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Supramolecular Self-Assembly of Multiblock Copolymers in Aqueous Solution

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A unique pH-dependent phase behavior from a copolymer micellar solution to a collapsed hydrogel with micelles ordered in a hexagonal phase was observed. Small-angle neutron scattering (SANS) was used to follow the pH-dependent structural evolution of a solution of a pentablock copolymer consisting of poly(diethylene glycol) (PDEAEM, 32b-PPO, 54b-PPO, 54b-PDO, 78b-PDEAEM, 32) between pH 3.0 and pH 7.4. Between pH 3.0 and pH 7.4, we observed the presence of charged spherical micelles. Increasing the pH of the micelle solution above pH 7.4 resulted in increasing the size of the micelles due to the increasing hydrophobicity of the PDEAEM blocks above their pKₐ of 7.6. The increase in size of the spherical micelles resulted in a transition to a cylindrical micelle morphology in the pH range 8.1–10.5, and at pH > 11, the copolymer solution undergoes macroscopic phase separation. Indeed, the phase separated copolymer sediments and coalesces into a hydrogel structure that consists of 25–35 wt% water. Small-angle X-ray scattering (SAXS) clearly indicated that the hydrogel has a hexagonal ordered phase. Interestingly, the process is reversible, as lowering of the pH below 7.0 leads to rapid dissolution of the solid into homogeneous solution. We believe that the hexagonal structure in the hydrogel is a result of the organization of the cylindrical micelles due to the increased hydrophobic interactions between the micelles at 70 °C and pH 11. Thus we have developed a pH-/temperature-dependent, reversible hierarchically self-assembling block copolymer system with structures spanning nanoscale to microscale dimensions.

1. Introduction

Nature exhibits a variety of self-assembled structures that researchers have tried to mimic to facilitate a bottom-up approach to materials design and fabrication. In particular, the self-assembly of organic molecules and synthetic polymers have been extensively investigated in recent years. These studies reported nanoscale to mesoscale morphologies such as spherical or cylindrical micelles, vesicles, ribbons, fibers, bowls, and toroids.

Of particular interest are stimuli-responsive materials that allow for the directed or modulated self-assembly on the nanoscale in aqueous solution. Materials with stimuli-responsive physical properties have potential uses in food, cosmetics, and drug delivery applications. In some instances, the presence of nanoscale morphologies formed through self-assembly translates into macroscopic phenomena such as the formation of a hydrogel phase. Hydrogel forming, block, and star copolymers have been synthesized that exhibit either temperature- or pH-responsive behavior by incorporation of blocks that exhibit lower critical solution temperature (LCST) and polyelectrolyte properties. The ability to control the block composition and copolymer architecture of these wholly synthetic materials allows for tuning the stimuli-responsive properties of these materials. Peptide-based materials have also been shown to form hydrogel networks in response to physical or chemical stimuli. These materials utilize the primary modes of self-association in peptides, the hydrophobic aggregation of β-strands and coiling of helices, to form long-range networks that lead to hydrogel formation. In this work, we have developed new synthetic block copolymers that exhibit either temperature- or pH-responsive behavior by incorporation of blocks that exhibit lower critical solution temperature (LCST) and polyelectrolyte properties.

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that respond to both pH and temperature, providing the ability to tune the nanoscale and macroscopic structures formed using two independent environmental stimuli, giving rise to unique phase behavior and formation of dehydrated elastic solids by self-assembly that has not been seen in other systems.

The synthesis of amphiphilic pentablock copolymers consisting of poly((diethylaminoethyl methacrylate)-b-(ethylene oxide)-b-(propylene oxide)-b-(ethylene oxide)-b-(diethylaminoethyl methacrylate)) (PDEAEMb55-PEO100b-PPO65b-PEO100b-PDEAEM23), which exhibits temperature- and pH-induced micelle self-association and gelation, was recently reported. The pentablock copolymer was designed to undergo thermoresponsive micellization due to the presence of the PPO block, which exhibits an LCST around 8 °C, and pH-responsive micellization due to the polycationic PDEAEM blocks. At physiological temperatures and pH conditions, aqueous solutions of the pentablock copolymers formed physical hydrogels due to micellar packing and interdigititation. This unique combination of properties makes the pentablock copolymer an attractive material for stimuli-responsive drug delivery applications. The hydrogel phase formed at physiological conditions maintains a constant weight fraction of water during the gelation process. Here, we describe the reversible temperature- and pH-responsive self-assembly of this pentablock copolymer in aqueous solutions to form organized elastic solids with substantially lower water content than the original copolymer solution. At pH 11 and 70 °C, the network of pentablock micelles precipitates and contracts as it expels water to reach the new equilibrium, resulting in a shrunk hydrogel that maintains the cross-sectional shape of the vial it is contained in. This phase transition was attributed to increasing hydrophobicity of the copolymer at conditions above the pKs of the PDEAEM blocks and the LCST of the PEO blocks. Herein we report a detailed investigation of origins and structure of this hydrogel phase.

2. Experimental Section

2.1. Sample Preparation. A pentablock copolymer poly((diethylaminoethyl methacrylate)-b-(ethylene oxide)-b-(propylene oxide)-b-(ethylene oxide)-b-(diethylaminoethyl methacrylate)) (PDEAEMb55-PEO100b-PPO65b-PEO100b-PDEAEM23) (Mn = 22,000 g/mol and PDI = 1.34), shown in Figure 1, was synthesized by atom transfer radical polymerization (ATRP). Details of the synthesis and characterization of these block copolymers were described previously.

The self-assembled macroscopic solids were prepared by first dissolving the copolymer at 5 wt % in water at pH 3. The solution was cooled overnight at 4 °C to ensure complete dissolution. The solution was titrated at room temperature to pH 11 with 2 mol/L HCl gas detector and neutrons with wavelengths in the range of 0.5 Å to 1 Å. Copolymer solutions were sealed in Suprasil cylindrical cells with 2 mm path length for the SANS measurements. A liquid flow thermostat was used to control the temperature to within ±1 °C. The scattering data were corrected for empty cell and solvent scattering, detector sensitivity, and sample transmission. The differential scattering cross section I(Q) was placed on an absolute scale in units of cm⁻¹b by using a secondary standard of 50% deuterated polystyrene, whose absolute scattering cross sections is known.

2.3. Small-Angle X-ray Scattering. SAXS measurements were carried out on the instrument at the 12-ID beam line at the Advanced Photon Source. A 15 cm × 15 cm CCD detector was used to measure the intensity of scattering, and the transmitted beam intensity was measured using a photodiode. Samples were held in quartz capillaries with 1.5 mm outer diameter and 0.01 mm wall thickness. Data were collected at 0.5 s exposure times at incident beam energies of 12 keV (λ = 1.035 Å). The distance between the detector and the sample was 2 m. The scattering data were appropriately corrected and azimuthally averaged to obtain I(Q). The scattering intensity data were normalized to an absolute scale with a polyethylene standard. The one-dimensional data for five exposures were averaged for each sample. Scattering intensity from an empty quartz capillary and fitted power-law scattering in the low Q region was subtracted from the sample data.

2.4. Dynamic Mechanical Analysis. A Perkin-Elmer 7e dynamic mechanical analyzer (DMA) was used to measure the thermal/mechanical properties of pentablock copolymer and self-assembled solids. A cup-and-plate geometry (5 mm diameter) was utilized, and the sample was tested in compression, in controlled stress mode, at 1 Hz. The static and dynamic forces applied were 25 and 20 mN, respectively. Samples were heated from 10 to 90 °C at 3 °C/min.

3. Results and Discussion

Temperature- and pH-responsive amphiphilic copolymers are a new class of materials with interesting properties. The combination of polyelectrolyte and hydrophilic blocks that exhibit a lower critical solution temperature (LCST) results in multi-responsive copolymers. The pentablock copolymer combines the LCST properties of the Pluronic F127 triblock copolymer with PEO and PPO blocks and the pH-responsive properties of a cationic polyelectrolyte block of PDEAEM. Aqueous solutions of PEO100-PPO55-PDEAEM triblock copolymers (MW = 12,600) form micelles and liquid crystal mesophases resulting in rigid gels as a function of temperature and concentration due to the LCST of the PPO block around 8 °C. PDEAEM is a cationic polymer that exhibits a sharp pH-sensitive solubility behavior.

The degree of ionization of the pendant amines of the PDEAEM
chains is highly dependent on the solution pH. The amines are cationic below the pK\textsubscript{a} of the polyelectrolyte and become deprotonated when the solution pH is greater than the pK\textsubscript{a}. Deprotonation of the tertiary amine pendant group of the DAEAEM unit at pH \( \approx 7.6 \) causes the PDAEM chain to transition from a highly hydrated expanded chain to a collapsed hydrophobic state.\textsuperscript{18} In aqueous solutions, the pentablock copolymer exhibits a thermoreversible sol–gel phase transition as well as pH-responsive micellization behavior.\textsuperscript{18}

SANS experiments were conducted to investigate the pH-dependent evolution of micellar structure in the pentablock copolymer solutions. Figure 2 shows the scattering data from 2 wt % copolymer solutions at pH 7.4, 7.7, 8.1, and 10.5 and at 75 °C. The scattering data collected at pH 3 (not shown) were identical, within instrumental error, with the data collected at pH 7.4. This indicates that in a wide pH range below the pK\textsubscript{a} of the PDEAEM blocks, the scattering intensity at low \( Q \) exhibited a negative slope, and the intensity peaks observed at pH 7.4 and 7.7 were no longer distinguishable. This is an indication of the further aggregation of micelles and agrees with previous light scattering studies that indicated the aggregation number of micelles increases dramatically above the pK\textsubscript{a} of the PDEAEM blocks.\textsuperscript{20} At pH 10.5, the scattering intensity in the low \( Q \) region exhibited a \( Q^{-1} \) power-law relationship that implies the presence of cylindrical micelles in solution. Figure 3 shows the modified Guinier plot for the rodlike particles of the SANS data for the solution at pH 10.5 and at 75 °C. The presence of a linear region with a negative slope is a good indication of the presence of cylindrical micelles. The measured cross-sectional radius of gyration of the rodlike micelles, \( R_g \), was 44.5 ± 0.4 Å, which corresponds to a radius of 62.9 ± 0.6 Å. The bend over in the low \( Q \) region indicates the presence of cylindrical micelles. The presented morphology of the pentablock copolymer transitioned from spherical to cylindrical micelles through a mechanism of micellar aggregation due to the increasing hydrophobicity of the PDAEM blocks with increasing pH.

At pH 11, the solution became turbid due to precipitation of the copolymer micelles. This precipitation occurred regardless of the temperature of the solution. At temperatures below 70 °C, the precipitant formed an easily disturbed layer and remained indefinitely. Upon heating the suspension of precipitated copolymer above 70 °C, the precipitate was observed to coalesce and assemble into an elastic solid hydrogel. The self-assembled solid was found to be a relatively dehydrated with only 25–35 wt % water. Figure 4 illustrates the stages of the self-assembly of the macroscopic solid. Interestingly, the shape of the macroscopic solids retained the cross-sectional shape of the vial in which they were formed, but their dimensions were smaller as revealed by the short cylindrical-shaped hydrogel in Figure 4. The process illustrated in Figure 4 occurred over the course of 24 h. We attribute the coalescence and self-packing of the precipitated copolymer micelles occurring above 70 °C to the much reduced solvating power of water for the PEO blocks under these conditions.\textsuperscript{27} That is, upon increasing the temperature of the copolymer suspension above 70 °C, the PEO blocks become more hydrophobic, leading to further self-association of the precipitated micelles into an organized solid. The hydrogel to 54.3 nm. At pH 8.1 the intensity of scattering at low \( Q \) continued to increase, indicating further aggregation of micelles. The scattering intensity at low \( Q \) exhibited a negative slope, and the intensity peaks observed at pH 7.4 and 7.7 were no longer distinguishable. This is an indication of the further aggregation of micelles and agrees with previous light scattering studies that indicated the aggregation number of micelles increases dramatically above the pK\textsubscript{a} of the PDEAEM blocks.\textsuperscript{18} At pH 10.5, the scattering intensity in the low \( Q \) region exhibited a \( Q^{-1} \) power-law relationship that implies the presence of cylindrical micelles in solution. Figure 3 shows the modified Guinier plot for the rodlike particles of the SANS data for the solution at pH 10.5 and at 75 °C. The presence of a linear region with a negative slope is a good indication of the presence of cylindrical micelles. The measured cross-sectional radius of gyration of the rodlike micelles, \( R_g \), was 44.5 ± 0.4 Å, which corresponds to a radius of 62.9 ± 0.6 Å. The bend over in the low \( Q \) region indicates the presence of cylindrical micelles. The presented morphology of the pentablock copolymer transitioned from spherical to cylindrical micelles through a mechanism of micellar aggregation due to the increasing hydrophobicity of the PDAEM blocks with increasing pH.

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Figure 4. (A) A 5 wt % solution of pentablock copolymer, PDEAEM$_{25}$—PEO$_{100}$—PP$_{0.65}$—PEO$_{100}$—PDEAEM$_{25}$, at room temperature. Adjusted from pH 3 to 10, resulting in an immediate increase in turbidity. (B) Upon heating to 70 °C the copolymer precipitant begins to sediment. (C) After 24 h the copolymer has assembled into a hydrogel. (D) The hydrogel (25–35 wt % water) is mechanically stable at room temperature in solution and can be removed from solution without losing its shape.

Figure 5. SAXS of self-assembled solid (□) and pentablock copolymer melt (□) annealed at 70 °C for 24 h. The scattering intensity data from the melt was multiplied 20× for clarity. Power-law scattering in the low Q region was subtracted to enhance the scattering peaks.

Exhibited very little temperature sensitivity after formation, exhibiting a small amount of swelling upon cooling to room temperature. The hydrogel was easily removed from solution and was mechanically stable at room temperature out of solution. However, the self-assembly behavior was found to be completely reversible with pH. When the pH was lowered to 7.0, the hydrogel dissolved again, but could be re-formed by increasing pH and temperature. $^1$H NMR and gel permeation chromatography were used to confirm the absence of polymer chain decomposition during this process.

SAXS was used to investigate the ordered phases in the macroscopic self-assembled solid. SAXS data from the self-assembled solid, shown in Figure 5, exhibited distinct diffraction peaks indicative of a hexagonally packed crystal structure \{1: $3^{1/2}; 4^{1/2}; 7^{1/2}; 9^{1/2}$\}, and the first-order peak corresponds to a d spacing of 151 Å. We interpret this to be due to the cylindrical micelles organized into an ordered hexagonal phase. This is in distinct contrast to the morphology of the precipitated copolymer in the bulk state, annealed for 24 h at 70 °C, that exhibited three broad peaks at $Q = 0.020, 0.036$, and 0.072 Å$^{-1}$ (Figure 5). We could not unambiguously attribute this scattering pattern to any specific ordered structure, and further scattering experiments will be necessary to characterize the morphology of the pentablock copolymer bulk phase. However, the ratio of 2 for the Q values of the second and third peaks may indicate the presence of a lamellar structure with a d spacing of 175 Å. Thus the organization of the bulk copolymer is quite different from that in the self-assembled hydrogel.

Dynamic mechanical analysis was used to investigate the mechanical properties of the self-assembled solid. The elastic storage modulus of the self-assembled solid and that of the bulk pentablock copolymer are shown in Figure 6. The bulk copolymer sample melts at 35 °C as noted by the loss of elastic properties, whereas the self-assembled solid maintained mechanical stability up to 90 °C. This represents a remarkable shift in thermomechanical properties through an entirely self-directed self-assembly process. The increase in melting temperature is attributed to the presence of hexagonally packed cylindrical micelles forming a fibril-like crystalline phase. In an attempt to understand the role that elevated temperature plays in the self-assembly process, the precipitated copolymer was centrifuged at room temperature. The resulting granular pellet did not exhibit the elastic properties of the solid hydrogel phase formed at 70 °C.

These studies help elucidate the mechanism of self-assembly of the polymer at multiple length scales. The pentablock copolymer, in the charged state, forms micelles above a critical micellization temperature (CMT) due to the LCST of the PPO block. Above the LCST of the PPO block, spherical micelles consisting of a compact hydrophobic PPO core enclosed in a two-layer corona of PEO and charged PDEAEM form. The CMT of the ionized pentablock is attributed to the same hydrophobic driving force resulting in micellization of Pluronic copolymers. Micellization of the pentablock copolymer could also be induced by increasing the pH of the solution above the pK$_a$ of the PDEAEM block. Further increasing the pH of the pentablock copolymer solutions resulted in increasing the size of the micelle aggregates, followed by the transition to cylindrical micelle morphology as observed with SANS. As the size of the spherical micelles increased with increasing pH, the energetic penalty of stretching chains in the core of the micelle resulted in a transition to cylindrical micelles. This is consistent with molecular dynamics simulation studies of these systems showing that changes in hydrophobicity of the individual blocks relative to each other can lead to a shift from spherical to cylindrical micelles. Further growth and aggregation of the cylindrical micelles resulted in precipitation of the micelle clusters. At 70 °C, where the assembly of the solid hydrogel was observed, the increasing hydrophobicity of the PEO blocks at this temperature caused the aggregation of the cylindrical micelles into a hexagonal packed morphology. The ability to tailor such self-assembly behavior by two different parameters, temperature as well as pH, provides a powerful tool to control the morphology of the self-assembled solid.
method to tune the self-assembly behavior. This unique long-range reversible self-assembly behavior in solution, where the macroscopic solid exhibits a very ordered nanostructure, is important in bottom-up approaches for materials design.

4. Conclusions

In this paper we have demonstrated a unique transition between a homogeneous micellar solution and a phase-separated, self-assembled elastic solid phase. Aqueous solutions of the pentablock copolymer at pH < 7.5 formed charged spherical micelles as determined by SANS. Increasing the pH above 7.6 caused the cationic PDEAEM blocks to deprotonate and become hydrophobic. This alteration of the hydrophobic/hydrophilic balance of the block copolymer resulted in increased micelle size and a transition from spherical to cylindrical micelles. At pH 11 the copolymer micelles precipitated from solution. Further self-assembly of the cylindrical micelles into ordered hexagonal phase occurred at even higher temperatures due to the decreased solubility of the PEO blocks in water above 70 °C. The ability to trigger this unique reversible self-assembly at multiple length scales ranging from nanoscale to macroscale by changing pH and temperature conditions offers exciting possibilities in bottom-up approaches to materials design and fabrication.

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