Micellization of Thermo- and pH-Responsive Triblock Copolymer of Poly(ethylene glycol)-*b*-poly(4-vinylpyridine)-*b*-poly(*N*-isopropylacrylamide)

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ABSTRACT: Thermo- and pH-responsive micellization of poly(ethylene glycol)-*b*-poly(4-vinylpyridine)-*b*-poly(*N*-isopropylacrylamide) in water was studied. Micellization of the triblock copolymer, which was synthesized by sequential atom transfer radical polymerization of 4-vinylpyridine and *N*-isopropylacrylamide, occurred with combined stimulus of temperature and pH changes to form various morphological micelles. The copolymer existed as unimers at pH 2.0 and then associated into spherical core−corona micelles when pH increased from 2.0 to 6.5 at 25 °C. The critical aggregation temperature of the copolymer was about 34.6 °C, which was a little higher than poly(*N*-isopropylacrylamide). When the copolymer solution was heated above the critical aggregation temperature, the copolymer first self-assembled into compound core−corona micelles or micellar cluster and then converted into core−shell−corona micelles with pH increasing from 2.0 to 6.5. When temperature decreased from 50 to 25 °C, the core−shell−corona micelles further rearranged into core−corona micelles.

1. Introduction

The interest in stimulus-responsive copolymers has increased during the past decade since they have the potential to obtain sensitive materials.[1] Of all the stimulus-responsive copolymers, block copolymers consisting of pH-responsive block such as poly(acrylic acid) (PAA) and poly(4-vinylpyridine) (P4VP) and thermo-responsive block such as poly(*N*-isopropylacrylamide) (PNIPAM) are of interest due to their smart response to stimulus.[2−10] pH-responsive polymers such as PAA or P4VP can respond to pH change and then adjust its morphology and structure. For example, P4VP is soluble and exists as unimers in water at pH < 5, while precipitation occurs at pH > 5.[2] PNIPAM is one of the most studied thermo-responsive polymers that exhibits a lower critical solution temperature (LCST) in water around 32 °C.[11] Block copolymers containing both pH-responsive and temperature-responsive blocks are expected to respond to combined stimulus. Recently, the micellization of such systems as poly(acrylic acid)-*block*-poly(*N*,*N*-diethylacrylamide) and PNIPAM-*b*-PAA has been studied.[12] However, just as Muller et al. indicated, the resultant micelles of such systems would become instable under a certain combined stimulus.[12]

Herein, thermo- and pH-responsive micellization of poly(ethylene glycol)-*b*-poly(4-vinylpyridine)-*b*-poly(*N*-isopropylacrylamide) (PEG-*b*-P4VP-*b*-PNIPAM), which contains a soluble PEG block and thermo- and pH-responsive blocks of PNIPAM and P4VP, is studied. It is found the triblock copolymer can smartly respond to combined stimulus of temperature and pH changes to form various morphological micelles. Compared with diblock copolymers such as poly(acrylic acid)-*block*-poly(*N*,*N*-diethylacrylamide) and PNIPAM-*b*-PAA, the present triblock copolymer has a advantage that the resultant micelles can keep suspending and no precipitation occurs during the combined stimulus of the temperature and pH changes.

2. Experimental Section

Materials. PEG_{110}-*b*-$P4VP_{35}$-*b*-$PNIPAM_{22}$ was synthesized by sequential atom transfer radical polymerization of 4-vinylpyridine and *N*-isopropylacrylamide. The composition of the copolymer is determined by ^1H NMR spectra. The polydispersity index PDI of the copolymer and its precursors of PEG_{110}-*b*-$P4VP_{35}$ and PEG_{110}-Br measured by GPC is 1.18, 1.10, and 1.05, respectively. The detailed synthesis and characterization of the copolymer can be found in the Supporting Information.

Characterization. Dynamic laser scattering (DLS) and static laser scattering (SLS) measurements were performed on a laser light scattering spectrometer (BI-200SM) equipped with a digital correlator (BI-9000AT) at 514 nm at a given temperature. The detailed method of DLS and SLS measurements can be found elsewhere.[13] Transmission electron microscopy (TEM) measurement was conducted by using a Philips T20ST electron microscopy at an acceleration voltage of 200 kV, whereby a small drop of micellar solution was first heated at a given temperature, and then the micellar solution was deposited onto a preheated carbon-coated copper EM grid and dried at the same temperature at atmospheric pressure.

3. Results and Discussion

pH-Responsive Micellization of PEG-*b*-P4VP-*b*-PNIPAM. Usually, P4VP is insoluble at pH > 5 at room temperature. However, PEG_{110}-*b*-$P4VP_{35}$-*b*-$PNIPAM_{22}$ can easily “dissolve” in water at pH 6.5 at 25 °C to form micelles, which is possibly due to the relatively long soluble PEG and PNIPAM blocks. Figure 1B shows the hydrodynamic diameter distribution $f(D_h)$ of the resultant micelles. Clearly, the hydrodynamic diameter D_h of the micelles is much narrowly distributed, and the relative width μ_2/Γ^2 measured by DLS is as low as 0.04. The average D_h of the micelles is 41.7 nm, and it remains almost a constant when the copolymer concentration ranges from 0.10 to 2.0 mg/mL. The apparent radius of gyration R_g of the micelles is about 14.3 nm. Based on the specific refractive index increment d*n*/d*c* of the micellar solution, which is 0.172 mL/g, the weight-average molar mass M_w, 2.64×10^6 g/mol, and the apparent aggregation number N^{agg}, 205, of the micelles are calculated. The R_g/R_h value of the micelles,

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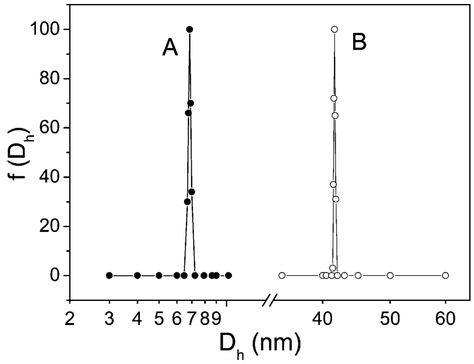

Figure 1. Hydrodynamic diameter distribution $f(D_h)$ of the unimers (A) and micelles (B) formed at pH 2.0 and 6.5 at 25 °C, respectively, where the copolymer concentration is 0.50 mg/mL.

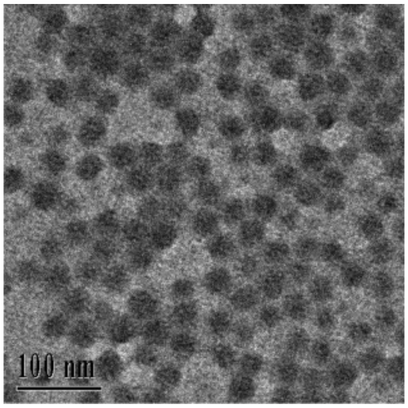

Figure 2. TEM image of the core−corona micelles formed at pH 6.5 at 25 °C, where the copolymer concentration is 0.50 mg/mL.

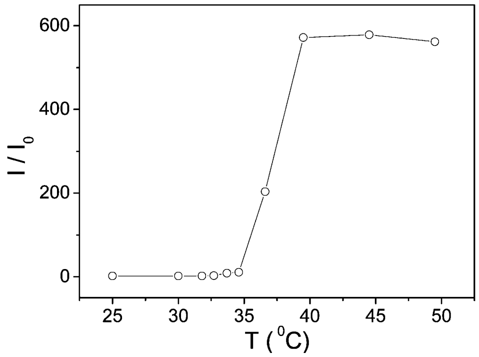

Figure 3. Ttemperature dependence of the normalized intensity I/I_0 of the copolymer solution at pH 2.0 with copolymer concentration at 0.50 mg/mL.

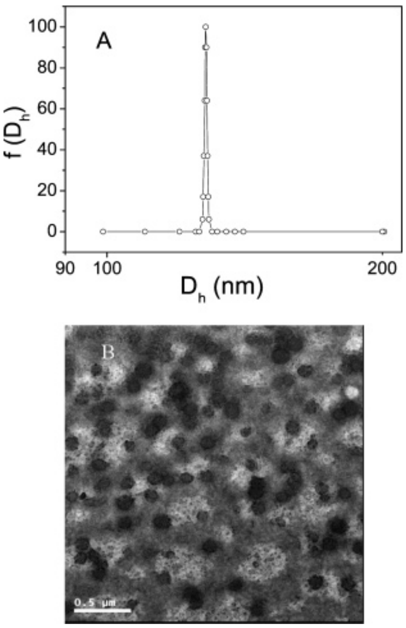

Figure 4. Hydrodynamic diameter distribution $f(D_h)$ (A) and TEM image (B) of micelles formed at pH 2.0 at 50 °C, where the copolymer concentration is 0.50 mg/mL.

which is about 0.68, suggests that the micelles are spherical.[14−16] The micelles are expected to have a core−corona structure, where the insoluble P4VP block forms the core and the soluble PEG and PNIPAM blocks form the corona. The core−corona micelles can further give response to temperature stimulus, which will be studied further in future. At pH < 5, the micelles of PEG$_{110}$-*b*-P4VP$_{35}$-*b*-PNIPAM$_{22}$ disassociate into unimers. The average D_h of the unimers is about 6.8 nm, the distribution of which is shown in Figure 1A.

Figure 2 shows the TEM image of the core−corona micelles. Clearly, the aggregates are uniform spheres with diameter about 30 nm. It should be noted that the D_h of the micelles measured by DLS are a little larger than those observed by TEM since the micelles are swollen in water, while TEM observation shows the dried aggregates.

Thermo-Responsive Micellization of PEG-*b*-P4VP-*b*-PNIPAM. Figure 3 shows the temperature dependence of the normalized intensity of the copolymer solution at pH 2.0. Clearly, the sharp increase of the scattering intensity implies occurrence of micellization. From Figure 3, the critical aggregation temperature of the copolymer, 34.6 °C, is calculated. Compared with the homopolymer of PNIPAM, the critical aggregation temperature is a little higher,[11] which is possibly due to the soluble PEG and P4VP blocks at pH 2.0.

The hydrodynamic diameter distribution $f(D_h)$ of the copolymer micelles formed at 50 °C at pH 2.0 is shown in Figure 4A. The micelles are expected to have a core−corona structure, where the insoluble PNIPAM block forms the core and the soluble PEG/P4VP blocks form the corona. The D_h of the micelles is about 130.2 nm. The R_g of the micelles is about 38.3 nm, and the R_g/R_h is about 0.60. The apparent weight-average molar mass M_w and the aggregation number N^{agg} of the micelles is 1.65×10^7 g/mol and 1.28×10^3, respectively. Figure 4B shows the TEM image of the micelles. Clearly, the aggregates are spheres with average diameter at about 100 nm. Compared with micelles formed at 25 °C at pH 6.5, the present micelles is much larger, which possibly suggests the present micelles are compound micelles or micellar clusters.[17]

The micelles mentioned above, which have a pH-sensitive P4VP/PEG corona, can further respond to pH change. When pH increases from 2.0 to 6.5, the D_h of the micelles decreases from 130.2 to 118.1 nm, as shown in Figure 5. The possible reason is that the stretching P4VP block collapse onto the PNIPAM shell of micelles when pH increases. The resultant micelles are expected to have a core−shell−corona structure,[18−20] where the insoluble PNIPAM block forms the core, the collapsed P4VP block forms the shell, and the PEG block forms the corona. The core−shell−corona micelles can further rearrange and convert into small micelles with D_h at about 41.2 nm, as shown in Figure 5C when temperature decreases from 50 to 25 °C. Clearly, the D_h of these

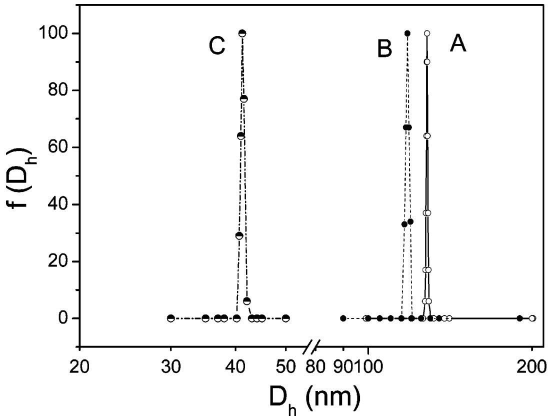

Figure 5. Hydrodynamic diameter distribution $f(D_h)$ of the compound core−corona micelles (A), the core−shell−corona micelles (B), and the core−corona micelles (C) formed at pH 2.0 at 50 °C, at pH 6.5 at 50 °C, and at pH 6.5 at 25 °C, respectively, where the copolymer concentration is 0.50 mg/mL.

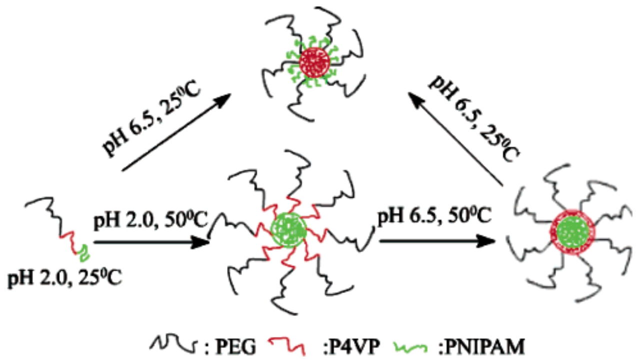

Figure 6. Scheme of the thermo- and pH-responsive micellization of PEG$_{110}$-*b*-P4VP$_{35}$-*b*-PNIPAM$_{22}$.

small micelles is almost the same as those shown in Figure 1B. The TEM image of these small micelles also shows that the micelles are spheres with diameter at about 30 nm. This suggests that the micelles shown in Figures 1B and 5C have the same structure.

Conclusively, thermo- and pH-responsive micellization of the triblock copolymer of PEG$_{110}$-*b*-P4VP$_{35}$-*b*-PNIPAM$_{22}$ and the structure of resultant micelles can be schemed out in Figure 6.

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Supporting Information Available: Text giving synthetic procedures for the triblock copolymer; figures showing ^{1}H NMR and IR spectra of GPC chromatogram of the triblock copolymer. This material is available free of charge via the Internet at http://pubs.acs.org.

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