Short-Life Core–Shell Structured Nanoaggregates Formed by the Self-Assembly of PEO-b-PAA/ETC (1-(3-Dimethylamino-propyl)-3-ethylcarbodiimide Methiodide) and Their Stabilization

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Core–shell structured polymeric nanoaggregates of various morphologies have raised great interest in the scientific literature.1 Among them, the water-soluble ones formed by double-hydrophilic block copolymers (DHBCs) in water are particularly attractive due to their potential applications in the fields of biological and medical sciences.2 Usually, the polymeric nanoaggregates are the results of the self-assembly of block copolymers in selective solvents.3 Although water is the common solvent for DHBCs under normal condition (room temperature and pH 7), it may become the selective solvent when the pH4 or the temperature is changed.5 So, in some cases, altering the pH or the temperature can lead to the self-assembly of DHBCs in water, resulting in the polymeric nanoaggregates being sensitive to the environmental changes. In addition, it is reported that the complexation of DHBCs in water with either the oppositely charged polymer chains6 or surfactants7 can also induce the self-assembly, producing water-soluble polymeric nanoaggregates as well. The complexation of DHBCs with surfactants has been especially focused on, since there are a wide variety of available surfactants for one’s choices and the composition of the resultant complexes is readily adjustable.8 Through introducing surfactants to the aqueous solutions of DHBCs, Kabanov and Eisenberg and Jerome et al. prepared water-dispersible spherical micelles, vesicles, and their mixtures.7 Considering that the complexes formed by single-tail surfactants are not stable enough to keep their integrity upon dilution in biological fluids, Kabanov and Eisenberg further stabilized them by chemically linking the surfactant components with each other.9

This paper deals with self-association of complexes of ETC (1-(3-dimethylamino-propyl)-3-ethylcarbodiimide methiodide) and PEO-b-PAA. ETC is a small molecular mass organic compound. It was selected for the following reasons: it can be molecularly solubilized in water and react with AA units promptly; it is the necessary catalyst to cross-link PAA with a water-soluble diamine at room temperature.10 This catalyzed cross-linking reaction was used to stabilize formed aggregates for the preparation of “SCK” particles.10a A more remarkable work,10a concerning the use of ETC and the cross-linking reaction, demonstrates a rod-to-sphere morphological transition, induced by the reaction between ETC and the PAA block in the shell of rod-like aggregates, and shows clearly the trapped intermediate morphology of the transition by subsequent cross-linking reaction with diamine. In our study, the reaction of ETC with the PAA block of molecularly dispersed PEO-b-PAA in water leads to the self-association, resulting in the aggregates with the morphologies of short rods, vesicles, encapsulated spheres, and long fibers. It is interesting to find that the aggregates have the unique feature of “autodissociation” and exist in the aqueous solutions only for 1–3 weeks. On the other hand, these aggregates can be readily stabilized by the ETC-catalyzed cross-linking reaction.

The block copolymer used for this study is PEO113-b-PAA70 (the subscripts indicate the average number of repeat units for each block; the polydispersity index of the precursor PEO113-b-PtBA70 measured by SEC is 1.20). Either the block copolymer or ETC can be molecularly dispersed in their respective aqueous solutions, while PEO113-b-PAA70 was mixed with ETC in water at a fixed polymer concentration of 0.5 mg/mL but with varying [ETC]/[carboxyl group] ratios (denoted as MR) of 0.5, 1.0 and 1.5, a bluish tint appeared simultaneously. The resultant solutions were measured by dynamic light scattering (DLS) 3–4 h after the mixing (it is proven by DLS measurements that after the duration, no remarkable changes were detected for the solutions in the subsequent 3–4 days). The characterization data are presented in Table 1 (line 1).

The data in Table 1 (line 1) indicate that the self-association took place after the mixing, leading to the formation of the aggregates with the sizes around 110 nm. The morphologies of the resultant aggregates were observed by transmission electron microscopy (TEM, the preparation of the specimens for TEM observations is described in the Experimental Section). The TEM images for different MR are shown in Figure 1. As is shown in Figure 1, parts a, b, and c, different morphologies of resultant aggregates were obtained corresponding to different values of MR. When MR is 0.5/1, the resultant aggregates are mainly of a short rodlike morphology with the aspect ratios between 2 and 5 (Figure 1a), leading to a relatively large value of PDI measured by DLS (0.25, Table 1). At MR of 1/1, vesicles with a wall of uniform thickness and with a relatively low PDI (0.13) are obtained (Figure 1b). In principle,10 when MR is 1.5/1, there should be a remarkable amount of ETC molecules free from reacting with the block copolymer. Nevertheless, it is found that these unreacted ETC molecules have a great effect on the behavior of the self-association, compared with that at MR 1/1. The self-association at MR of 1.5/1 results in nanoaggregates with the morphology of a solid sphere surrounded by a peripheral cycle (Figure 1c), and the solid sphere appears to be separated with the cycle. This morphology is different from that of core–shell micelles but similar to that of the encapsulated ones.12 It is noted that the average diameters of the vesicles (Figure 1b) and the aggregates shown in Figure 1c based on the TEM observations are 60 and 40 nm, respectively, smaller than that observed by DLS. A similar phenomenon was reported by Jerome et al. and was accounted for by the fact that the contrast of the PEO shell is too low to be seen by TEM.13 In addition, Chi Wu et al.14 proved that a core of a copolymer aggregate contained more than...
...the aggregates disappear. It is reported that the reaction of ETC with the acrylic acid groups may drive the self-association and the formation of a considerable amount of anhydride active intermediates and finally return to the acrylic acid functionalities again. As is indicated in Scheme 1, the production of acylisourea makes a part of PAA block be cross-linked aggregates, after dialysis. The solutions of cross-linked aggregates were further dialyzed against water. The \( D_h \) and PDI values of cross-linked aggregates after the dialysis are presented in Table 1, line 3. It is exhibited that little change due to the dialysis is found in the \( D_h \) values at MR of 0.5/1, 1/1, and 1.5/1 and the PDI value at MR of 0.5/1. Remarkable changes due to the dialysis are detected in the PDI values at MR of 1/1 and MR of 1.5/1. These values drop from 0.18 and 0.21 to 0.09 and 0.14, respectively. These changes may be related to the release of ETC from the aggregates due to the dialysis. The release of the ETC also leads to the decrease in the contrast of the aggregates in TEM image (Figure 2a).

In addition, the self-assembly of ETC/PEO-b-PAA at the concentration of the block copolymer of 0.1 mg/mL and MR of 1/1 leads to the formation of long nanofibers of \( \sim 30 \) nm wide and tens micrometers long or even longer (Figure 2b). This fiberlike morphology was viewed by TEM and AFM. The fiberlike aggregates can be readily stabilized by the ETC-catalyzed cross-linking reaction as well.

It is well-known that the self-assembly of block copolymers in selective solvents can result in nanoaggregates of different morphologies such as spheres, vesicles and wormlike micelles. According to Eisenberg, the formation of different morphologies can be explained by considering a balance between three major forces acting on the system: the stretching of the core-forming blocks, the interfacial tension between the core and the solvent, and the intercorona repulsion. In the present study, the change in MR will result in variation in the composition of the core of the aggregates, leading to alteration in the Coulombic interactions within and...
the hydrophilicity of the core. This alteration should be responsible for the morphological transition. The self-association and morphological transition of a diblock copolymer driven by a similar mechanism was reported by Jerome et al.6d In addition, when MR increases to 1.5/1, each of the resultant aggregates in the TEM image (Figure 1c) contains a solid sphere in the center. It was also reported for the complexes of block copolymers and surfactants that the excess surfactants may be encapsulated.17 So, we are inclined to think that in this case the excess ETC molecules are encapsulated as well. The encapsulated ETC molecules and the PAA connected ones maybe separated during evaporation, as is indicated by an empty gap between them. While the concentration of PEO-b-PAA is 0.1 mg/mL, at MR of 1/1, long nanofibers are produced. This effect of dilution may be related to the concentration sensitive equilibriums between the reactants and the products of the mentioned reactions. Further study on the mechanism is needed.

In conclusion, the self-association takes place in the aqueous solution of PEO-b-PAA/ETC at the early stage of the reaction between PAA and ETC. At the concentration of PEO-b-PAA of 0.5 mg/mL, when MR is 0.5/1 and 1/1, rodlike aggregates and vesicles were obtained respectively; while MR is 1.5/1, the excess ETC molecules maybe encapsulated and the resultant aggregates are with the morphology of a solid sphere encapsulated by a peripheral circle in the TEM image. The self-association at MR of 1/1 and the concentration of the block copolymer of 0.1 mg/mL leads to the formation of long nanofibers. Because of the reaction cycle of ETC with PAA, the aggregates have a limited life in water. After staying unchanged for several days in the aqueous solutions, the aggregates dissociate and finally disappear 1–3 weeks after their formation. While through the ETC-catalyzed cross-linking reaction, the aggregates can be stabilized. Except for the vesicles, the morphologies of short rods, encapsulated spheres, nanofibers are seldom reported for the systems of DHBCs/small molecules. Besides, the biocompatible and water-soluble properties along with the autodissociation feature of the un-cross-linked aggregates will make this system very promising in addressing various theoretical and practical problems.

Experimental Section

The PEO113-b-PtBA70 was prepared from hydrolysis of a PEO113-b-PtBA copolymer through treating this precursor with trimethylsilyl iodide and subsequently with aqueous acid. The precursor was synthesized by bulk ATRP using PEO-Br as the macroinitiator.18 The polydispersity index of the precursor is 1.20, measured by SEC.

The specimens for TEM observations were prepared 3 to 4 h after the mixing of ETC with the PEO-b-PAA by immersing a copper grid, which was coated with thin films of Formvar and carbon successively, into a micelle solution. Then the copper grid was freeze-dried in vacuo for 2 days.

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References and Notes


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