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Large complex micelles formed from amphiphilic H-shaped terpolymers with adjustable block ratio by ultrasonic vibration

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ABSTRACT

Large complex micelles based on H-shaped terpolymers (poly(ethylene glycol))(poly(N,N-dimethylaminoethyl methacrylate))-polytetrahydrofuran-(poly(N,N-dimethylaminoethyl methacrylate)) (poly(ethylene glycol)) ((PEG)(PDMA)-PTHF-(PDMA)(PEG)), with proper block ratio, are obtained through ultrasonic vibration. However, similar micellar morphology is not found using other traditional methods, such as evaporation and dialysis. According to the predicted thermodynamic analysis, large complex micelles consisting of several multimicelles are a result of the cooperative effects of ultrasonic vibration, hydrophobic–hydrophilic block ratio, and H-shaped branched architecture. These findings may lead to new strategies in designing supramacromolecular materials that exhibit special properties.

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1. Introduction

In recent decades, supramolecular self-assembly of amphiphilic block copolymers has attracted a great deal of attention from academicians [1–7]. As the most widely reported supramolecular aggregates, micelles formed from these polymers can be classified into simple and complex micelles, according to differences in their structure and size [8]. Compared with simple micelles, complex micelles are important in the study of morphological diversity and may also have potential applications in drug delivery, biomedical engineering, and nanocomposite materials [9–11]. Thus, the preparation of complex micelles has become a cutting-edge issue in the field of macromolecular self-assembly. Several research groups have reported the preparation of some types of complex micelles with larger size and more complicated structure. For example, Eisenberg et al. [8] discovered large compound micelles formed from several small reverse crew-cut micelles, whereas the molar ratio of the hydrophobic chains was high in the amphiphilic block copolymer, polystyrene-block-poly(acrylic acid). Moreover, large complex micelles (“supermicelles”) formed from further aggregation of Janus micelles from the triblock copolymer, polystyrene-

block-polybutadiene-block-polymethylmethacrylate, were discovered by Müller's group [11].

To date, however, less attention has been directed on complex micelles formed from the self-assembly of nonlinear amphiphilic polymers [9,10], compared with the earlier mentioned amphiphilic block polymers. Nonlinear amphiphilic polymers with more structural variations may lead to subtle thermodynamically stable structures. For example, Yan et al. [9,10] have reported on large multimicelle aggregates (MMAs) formed by the aqueous self-assembly of hyperbranch-cored star polymers. MMAs are one type of complex micelles formed by secondary aggregation of unimolecular micelles under high concentration conditions. As earlier mentioned, although hydrophobic–hydrophilic ratio is recognized as a key factor in the formation of large complex micelles, the influences of other factors, such as different preparation methods for micelles or topological structure of nonlinear polymers, are still not fully considered. In addition, studies on complex micelles formed from other nonlinear polymers and their corresponding formation mechanisms are still needed [12].

H-shaped polymers, as a special type of nonlinear polymers, have one main backbone chain and four side chains linked to the main chain ends [13–17]. Owing to their unique architecture, H-shaped polymers show different micellar properties and special self-assembly morphologies compared with linear and other branched block copolymers. To date, all studies on self-assembly of H-shaped polymers are focused on A_2BA_2 -type copolymers

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Table 1
Characterization data of all the H-shaped terpolymers.

	M_{nSEC}^a (g/mol)	$M_{w,SEC}^a$ (g/mol)	M_w/M_n^a	dn/dc^a (mL/g)	M_{nSEC}^c (g/mol)	M_w/M_n^c	dn/dc^c (mL/g)	$M_{n,NMR}^b$ (g/mol)
H-1	18,230	19,690	1.08	0.072	18,570	1.07	0.072	17,274
H-2	15,530	16,770	1.08	0.074	16,020	1.08	0.073	16,292
H-3	13,250	13,490	1.02	0.075	13,650	1.04	0.075	15,402

^a Measured by SEC/MALLS.

^b Calculated based on the signals at $\delta = 3.42$ ppm to the signals at $\delta = 2.29$ ppm and $\delta = 1.67$ ppm.

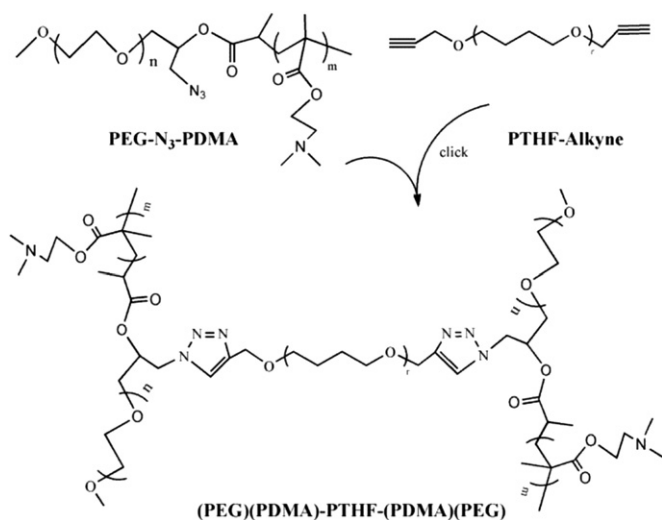
^c After ultrasonic treatment, measured by SEC/MALLS.

[15–17]. Different self-assembly morphologies from these polymers (e.g., vesicle, spherical, and worm-like micelles) can be constructed based on the variable hydrophobic–hydrophilic ratios of their macromolecular structures [17]. However, large complex micelles were still not found in H-shaped polymers, and the effect of different preparation methods on micellar morphology also lacks systemic studies. The present study investigates the self-assembly of amphiphilic (AC)B(AC) type H-shaped terpolymers. Three different self-assembly morphologies, namely, large complex micelles, dot-like micelles, and worm-like micelles were obtained through ultrasonic vibration, evaporation, and dialysis methods, respectively. In particular, the cooperative effects of ultrasonic vibration, proper hydrophobic–hydrophilic block ratio, and H-shaped branched architecture were responsible for the formation of large complex micelles.

2. Experimental

2.1. Synthesis

A series of H-shaped terpolymers (PEG)(PDMA)-PTHF-(PDMA)(PEG) (Table 1), consisting of one main PTHF chain and two PEG- N_3 -PDMA side chains, were used to investigate the self-assembly. The main preparation procedure for the H-shaped terpolymers is shown in Scheme 1. The PTHF-Alkyne polymerized by the cation ring-opening polymerization of THF was terminated by propynol (Scheme S1). The chain length of PTHF-Alkyne can be regulated by changing the reaction time to obtain H-shaped terpolymers with different hydrophobic–hydrophilic block ratios. PEG- N_3 -PDMA was synthesized through sequential end group modifications and the ATRP technique (Scheme S2). PEG and PDMAEMA (in neutral pH) are water-soluble in nature, whereas



Scheme 1. Synthesis strategy for H-shaped terpolymers.

PTHF are insoluble in aqueous solutions. Hence, H-shaped terpolymers possess an amphiphilic structure, with one hydrophobic PTHF main chain and two hydrophilic PEG- b -PDMA side chains.

2.2. Characterization

The polymer structures of PTHF-Alkyne, PEG- N_3 -PDMA, and (PEG)(PDMA)-PTHF-(PDMA)(PEG) were characterized using Fourier Transform Infrared (FT-IR), H nuclear magnetic resonance (1H NMR) (Fig. S1–S5), and size exclusion chromatography/multiangle laser light scattering (Table 1). The self-assembly of H-shaped terpolymers was investigated in detail using Dynamic Light Scattering (DLS), Transmission Electron Microscope (TEM), and 1H NMR.

3. Results and discussion

Ultrasonic vibration was performed to accelerate the dissolution of the polymers and disperse the micellar solutions [18]. However, its influence on the morphologies of nano-assemblies has not been reported in detail. Hence, we wonder whether ultrasonic vibration can change the final morphology of the micelles during the self-assembly process. H-shaped terpolymers mixed with H_2O were treated using an ultrasonic vibration equipment to prepare a micellar solution through direct dissolution method (See Supporting Information) [19]. Light blue H-2-1 micellar solutions were obtained. DLS results (Fig. 1-F) proved the coexistence of two kinds of nano-assemblies, with sizes around 90 and 600 nm in the H-2-1 aqueous solution. The morphologies of the nano-assemblies were observed by TEM. The typical TEM images are shown in Fig. 1-B, -D and -E. The nano-assemblies constructed from the H-shaped terpolymers showed a light core surrounded by a relatively dark dense corona, presenting a typical micellar characteristic (Fig. 1-B). Furthermore, H-2-1 can self-assemble into large area complex micelles (Fig. 1-D), with significant core–shell structure of about 270 nm–500 nm. After careful observation of the micellar structure (Fig. 1-E), the particles were found to contain abundant small cavities, rather than a whole solid structure. This result indicates that the large complex micelles consisted of several primary micelles (20 nm–30 nm). Moreover, the architecture of the nano-assemblies from the H-shaped terpolymers was well confirmed by 1H NMR in D_2O . Fig. S5 shows the typical 1H NMR spectrum recorded for H-2-1. Compared with the 1H NMR spectrum of H-2-1 in $CDCl_3$ (Fig. S-5-A), Fig. S-5-B shows that the partial signals of PTHF disappeared in D_2O , whereas the signals from the PEG and PDMA blocks were still clearly visible. This result indicates that large complex micelles were formed from H-2-1, consisting of hydrophobic PTHF moiety and hydrophilic PEG and PDMA moieties.

The preparation method for micelles may influence the thermodynamic equilibrium that they finally reached because of the slow movement of the segment [11]. Hence, we wonder whether different methods can produce different results in the self-assembly of H-shaped terpolymers. To clarify this question, we adopted two other preparation methods for micellar solutions (See Supporting Information), namely, the evaporation (H-2-2) and

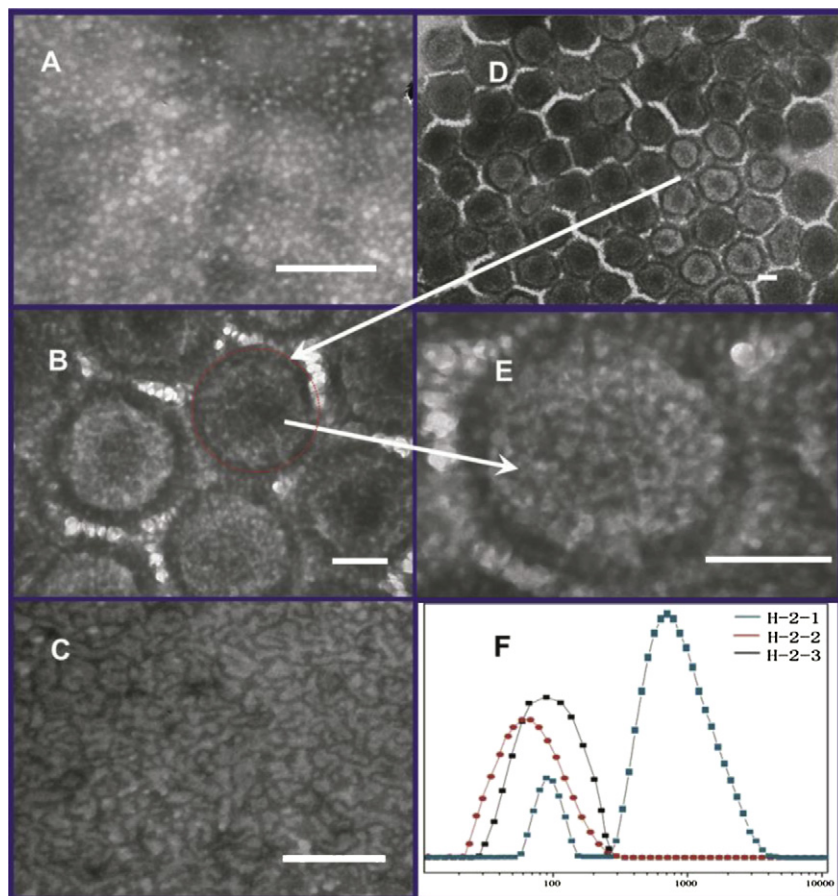
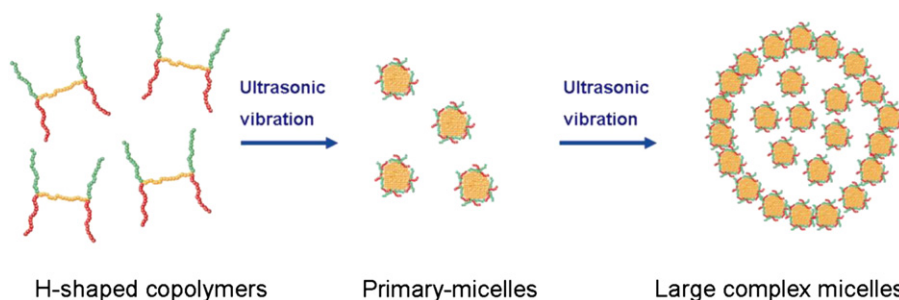


Fig. 1. (A–E) The TEM images of aggregates formed by the self-assembly of H-2 in water at the concentration of 1 mg/mL. All scale bars are 200 nm. Different methods used to prepare micelles: Image A evaporation method (H-2-2), Image B ultrasonic method (H-2-1), Image C dialysis method (H-2-3); Image D is the whole screen of image B, Image E is the magnification of image B; (F) DLS traces of the aggregates formed by H-2-1 (1 mg/mL), H-2-2 (1 mg/mL), H-2-3 (1 mg/mL) in aqueous solution.

dialysis methods (H-2-3) without ultrasound vibration. The self-assembly of H-2 prepared through different methods were investigated using TEM. As shown in Fig. 1, neither H-2-2 nor H-2-3 can form large complex micelles like H-2-1. Instead, H-2-2 formed primary dot-like micelles with sizes of about 20 nm, whereas H-2-3 produced worm-like micelles with sizes ranging from 30 nm to 50 nm. The D_z values of H-2-2 and H-2-3 prepared by evaporation and dialysis methods were about 60 and 80 nm, respectively (Fig. 1–F). Compared with them, the coexistence of two kinds of particles with dimensions around 90 and 600 nm in the aqueous solution of H-2-1 also agreed with the TEM results. Therefore, we conclude that the different morphologies produced by these different methods are attributed to the following. The quick evaporation of

the co-solvent during the preparation of H-2-2 may have induced a quick collapse of the hydrophobic core chains, eventually leading to the formation of regular dot-like micelles. Compared with evaporation, the dialysis of the co-solvent during the self-assembly of H-2-3 contributed to the slow formation of the small multi-micelle aggregates. Furthermore, the entangling and crumpling of PDMA chains may cause the primary dot-like micelle aggregated, followed by the generation of irregular worm-like micelles. Although the micellization of copolymers in aqueous solutions is an entropy-driven process, the most stable thermodynamic structure cannot be obtained because of kinetics [11]. Thus, the preparation method for nano-assemblies can influence the final morphology of the nano-assemblies. In addition, ultrasonic vibration possibly



Scheme 2. Possible formation mechanism for the large complex micelles from amphiphilic H-shaped terpolymer with a proper hydrophobic–hydrophilic block ratio under ultrasonic vibration condition.

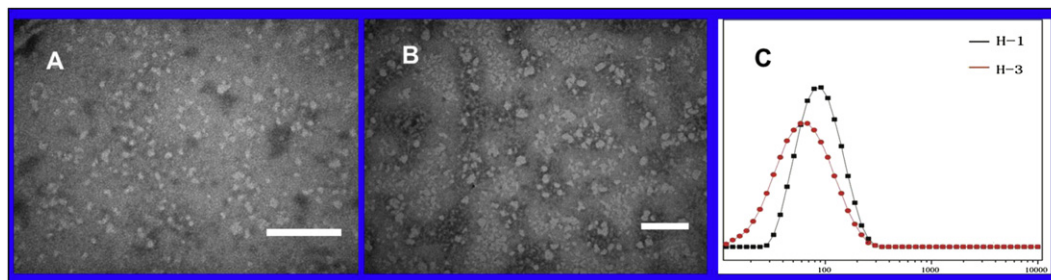


Fig. 2. TEM images and DLS traces of aggregates formed by the self-assembly of H-1 (A), H-3 (B) in water. All scale bars are 200 nm.

influences the thermodynamic equilibrium in the self-assembly process.

Ultrasonic vibration generates great frictional heat for a short processing time, and the heat-affected zone is limited [20]. Our previous studies also indicated that ultrasonic vibration can act on the polymer chains on two aspects: heating and cavitation under confined nanoscale [21]. Thus, the periodic compression and pyrolysis of the cavitation bubbles at the interfaces may have increased the extreme temperature and pressure caused by the shear forces generated around the collapsing cavitation bubbles when ultrasonic vibration was applied to the preparation of micelles. The microscopic cavitation bubbles generated powerful shock waves and micro jets that caused effective stirring/mixing and periodic shaking force on the water when they collapsed near the surface. The after-effects of the cavitations were hundreds of times greater in heterogeneous systems than in homogeneous systems [22–24]. In this study, the most stable state of thermodynamic equilibrium was still prevented by the slow movement of segments (T_g s of PEG and PTHF were lower than room temperature). Ultrasonic vibration can provide more energy to accelerate the movement of the chains and promote the entanglement of hydrophobic moieties. Meanwhile, according to literature [25], inter-chain entangling and crumpling of PDMA chains may cause micelle aggregation because of weak hydrophobic interaction. Hence, ultrasonic vibration may offer sufficient energy to accelerate the movement and increase the entangling of PDMA chains, finally leading to the formation of large complex micelles, which is a typical structure of multimicelle aggregates [9,10]. To further prove the effect of ultrasonic vibration, H-2-2 and H-2-3 were also treated by this method. Interestingly, the similar structure of large complex micelles with a size of 500 nm appeared again, as shown in Fig. S6. Therefore, it is credible that the ultrasonic vibration method as a new strategy can be applied to prepare the large complex aggregates. Scheme 2 shows the possible mechanism for the formation of large complex micelles from amphiphilic H-shaped terpolymers. Additionally, to prove that the ultrasonic vibration cannot induce the degradation of the polymer chain, the micellar solution was frozen and characterized by SEC/MALLS again. The final data was in agreement with the previous results (Table 1). This means that the ultrasonic vibration has little influence on the polymer structure of H-shaped terpolymers.

The cooperative influence of other factors, such as hydrophobic–hydrophilic ratio, on the morphology of large complex micelles during the self-assembly process must also be considered when large complex micelles are obtained. Thus, H-shaped terpolymers H-1 and H-3, with high and low hydrophobic–hydrophilic ratios compared with H-2, were synthesized by regulating the length of the PTHF chain (See Table 1). The D_z values of H-1 and H-3 prepared by ultrasonic method were about 50 and 70 nm, respectively (Fig. 2-C), the results agreed with the TEM findings too. The typical TEM images of H-1 and H-3 are shown in Fig. 2. Apparently, compared with large complex micelles

generated from H-2 (Fig. 1-B), those generated from H-1 (Fig. 2-A) and H-3 (Fig. 2-B) can only self-assemble into simple small micelles, with average sizes of 20 nm–30 nm.

As reported [11,12], the morphology of the aggregates during the self-assembly process can be influenced by the degree of polymerization of the hydrophobic chains in the core and by the surface area per corona chain at the interfaces of the core/corona shell. Eisenberg et al. reported that even a small increase in the length of the hydrophobic chains can change the morphology of the micelles when di-block copolymers self-assemble in water. In the present study, some structural parameters of the micelles changed (e.g., as the R_{core} and average surface area per corona chains increased, the steric repulsion decreased) as the PTHF chain length was increased. According to Ref. [26], R_{core} is proportional to N_c (where N_c is the number of carbon atoms in the hydrophobic chains). The surface area per corona chain (PEG-*b*-PDMA) also increases when R_{core} is increased, leading to reduced steric repulsion [27–29]. As earlier mentioned, the aggregation of more PTHF chains and the increase in core radius were unfavorable to entropy change. Hence, the morphology of the aggregates can change under proper conditions. Proper hydrophobic–hydrophilic block ratio provides proper interaction for the formation of large complex micelles. Based on the foregoing analysis, the large complex micelles discovered in our experiment may be the result of the cooperative effects of several factors. First, the application of ultrasonic vibration and the special branched structure of H-shaped terpolymers contributed to increased entanglements in the PDMA chains due to the weak hydrophobic interaction, leading to the fast aggregation of micro-micelles. Second, the inter-micellar interaction, including hydrophobic core attraction and steric repulsion, provides proper balance among the micelles.

4. Conclusion

In conclusion, the use of ultrasonic vibration, evaporation, and dialysis methods for the preparation of amphiphilic H-shaped terpolymers micelles can produce different micellar morphologies in water, including large complex micelles, dot-like micelles, and worm-like micelles. The formation of large complex micelles depends on the hydrophobic–hydrophilic ratios of the different blocks in the H-shaped terpolymers. Furthermore, the large complex micelles discovered were the result of the cooperative effects of ultrasonic vibration, proper hydrophobic–hydrophilic block ratio, and H-shaped branched architecture. Therefore, these results will further broaden the exploration of complex micelles as robust building blocks for the formation of self-assembly nanostructures with unprecedented functional features.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.polymer.2013.01.054>.

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