in the reaction system were 4 : 1 and 0.9 : 1, respectively). When the system was heated to 65 °C, the copolymerization of NIPAM and MBA initiated by the free-radical initiator AIBN took place (the evidence for the polymerization is given in Fig. S1 in the ESI†). The copolymerization lasted for 4 hours. The changes in the size and morphology of the aggregates in the reaction system were tracked by DLS (Fig. 2) and TEM (Fig. 3).

The Z-averaged curves of \(f(R_h)\) versus \(R_h\) show multi modal size distributions. The peaks at 30 nm (Fig. 2) are coincident with the peak of the primary micelles shown in Fig. 1a, and are thus assigned to the primary micelles. Signals that peaked at larger \(R_h\) values appear after polymerization, indicating the formation of large aggregates. In the curves, it is found that the relative signal intensity of the primary micelles decreases, whereas both the \(R_h\) value and the relative signal intensity of the large nanoaggregates increase with polymerization time.

The TEM observations revealed that the nanoparticles in the system at different polymerization times were either primary micelles or nanofibers (Fig. 3); no other nanoaggregates were observed. This indicates that the large nanoaggregates resulting from the polymerization are nanofibers. In the TEM images, the width of the nanofibers is close to the diameter of the primary micelles. The outlines of the spherical micelles are visible in the nanofibers formed at the beginning of the polymerization (Fig. 3a, indicated by red arrows). Besides, the nanofibers formed in the early period of the polymerization are short (Fig. 3a and b), but their lengths increased remarkably with polymerization.

![Fig. 1](image-url) (a) The hydrodynamic radius distribution of the PEG-b-P4VP micelles formed in the water–methanol (9 : 1, v/v) mixture, and (b) the TEM image of the PEG-b-P4VP micelles.
The length of the final nanofibers increased to several or even tens of micrometres. In addition, in the final product, a large part of the nanoparticles are nanofibers based on an unbiased observation of the TEM images. This is also consistent with the abovementioned DLS results in that both the relative signal intensity and $R_h$ of the large particles increased with polymerization time (Fig. 2).

Now, the question that would arise is: whether the nanofibers are just worm-like micelles resulting from the self-assembly of the block copolymer; the spherical micelles transformed to worm-like micelles due to the change in temperature and composition of the medium. This possibility was excluded by following control experiments. In control experiment 1, a mixture of the same components, but without AIBN, at the same respective concentrations in the water–methanol solvent was heated at 65 °C for 4 hours. In control experiment 2, a PEG$_{110}$–b–P4VP$_{90}$–AIBN–water–methanol (50 mg : 8 mg : 45 mL : 5 mL) mixture system, without the addition of NIPAM and MBA, was heated at 65 °C for 4 hours. Then, for both the control experiments, TEM specimens were prepared and dried at both room temperature and 65 °C, and no considerable amount of nanofibers was observed by TEM (see Fig. S2 in the ESI†). Besides, the DLS measurements detected no obvious changes in the sizes of the aggregates in the two control systems (see Fig. S2 in the ESI†). In control experiment 3, under the same conditions for forming the nanofibers except that the hydrophilic free-radical initiator K$_2$S$_2$O$_8$ was used in place of AIBN, large amounts of irregular precipitates formed in the system. Therefore, the nanofibers should result from the linear core–core coupling of the primary micelles caused by the polymerization initiated by AIBN.

It is known that, in a stable system of spherical block copolymer micelles in a selective solvent, the solvophobic core is fully protected by the solvophilic shell. Gradually increasing the size of the solvophobic core by depositing solvophobic species on the core–shell interface will increase the possibility of core–core aggregation. At a certain stage, when the solvophobic core is too large to be protected by the shell, the core–core aggregation should take place. In the present study, $^1$H NMR characterization of the system of PEG$_{110}$–b–P4VP$_{90}$–AIBN–water–methanol (50 mg : 8 mg : 45 mL : 5 mL) confirmed that more than 61% AIBN was located in the core (see Fig. S3 in the ESI†). Considering the fact that the concentration of the PEG-b-P4VP in the suspension is only 1.0 mg mL$^{-1}$, the concentration of AIBN in the core is about three orders of magnitude higher than that in the solvent mixture. Therefore, the radical copolymerization of NIPAM and MBA mainly took place at the core–shell interface, and the copolymer should form and be deposited at the core–shell interface. This is further supported by the results of the control experiments that, without the micelles, in the same solvent mixture, the copolymerization of NIPAM and MBA at the same respective concentrations at 65 °C resulted in precipitates. In the presence of the micelles, the precipitation was avoided because the copolymer was deposited on the core–shell interface. In this way, the size of the core increased, which resulted in core–core coupling.

It should be mentioned here that, in the present study, the system contains 10% (v/v) methanol (the common solvent of the block copolymer), which provides the core with flexibility, as confirmed by $^1$H NMR characterization. It is noted that P4VP signals are invisible in the spectra at methanol–water volume ratios less than or equal to 6% (spectrum a, Fig. 4). When the volume ratio is 10%, the P4VP signals become visible (at 6.4 ppm and 8.3 ppm, spectrum b, Fig. 4), whereas their relative intensities are much lower than those of the P4VP signals in spectrum c, Fig. 4. The P4VP signals in spectrum b result from the mobility of the P4VP core rather than the molecularly dispersed block copolymer chains in the system. This is based on the fact that no signal from the molecularly dispersed PEG-b-P4VP chains was
detected in the number-averaged DLS curve at a volume ratio of 10%; the number-averaged DLS curve is very sensitive to individually dispersed polymer chains (see Fig. S4 in the ESI†). The effects of the flexibility on the coupling behaviors of the primary micelles are reflected by the dependence of the morphology of the final products on the volume ratio. When the methanol–water volume ratios were less than or equal to 6%, irregular micellar clusters were obtained (Fig. 5a and b). At a volume ratio of 10%, as mentioned before, the products are mainly nanofibers with widths close to diameter of the primary micelles and lengths of several or tens of micrometres. A further increase in the volume ratio to 20% leads to nanofibers as well. However, the nanofibers have more branching points as compared to those obtained at a volume ratio of 10% (as indicated by the red arrows in Fig. 5c).

To understand the mechanism for the linear core–core coupling of the micelles, how the shell-forming chains redistribute during the core–core coupling and how the redistribution protects the uncoupled area should be considered in detail. Taking one micelle (denoted here as micelle A) into account, it is imaginable that during the first core–core coupling of micelle B to micelle A, the shell-forming chains originally located at the coupling area should redistribute to the uncoupled area. As a result, after the core–core coupling, the density of the shell-forming chains on the uncoupled area of the core should be increased and the protection of this area by the shell-forming chains is thus enhanced. Then, the second core–core coupling of micelle C to micelle A should most likely occur on the area (on the core surface of micelle A) opposite to the B–A coupled area (Scheme 1b) for two reasons: (1) this area is furthest from the B–A coupled area and should be least affected by the redistribution of the shell-forming chains due to the B–A coupling; (2) micelle C coupling to this area is less hindered by micelle B. After the second coupling, two ends of micelle A have been coupled with micelle B and micelle C, and all the shell-forming chains of micelle A will locate on the remaining uncoupled area of micelle A. When the micelles are flexible enough, the A–B and A–C coupling areas should be relatively large to obtain enough enthalpy. This will increase the density of the shell-forming chains and hence enhance the protection of the uncoupled area of the core of micelle A remarkably. As a result, the third coupling of another micelle to micelle A should become much more difficult; micelle A can only couple with micelle B and micelle C like a monomer with two functionalities. When all the micelles behave like a “monomer” with two-functionalities based on the mechanism mentioned above during the core–core coupling, the micelles assemble linearly into linear superstructures (Scheme 1).

The MBA cross-linked poly N-isopropyl acrylamide (PNIPAM) deposited on the surface of the cores is not only hydrophobic at 65 °C but also reactive.32,33 Therefore, MBA cross-linked PNIPAM on the surfaces of different cores may react with each other once the cores aggregate together. The
MBA cross-linked PNIPAM will form a nanostructure within the nanofibers, which should be consistent with the structure expected based on the mechanism described by Scheme 1. For the observation of the structure of MBA cross-linked PNIPAM within the nanofibers, the PEG-b-P4VP in the nanofibers was removed by adjusting the pH value of the suspension to 3.0 and then dialyzing the suspension against acidic water at pH 3.0, in which the P4VP block chains were protonated and the block copolymer was soluble. Afterwards, the residual nanoaoggregates were stained by OsO₄ and then observed by TEM. The TEM image indicates that most of the residual nanoaoggregates have a linear structure, but the contrast is much less than that before removing the micelles. In addition, holes are distinguishable in the linear structure (the inset in Fig. 6), which should result from the departing of the block copolymer. The linear structure with holes is consistent with the structure of MBA cross-linked PNIPAM expected based on Scheme 1. It is also noted that the length of the linear structure in Fig. 6 is much shorter than that of the nanofibers in Fig. 3; the MBA cross-linked PNIPAM within the nanofibers did not form a continuous structure throughout the nanofibers (Fig. S5 in the ESI†).

To confirm whether the integrated micelles can construct the nanofibers, the core of the primary micelles formed in the PEG-b-P4VP–AIBN–water–methanol (50 mg : 8 mg : 45 mL : 5 mL) mixture system were cross-linked by 1,4-dibromobutane at room temperature. DLS measurements indicated that intra-micellar cross-linking took place exclusively (i.e., no inter-micellar cross-linking reaction occurred) (see Fig. S6 in the ESI†). The as-cross-linked micelles can keep their integrity after adding sufficient amount of HCl into the system (see Fig. S6 in the ESI†). Then, the cross-linked system was mixed with the same amount of NIPAM and MBA and followed by polymerization at 65 °C for 4 hours. Short fiber-like nanoaggregates formed in the system (Fig. 7a and b). In the nanofibers, the outline of individual micelles can be clearly seen. This is different from the fibers shown in Fig. 3; the un-cross-linked micelles fuse completely along the direction of the fiber axis due to their high flexibility so that the outline of the individual micelles almost disappeared. There are also more branches in the nanofibers constructed by the cross-linked micelles.

Furthermore, we demonstrated that two different kinds of the micelles can be "copolymerized" together. The "copolymerization" was carried out under the same conditions for the "homopolymerization" of the primary micelles except that the primary micelles were replaced by the same amount of the mixture of the primary micelles and the core-cross-linked micelles (the weight ratio of the cross-linked micelles to the primary micelles was1 : 1). In the TEM images, the linear combination of the cross-linked micelles and the primary micelles was observed (Fig. 7c and d). In the TEM image, the core-cross-linked micelles possess a high contrast due to the existence of bromide ions as the counter ions of pyridinium. The cross-linking decreased the size of the micelles. It

Fig. 6  A TEM image of the MBA cross-linked PNIPAM nanostructure formed in the nanofibers.

Fig. 7  TEM images of the nanofibers formed from the “homopolymerization” of core cross-linked micelles (a and b), and the nanostructure obtained from the “copolymerization” of micelles and the core cross-linked micelles (c and d).
should be mentioned here that the aggregates in Fig. 7 were unstained. The unstained MBA cross-linked PNIPAM, which is the linker of two connected micelles, is of low contrast or invisible. This is responsible for the low contrast in the area in between the two connected micelles.

4. Conclusions

We demonstrated a new and robust route to achieve the anisotropic aggregation of isotropic particles. The copolymerization of NIPAM and MBA on the core–shell interface was used to gradually increase the size of the attractive cores, leading to core–core coupling. During the core–core coupling, the shell-forming chains redistribute to the uncoupled area of the core surface. When the core is flexible enough, the redistribution results in the anisotropy of the micelle so that only the two opposite ends of the micelles are capable of coupling with the other micelles. This is responsible for the linear coupling of the isotropic spherical block copolymer micelles. The processes for increasing the size and flexibility of the attractive cores are very convenient and have good controllability. The resultant one-dimensional nano-aggregates are highly regular. This makes the method described in the present study very promising to address the theoretical and practical problems regarding isotropic particle self-assembly.

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Notes and references