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Reversible "Self-Locked" Micelles from a Zwitterion-Containing Triblock Copolymer†

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Introduction

Amphiphilic, zwitterionic copolymers are a class of macromolecules which have unique behavioral characteristics arising from interaction of the constituent charged segments with ionic species in the surrounding environment. Conformational changes in response to external stimuli including ionic strength and pH have been studied extensively for the two major classes of polyzwitterions, namely polyampholytes and polybetaines.[1,2] Interpolyelectrolyte complex formation and the "anti-polyelectrolyte" effect in aqueous media are two specific characteristics which can be capitalized on for construction of technologically advanced materials. The ability to synthesize precise polyzwitterionic block, star, and graft copolymers with potential for assembly into organized structures in water has until recently been limited. However, the advent of controlled radical polymerization (CRP) techniques[3,4] and more specifically reversible addition−fragmentation chain transfer (RAFT) polymerization[5] which can be conducted in a facile manner directly in water[6] now allows the level of control of molecular weight, segmental sequence, polydispersity and monomer selection necessary for regulated assembly.

Although relatively few studies utilizing RAFT-synthesized zwitterionic block copolymers have appeared in the literature,[7−14] unique biocompatible and stimuli-responsive characteristics in aqueous media suggest untapped potential for such materials in biologically relevant applications. Technologically promising cross-linking methodologies,[15] some of which are reversible, have also been developed within the past few years that allow "locking" of assembled (multimeric) nanostructures for delivery of diagnostic and therapeutic agents. In many cases disassembly can be triggered at specific sites in response to physiological conditions, leading to both controlled release of active agents and subsequent biological elimination of the constituent unimers.

As part of our continuing efforts to develop effective cross-linking chemistries in aqueous media,[16−20] we describe in this communication reversible "self-locked" (cross-linked) micelles assembled from a pH-responsive, zwitterionic triblock copolymer. We exploit the versatility of the aqueous RAFT process utilizing a trithiocarbonate chain transfer agent and monomers with zwitterionic, anionic, and neutral functionality which can be polymerized directly in water without the need of protecting groups.[6,21]

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Results and Discussion

A well-defined triblock copolymer composed of a permanently hydrophilic poly(*N,N*-dimethylacrylamide) (PDMA) block, a salt-responsive poly(3[2-(*N*-methyl acrylamido)ethyldimethylammonio]propanesulfonate) (PMAEDAPS) middle block and a pH-responsive poly(3-acrylamido-3-methyl butanoic acid) (PAMBA) block was prepared as illustrated in Scheme 1 by aqueous RAFT polymerization. *S*-ethyl-*S*′-(α,α′-dimethyl- α′′-acetic acid)trithiocarbonate (EMP) was chosen as the chain transfer agent since it works quite well with acrylamido monomers, affording excellent control over molecular weight and polydispersity, resisting hydrolytic degradation, and allowing rapid monomer conversion at low temperatures.[6,21] The $PDMA_{102}$-*b*-$PMAEDAPS_{64}$-*b*-$PAMBA_{69}$ triblock was prepared by first synthesizing the PDMA macroCTA and sequentially blocking with MAEDAPS and AMBA. The chain extension polymerizations were carried out in 0.5 M NaCl aqueous solution in order to prevent precipitation of the block copolymers. Molecular weights and PDIs of the PDMA macroCTA ($M_n = 10\,300$ g mol^{-1}, PDI = 1.05), the intermediate diblock ($M_n = 28\,200$ g mol^{-1} PDI = 1.04) and the final triblock ($M_n = 40\,000$ g mol^{-1}, PDI = 1.03) were obtained from MALLS−SEC analysis. Details of the synthesis and characterization are described in the Experimental Section.

Scheme 2 illustrates the aqueous solution behavior of this responsive system. Above pH 4.6 and in the presence of 0.5 M salt, the triblock copolymer is molecularly dissolved and exists in unimeric form. Lowering solution pH to a value below 4.6 leads to the formation of multimeric micelles. Under these conditions, the AMBA block that forms the micelle core is protonated and hydrophobic while the DMA and MAEDAPS blocks remain soluble and are in the corona of the micelle. The added salt disrupts the electrostatic interaction of the zwitterions allowing the MAEDAPS middle block to have an extended, more hydrated conformation. Removal of the salt by dialysis allows the zwitterionic moieties of the polybetaine segments to interact, resulting in "self-locking" of the structure. (Here, we use the term "self-locking" to clearly distinguish this process from cross-linking methods that require introducing an extrinsic cross-linking agent in order to maintain nanostructural integrity.) This cross-linking can be readily reversed by introduction of electrolyte at physiological pH.

Previously our group and others have reported shell cross-linking of charged block copolymer nanostructures by formation of interpolyelectrolyte complexes (IPECs),[15,17,18,22] for example, by adding a positively charged polyelectrolyte to a negatively charged corona of an assembled polymeric micelle or vesicle. Unlike their classical, covalently cross-linked counterparts, both IPEC complexes and the "self-locking" polybetaine-based systems reported here can be disassembled to their unimeric states by simply increasing ionic strength. However, an advantage of using betaine-containing triblock copolymer is that the hydrophilic, sterically stabilized corona present throughout the self-cross-linking process appears to preclude undesirable interparticle aggregation often observed with the interpolymer complexes.[17,18,22]

The formation of "self-locked" (cross-linked) micelles was accomplished as follows: the triblock copolymer (0.1 wt %) was first dissolved in 0.5 M NaCl solution at pH 7 and sequentially dialyzed against (i) 0.5 M NaCl solution at pH 7 (1 day) to ensure complete dissolution, (ii) 0.5 M NaCl solution at

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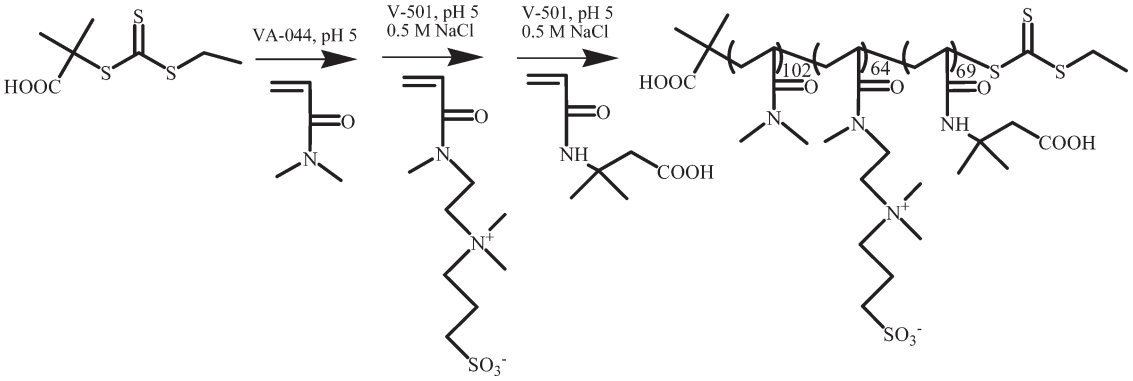
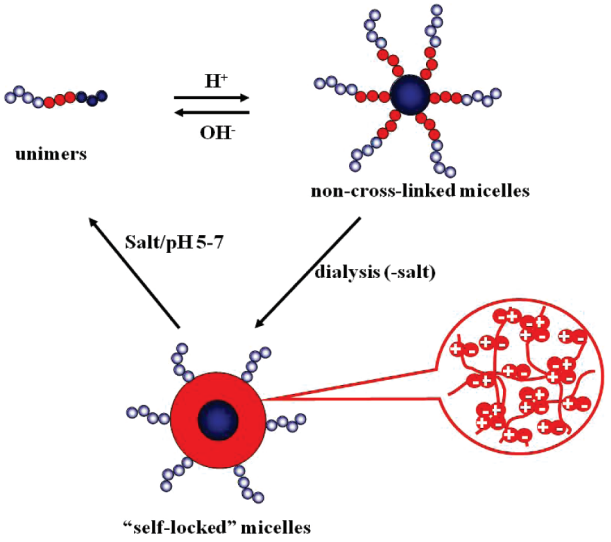
Scheme 1. Aqueous RAFT Polymerization $PDMA_{102}$-*b*-$PMAEDAPS_{64}$-*b*-$PAMBA_{69}$ Triblock Copolymer



Scheme 2. Reversible Self-Assembly of "Self-Locked" Micelles of $PDMA_{102}$-*b*-$PMAEDAPS_{64}$- *b*-$PAMBA_{69}$ Triblock Copolymer



pH 4 (1 day) to protonate the AMBA block and promote self-assembly, (iii) decreasing NaCl concentrations in pH 4 solutions (3 days), and (iv) DI water with pH adjusted to 4 (3 days) to finally obtain the "self-locked" micelles. Figure 1 shows the average hydrodynamic diameters (D_h) as determined by DLS after each stage of the above process. At pH 7, the triblock copolymers exist as unimers (a) having hydrodynamic diameters of approximately 10 nm while the micelles have unimodal, nearly identical sizes of approximately 35 nm before (b) and after (d) completion of cross-linking. (We have also observed the same sizes and size distributions from the assembly of 1.0 wt % solutions of the triblock copolymer. Temperature changes over the range 20 to 60 °C have no effect on the micelle dimensions.) Upon adjusting the pH of the solution containing the "self-locked" micelles to 6 (deprotonating the AMBA units), the assembly temporarily remains intact, but slowly dissociates into unimers in 2−3 days. By contrast, addition of salt at solution pH ranging from 5 to 7 results in immediate disassembly to the unimers (e) shown by the dashed line in Figure 1.

The importance of the balance of segments in the triblock polymer is also demonstrated during the self-locking process as shown in Figure 1. Micelles formed at pH 4 in 0.5 M NaCl have nearly identical dimensions to the "self-locked" micelles following salt removal by dialysis as previously mentioned. Adjustment of pH from 4 to 6 in the latter stages of dialysis, which might be expected to yield relatively larger dimensions due to ionization of the AMBA block, serves to decrease D_h, if only by a few nm. We originally proposed that changes in the core volume might be insignificant due to relatively short AMBA block as balanced by the nonionic and betaine blocks. An alternative explanation based on strongly interacting anionic/zwitterionic blocks in the absence of salt, previously postulated for styrene-based sulfonate/sulfobetaine copolymers, was suggested by a reviewer.[12]

It is important to note that the presence of the neutral, hydrophilic DMA sequence and its composition relative to the nearly equal number of acidic and betaine blocks are key to the stimuli-reversible assembly observed. First of all, the 102:64:69 experimentally determined ratio of DMA:MAEDAPS:AMBA units in the respective blocks confers water solubility at pH 7 to the unimers in 0.5 M NaCl. The pH dependence on aggregation behavior of the triblock copolymer in water was followed by DLS (Supporting Information, Figure S1). Unimers with D_h of ~10 nm are observed at neutral pH and maintain that size as pH is progressively lowered; at pH 4.6 (close to the pK_a of the AMBA block[23]) a sharp transition occurs; assembled structures ranging in size from 30 to 35 nm form as pH is further lowered. The relatively hydrophobic MAEDAPS units at progressively lower ionic strength likely contribute to some reorganization of the micelle core initially formed by protonated AMBA segments.

It is also instructive that the precursor $PDMA_{102}$-*b*-$PMAEDAPS_{64}$ diblock copolymer in aqueous saline solutions will form aggregates upon dialysis, behavior anticipated from poorly hydrated zwitterionic blocks upon removal of salt. These aggregates, however, have bimodal size distributions (for example see Figure S2 of the Supporting Information) which are not consistent in size or composition. This behavior contrasts the facile formation of the uniform self-assembled micellar structure from the triblock which we attribute to the sufficiently hydrated DMA block which prevents intermicellar zwitterionic interactions.

The ratio of hydrophilic to hydrophobic components of a copolymer determines the shape of self-assembled nanostructures.[24] The apparent radius of gyration, R_G, of the micelles is 12.5 nm as shown in the Zimm plot (Figure S3, Supporting Information). Using the same polymer solutions, the corresponding average apparent hydrodynamic radius, R_H, obtained from DLS is 15.0 nm. The ratio R_G/R_H (0.83) is indicative of spherical or micellar structure which is the expected shape based on the relative block lengths of the triblock copolymer.[25−28] From the Zimm plot and the molecular weight of the unimers, the aggregation number for the self-assembled micelles was calculated to be 29.

The self-assembly of the triblock copolymer was followed using ^{1}H NMR spectroscopy (Figure 2). For the diblock copolymer precursor, there are no discernible differences in the spectra of the unimers (with the added salt) and aggregates (without salt). The signals attributed to protons in the MAEDAPS block decrease in intensity but are still prominent in the solution

containing the aggregates. The zwitterionic block that is responsible for aggregation of the diblock copolymer is thus sufficiently solvated to not restrict motion on the NMR time scale. This observation is in accordance with a previously reported zwitterionic copolymer system.[8] In the case of the triblock copolymer,

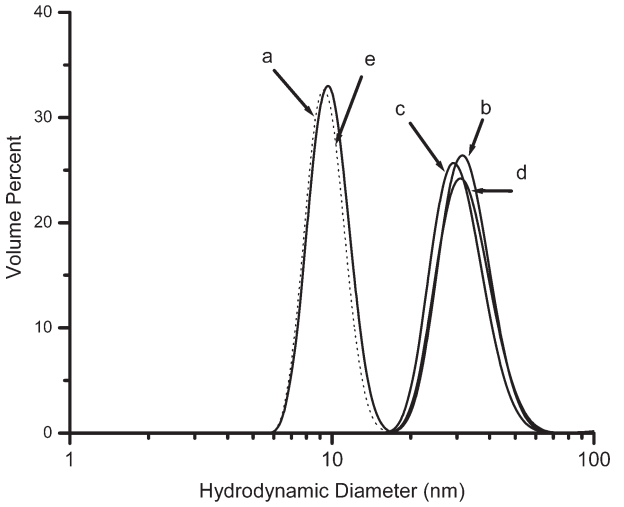


Figure 1. Hydrodynamic diameter (D_h) distribution of triblock copolymer (0.1 wt %): (a) unimers (0.5 M NaCl at pH 7), (b) noncross-linked micelles (0.5 M NaCl at pH 4), (c) "self-locked" micelles at pH 4 (no salt), (d) "self-locked" micelles at pH 6 (no salt), and (e) after addition of salt to "self-locked" micelles at pH 6−7.

however, when micelles are formed, the signals due to the AMBA block are significantly attenuated and the associated resonances broaden and shift upfield. As with the diblock, the signals due to the MAEDAPS block of the shell cross-linked micelles are also visible.

The formation of hydrophobic domains during micelle formation was also investigated by fluorescence spectroscopy using pyrene and 8-anilino-1-naphthalenesulfonic acid (ANS). Pyrene is a hydrophobic probe that shows a red shift in its excitation spectra and a change in the relative intensities of its emission bands, while ANS exhibits a blue shift accompanied by an increase in its emission intensity when confined within a more hydrophobic environment.[28−32] The pyrene excitation band shifts from 330 to 337 nm in the presence of triblock copolymer at pH 7 (Figure S4 in the Supporting Information). However, the excitation spectrum is only slightly red-shifted when the micelles are formed at pH 4. The ratio of I_3 and I_1 in the pyrene emission spectrum as shown Figure 3a increases from 0.62 to 0.77 when solution pH was adjusted from 7 to 4. This increase in the intensity ratio signifies a change in polarity of the immediate surroundings of the probe which can be correlated to micelle formation.[32] Zwitterionic aggregates do not favor solubilization of the highly hydrophobic probe,[8] and hence, it can be postulated that the pyrene preferentially goes into the core of the triblock copolymer micelle which is formed by the protonated AMBA block. When ANS is added to a solution containing preassembled triblock copolymer micelles at pH 4, the fluorescence spectrum is similar to that at pH 7 where the copolymers exist as unimers. In this case, the probe is likely situated on the zwitterionic shell of the

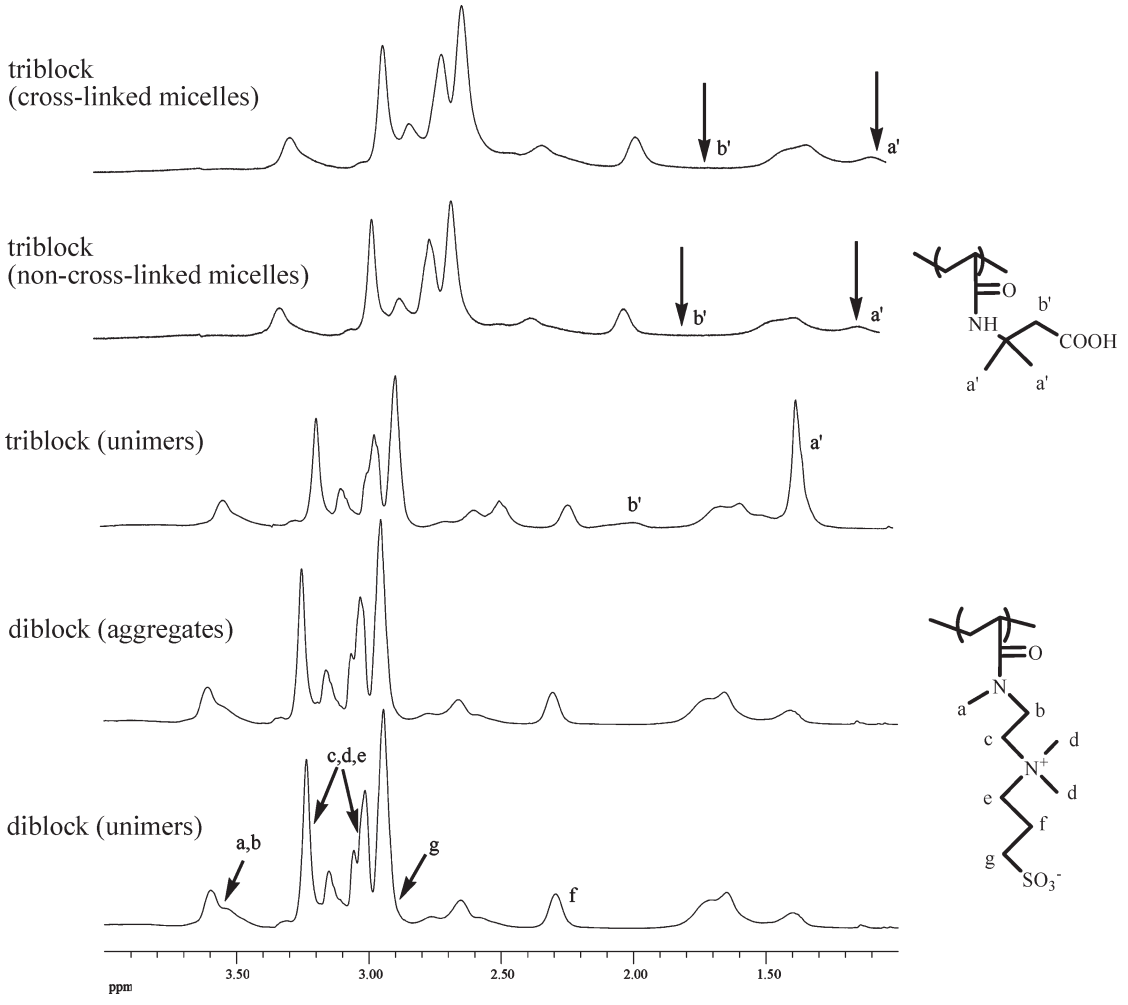


Figure 2. ^{1}H NMR spectra of unimers and self-assembled aggregates of diblock and triblock copolymers.

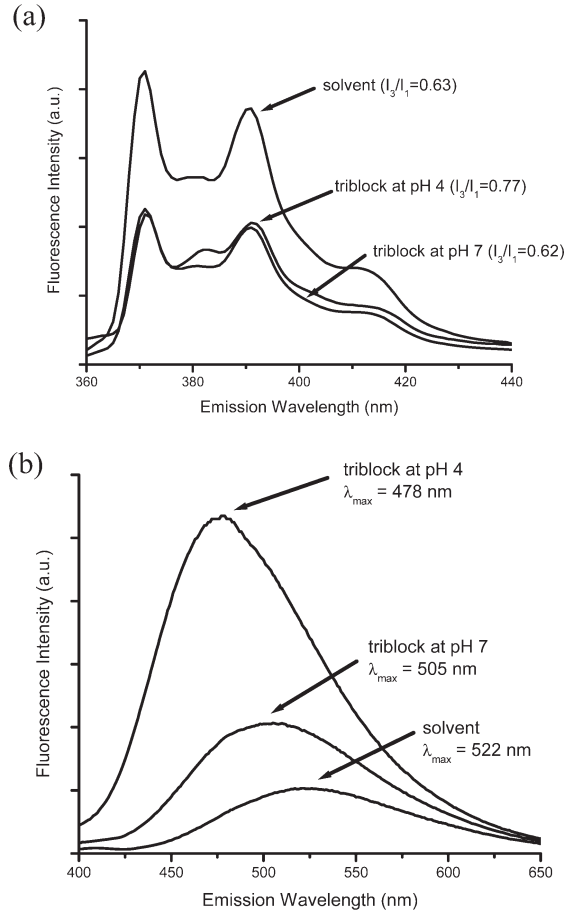


Figure 3. (a) Pyrene (λ_{ex} = 339 nm) and (b) ANS (λ_{ex} = 360 nm) emission fluorescence spectra with the triblock copolymer (Cp = 1.0 wt %, [pyrene] = 0.54 μM, [ANS] = 50 μM).

micelles. The interaction of the charged groups of ANS and the copolymer prevent the fluorescent probe from diffusing into the core of the micelles. To circumvent this problem, the unimers and the fluorescent probe were first mixed and the pH of the solution was slowly adjusted to form the micelles. With the added polymer, the emission wavelength of maximum intensity shifts from 522 to 505 nm (Figure 3b). When the micelles are formed, a further blue shift to 478 nm is observed along with a large increase in fluorescence intensity.

Conclusions

In summary, we have demonstrated a facile cross-linking method for forming polymeric micelles from a well-defined ABC triblock polymer synthesized directly in water that does not require the addition of an external cross-linking agent. The formation of "self-locked" micelles is induced by first lowering solution pH below the pK_a of the AMBA block at a salt concentration sufficient to hydrate the MAEDAPS block and subsequently removing the salt by dialysis. The reversible cross-links from the interaction of the zwitterionic groups are readily broken by the addition of electrolyte, resulting in a micelle disassembly into unimers. We are currently exploring the utility of this triblock and other related systems as potential nanocarriers for controlled delivery of therapeutic and diagnostic agents.

Experimental Section

Materials. *S*-ethyl-*S*′-(α,α′-dimethyl-α′′-acetic acid)trithiocarbonate (EMP) RAFT chain transfer agent was synthesized previously.[33] 4,4′-Azobis(4-cyanopentanoic acid) (V-501) and 4,4′-azobis[2-(imidazolin-2-yl)propane] dihydrochloride (VA-044) were donated by Wako Chemicals and were recrystallized twice from methanol before use. *N,N*-Dimethylacrylamide (DMA) was distilled under reduced pressure and stored in freezer prior to use. Synthesis of 3-acrylamido-3-methylbutanoic acid (AMBA) and 3-[2-(*N*-methylacrylamido) ethyldimethylammonio]propanesulfonate (MAEDAPS) were previously reported.[7,34,35]

RAFT Polymerization. DMA (5.0 g, 51 mmol), EMP (110 mg, 0.50 mmol) and VA-044 initiator (33 mg, 0.10 mmol) were dissolved in DI water (50 mL) at 0 °C. The pH of the solution was adjusted to 5 to completely dissolve the CTA and initiator. The solution was purged with nitrogen for 30 min and polymerization was carried out at 40 °C for 5 h. The reaction was quenched by cooling the flask in liquid nitrogen. The polymerization mixture was dialyzed against DI water for 3 days (MWCO = 1000) and subsequently lyophilized to obtain the PDMA macroCTA (M_n = 10 300, PDI = 1.05, dn/dc = 0.16). The PDMA macroCTA (2.0 g, 0.19 mmol) was chain-extended with MAEDAPS (4.0 g, 14 mmol) using V-501 (10. mg, 0.036 mmol) as free radical source in 0.5 M NaCl solution (0.7 M monomer concentration). The solution was purged with nitrogen for 30 min and reacted at 70 °C for 4 h. The diblock copolymer (M_n = 28 200, PDI = 1.04, dn/dc = 0.14) was purified by dialysis (MWCO = 6−8 kDa) and dried by lyophilization. To obtain the triblock copolymer, diblock macro CTA (2.0 g, 0.071 mmol), AMBA (1.1 g, 6.4 mmol), and V-501 (4.9 mg, 0.017 mmol) were dissolved in 0.5 M NaCl solution at pH 5 (0.3 M monomer concentration). Polymerization was carried out at 70 °C for 4 h. The polymerization mixture was dialyzed (MWCO = 12−14 kDa) against DI water for 3 days and dried by lyophilization to yield the triblock copolymer (M_n = 40 000, PDI = 1.03, dn/dc = 0.14). The chain extension polymerizations were carried out in 0.5 M NaCl aqueous solution in order to prevent precipitation of the block copolymers.

Characterization. The molecular weights and polydispersities of the (co)polymers were determined using a Wyatt Technologies aqueous size exclusion chromatography (ASEC) equipped with Viscotek G4000 PW_{XL} column, LC 1200 UV−visible photometer, DAWN DSP multiple angle laser light scattering detector and Wyatt Optilab DSP interferometric refractometer. The mobile phase consisted of 80% 0.5 M NaBr and 20% acetonitrile. Flow rate was maintained at 0.5 mL min^{-1} using an Agilent 1100 series pump. Wyatt Astra SEC/LS software version 4.9 was used to obtain and process the data. ^{1}H NMR spectra (in 90/10 H_2O/D_2O mixture) were generated *via* manual solvent suppression technique using Varian INOVA 500 MHz NMR spectrometer. Dynamic light scattering studies were conducted at 25 °C using a Malvern Instruments Zetasizer Nano series instrument equipped with a 22 mW He−Ne laser with a wavelength of 632.8 nm, an avalanche photodiode detector with high quantum efficiency, an ALV/LSE-5003 multiple tau digital correlator electronics system. Static light scattering was performed using Wyatt DAWN Enhanced Optical System (DAWN^R EOS) 18-angle laser light scattering detector in batch mode. The polymer was dissolved in 0.1 M NaCl at pH 7. The solution was dialyzed against DI water at pH 4 to remove the salt. The resulting solution was diluted to yield the desired polymer concentrations (0.2−1.0 wt %). Solutions were filtered using 0.2 μm nylon membrane directly into the light scattering cell. Fluorescence studies were performed using Photon Technology International QuantaMaster fluorimeter and FeliX32 software. Aliquots (10 μL) of 5.4 × 10^{-4} M pyrene in acetone were added into vials and

the solvent was allowed to evaporate. Polymer solution (10 mL) at pH 7 was added into the vials to yield 1.0 wt % polymer concentration. With ANS, 10 μL of 50 mM ANS aqueous solution was added into 10 mL of 1.0 wt % polymer solution at pH 7. After 5 h, the pH of the solution was slowly adjusted to 4 with 0.1 M HCl. The solutions were left at room temperature overnight before measurement. The concentrations of the probe were 0.54 μM and 50 μM for pyrene and ANS, respectively.

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Supporting Information Available: Figures showing a plot of the DLS data for the triblock copolymer dimensions in water as a function of pH and for diblock aggregation, a Zimm plot, and fluorescence data. This material is available free of charge via the Internet at http://pubs.acs.org.

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