Multicompartment Micelle Morphology Evolution in Degradable Miktoarm Star Terpolymers

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The covalent convergence of three chemically distinct polymeric segments at a common juncture point gives mixed (mikto) arm star (μ-ABC) terpolymers. If one of the blocks is water-compatible, μ-ABCs can self-assemble into an assortment of multicompartment micelle structures (supramolecular aggregates with subdivided hydrophobic cores) in aqueous dispersions that transcend the default core−shell−corona structures observed in linear ABC terpolymers with one water-compatible block.[1−10] For example, we have recently demonstrated the formation of multicompartmented hamburger, segmented wormlike, raspberry, multicompartmentalized wormlike, and nanostructured bilayer micelles from μ-[poly(ethylethylene)][poly(ethylene oxide)]-[poly(perfluoropropylene oxide)] (μ-EOF) terpolymers.[9,11−13] We also explored blends of μ-EOF with the corresponding EO diblock copolymers and showed how multicompartment micelle structure can be tuned by this blending strategy.[14] We proposed chain-packing motifs to account for the various multicompartment micelle structures based on the key features that (i) the miktoarm star architecture enforces the formation of structures in which the three immiscible domains intersect along curves in three dimensions, and (ii) the relative interfacial tension of the hydrophobic E and F blocks against water controls the packing of E and F domains within the micellar cores.[12] On the one hand, multicompartment micelles represent a first step toward much more elaborate multifunctional self-assembled structures, inspired by nature (*e.g.*, eukaryotic cells).[15] On the other

hand, we have proposed that μ-ABC systems represent a powerful strategy for the formation of hierarchically structured micelles for advanced applications; distinct A and B domains can be used to store, transport, and deliver different payloads to the same site at the same time.[16]

It is possible to expand this strategy by making the multicompartment micelles stimuli-responsive, such that the contents of distinct domains can be released at different times. The incorporation of stimulus-responsive polymeric segments into amphiphilic diblock copolymers and more complex linear ABC terpolymers can lead to micelles that adopt various structures depending on, for example, temperature, pH, and ionic strength. This approach has received a great deal of attention due to the attractive technological potential of such "smart polymeric micelles".[17−19] For example, responsive block polymer systems

ABSTRACT Multicompartment micelles with segmented wormlike structures consisting of alternating poly(ethylethylene) (PEE) and poly(γ-methyl-ε-caprolactone) (PMCL) layers were formed upon dispersing samples of μ-[PEE][poly(ethylene oxide)][PMCL] (μ-EOC) miktoarm star block terpolymers in neutral water. Subjecting these dispersions to a pH 12 aqueous buffer at 50 °C led to the hydrolytic degradation of the PMCL chains. After 4 weeks, the majority of the μ-EOC molecules were degraded into PEE-*b*-poly(ethylene oxide) (EO) diblocks and PMCL homopolymers. Although the resulting EO diblocks were expected to assemble into simple cylindrical micelles, the actual "daughter micelle" morphologies were much richer. The initial segmented wormlike micelles evolved into raspberry-like vesicle structures composed of spherical PMCL subdomains embedded in a PEE matrix. This dramatic change in the morphology of the multicompartment micelles is due to rearrangement of μ-EOC/EO/PMCL composite micelles to a structure that minimizes unfavorable interfacial interactions between the three mutually immiscible polymers. This type of micelle-to-micelle morphological evolution induced by block degradation in a miktoarm star terpolymer system holds promise for the development of "smart" delivery capabilities.

KEYWORDS: block copolymer · miktoarm star terpolymer · multicompartment micelles · degradable polymers

TABLE 1. Molecular Parameters of EO Diblock and μ-EOC Triblock Copolymers

| sample ID[a]	N_{PEE}[b]	N_{PEO}[b]	N_{PMCL}[b]	w_{PEE}[c]	w_{PEO}[c]	w_{PMCL}[c]	M_n[d]	PDI[e]
EO(2-5)	43	109		0.32	0.68		7.4	1.12
μ-EOC(2-5-14)	43	109	110	0.11	0.23	0.66	21.4	1.17

[a]The numbers in parentheses correspond to the molecular weights of PEE, PEO, and PMCL blocks, respectively, in kg/mol. [b]Number-averaged degree of polymerization calculated using ^{1}H NMR spectroscopy. [c]The w denotes weight fraction of each block. [d]Calculated using ^{1}H NMR spectroscopy. [e]Determined by SEC using PS standards and CHCl₃ as an eluent at 35 °C.

containing an ezymatically cleavable group,[20] redox-active groups,[21] and photochemically sensitive groups[22] have been recently reported. We recently developed a responsive μ-ABC system that adopts different micelle structures upon changes in pH through the incorporation of poly(2-(dimethylamino)ethyl acrylate).[23] In an effort to develop a responsive μ-ABC terpolymer that was susceptible to hydrolytic degradation, and thus more amenable to biomedical applications, we prepared μ-[poly(ethylethylene)][poly(ethylene oxide)][poly(γ-methyl-ε-caprolactone)] (μ-EOC) terpolymers.[24] Like other aliphatic polyesters, poly(γ-methyl-ε-caprolactone) (PMCL) is sensitive to high and low pH conditions and can degrade through simple ester hydrolysis.[25,26] Furthermore, poly(ethylene oxide) is well-established as a biocompatible polymer.[27] We demonstrated that, in neutral water, μ-EOC micelles formed stable hamburger, raspberry, and segmented wormlike micelles as in the related μ-EOF systems. In this report, we subject a dispersion of μ-EOC multicompartment micelles to an aqueous pH 12 buffer solution at 50 °C and demonstrate how degradation of the PMCL block leads to a remarkable and unexpected evolution of the multicompartment micelle structure. We end with a proposed mechanism for the formation of the observed "daughter" micelle structures.

RESULTS AND DISCUSSION

A mid-hydroxyl-functionalized poly(ethylethylene)-*b*-poly(ethylene oxide) (EO) diblock copolymer was prepared by two successive living anionic polymerizations, and the μ-EOC terpolymer was obtained through one controlled ring-opening polymerization using the EO diblock copolymer as macroinitiator, as reported in detail elsewhere.[24,28] The characteristics of the polymers employed in this study are summarized in Table 1, and the chemical structure of the miktoarm star is illustrated in Figure 1.

Representative cryogenic transmission electron microscopy (cryoTEM) images for a 0.5 wt % aqueous dispersion of μ-EOC(2-5-14) are shown in Figure 2 and Figure S1 (Supporting Information). μ-EOC(2-5-14) forms predominantly elongated, multicompartmented wormlike micelles. We attribute the alternating dark and light stripes observed in the core of the micelles to PMCL and PEE domains, based on
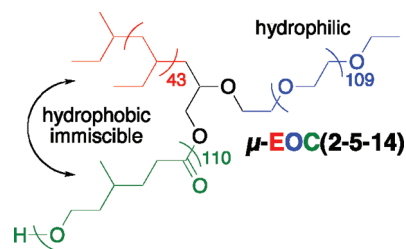
Figure 1. Chemical structure of μ-EOC(2-5-14).

their respective electron densities of 0.60 and 0.50 mol e⁻ cm⁻³. The predominant wormlike micelles have lengths ranging from 100 nm up to 1 μm. The average width of the wormlike structures is 36 ± 10 nm, which exceeds two times the fully stretched average PEE block (*ca.* 11 nm); thus, the structures are flat and segmented (*i.e.*, tapeworm-like), rather than cylindrically symmetric. Given the anticipated (super)strong segregation in these structures, we expect that the PEE chains are quite stretched, leading to thickness of the (tape)wormlike structures of approximately 20 nm, although this cannot be independently verified.[24] The spherical-like end caps apparent in the elongated structures in Figure 2 have also been observed in diblock copolymer derived wormlike micelles.[29] Dispersions of μ-EOC(2-5-14) in neutral water at room temperature retained the predominant wormlike structures after 7 weeks, and no degradation was observable by SEC over this same time period.

To effect the degradation of the PMCL block, we subjected 2 mL of a 0.5 wt % dispersion of the μ-EOC structures in neutral water to a high pH solution by diluting it with 1 mL of pH 12 Na₂HPO₄/NaOH buffer. The dispersion was degassed, sealed in a glass tube, and then stirred at 50 °C. Samples of the dispersion were removed and analyzed by cryoTEM as a function of time in the degradation solution. The degradation products at each time interval were also analyzed by SEC post-lyophilization of the samples.

The SEC data for the starting μ-EOC, the EO diblock precursor, and the degradation products as a function of degradation time at 50 °C are shown in Figure 3. The SEC data for the degradation products suggest that PMCL chains were cleaved close to the star terpolymer junction, leaving a mixture of μ-EOC triblock, EO diblock, and PMCL homopolymer. This is particularly evident in the sample after 28 days that gives a distinct peak at an elution volume between μ-EOC and EO. If this peak was due to PMCL homopolymer, the peak molar mass (based on SEC calibration with related PMCL homopolymers) would be 12 kg mol⁻¹, which is close to 14 kg mol⁻¹ of the PMCL chains in μ-EOC. In fact, we were able to model the SEC traces of the degradation products using SEC data from the μ-EOC triblock, the EO diblock, and a representative PMCL homo-
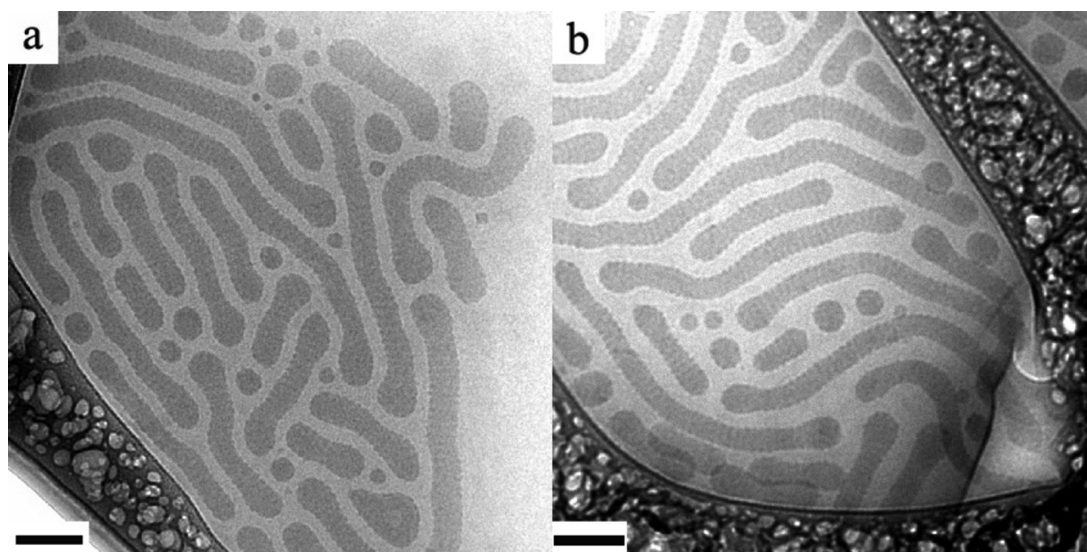
Figure 2. CryoTEM image of a 0.5 wt % dispersion of μ-EOC(2-5-14) in neutral water. Scale bars indicate 100 nm.

polymer sample with a number average molar mass of 12 kg mol^{-1} (PDI = 1.15), as shown in Figure 4.

When it is assumed that the degraded μ-EOC molecules underwent a single cleavage event at the juncture, the mole fractions of μ-EOC, EO, and PMCL calculated from the SEC data after 28 days in the hydrolysis solution are approximately 0.20, 0.55, and 0.25, respectively. As the mole fractions of PMCL and EO chains should be the same under the assumption of a single cleavage event at the juncture, the actual process is likely more complicated. While the ester bond at the juncture of the μ-EOC triblock must be close to the interface with water, cleavage of the PMCL chains could also occur some repeating units away from the juncture, leaving a somewhat smaller PMCL fragment and a μ-EOC fragment with a short PMCL chain. In fact, the peak in the SEC associated with the EO diblock from the degradation process is centered at slightly lower elution volume than the parent EO, consistent with this hypothesis. In addition, the cleaved PMCL chains

could undergo further degradation and be spread under the EO peak. The ^{1}H NMR data from the degradation products are consistent with some reduction in the PMCL content (Supporting Information Figure S2). In summary, these data are consistent with cleavage of the PMCL chains close to the core−corona interfaces in the wormlike structures, to give a mixture of EO diblock, PMCL homopolymer, and some remaining μ-EOC chains with varying PMCL chain lengths.

We examined the morphological evolution of μ-EOC micelles by cryoTEM as a function of time in the pH 12 buffer (Figure 5 and Figure S3). Immediately after addition of the buffer, the segmented structures previously observed (Figure 2) were retained. After 2 days, however, the original segmented structures transform into an array of irregularly shaped micelles with clear internal structure (Figure 5a). After 7 days, the predominant
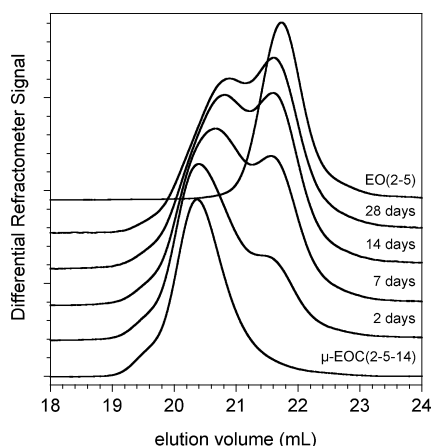

Figure 3. SEC curves obtained from dilute dispersions (0.33 wt %) of μ-EOC(2-5-14) after hydrolysis in pH 12 buffer solutions at 50 °C for prescribed times.
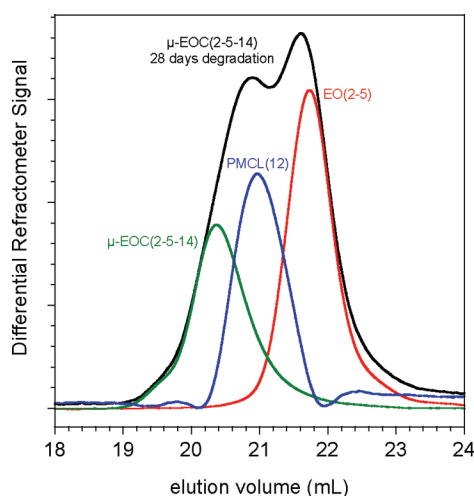

Figure 4. SEC curve modeling: SEC curve of μ-EOC(2-5-14) micelles after 28 days of degradation (black); SEC curve of the EO(2-5) (red); SEC curve of the μ-EOC(2-5-14) (green); SEC curve of PMCL(12) (blue).
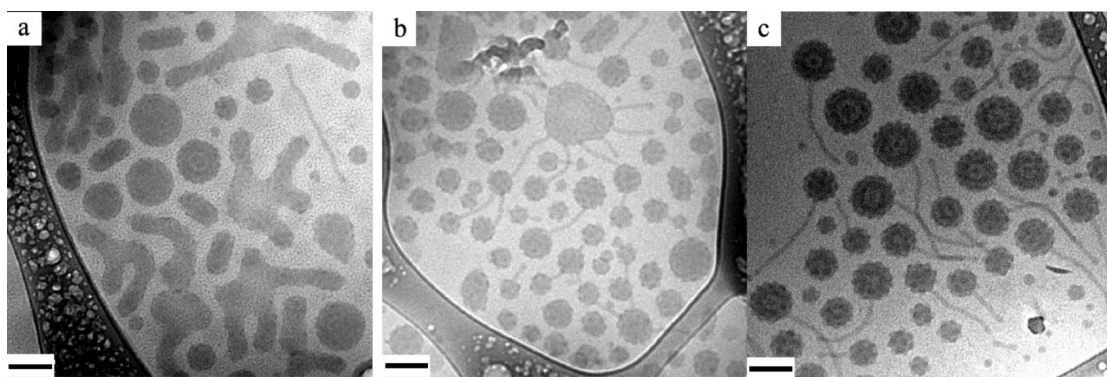
Figure 5. CryoTEM images obtained from dilute dispersions (0.33 wt %) of μ-EOC(2-5-14) after hydrolysis in pH 12 buffer solutions at 50 °C for prescribed times: (a) 2 days, (b) 7 days, (c) 14 days. Scale bars indicate 100 nm.

structures appear as circular objects with two distinctive features: cores, containing isolated dark (PMCL) domains, and thin wormlike features emanating from the cores (Figure 5b). After 14 days, the structured assemblies appear to have more uniform sizes and most are connected to a single wormlike structure. No further significant changes in the structures were observed after 28 days.

The structures evident in Figure 5 are remarkable and certainly not in accordance with naïve expectations. For example, as shown in Figure 6, the pristine EO(2-5) diblocks form "conventional" cylindrical wormlike micelles. As the PMCL blocks are progressively degraded, one might have anticipated the "parent", segmented wormlike multicompartment micelles to have spawned simply "daughter" EO worms and PMCL degradation products. As the PMCL chains are not themselves water-soluble, they could have undergone a combination of phase separation and further degradation to soluble, small molecule byproducts. However, the microscopy results are unequivocal in showing that a different outcome
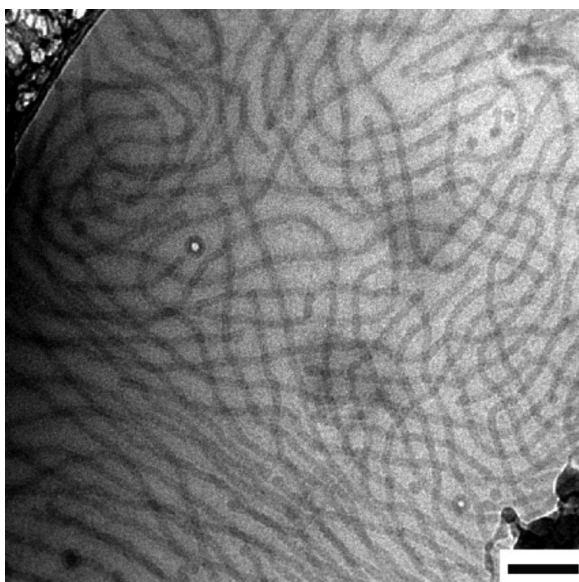
is realized. In fact, the daughter micelles are themselves multicompartment, with distinct spherical PMCL domains arranged in near regular patterns around overall larger spherical assemblies. Thus, the cleaved PMCL chains are retained within the micelle structures, and the new degree of freedom afforded by decoupling one block allows the system to undergo a micelle-to-micelle morphological change to reduce the overall free energy. From the cryoTEM images, it is not possible to discern whether the PMCL spheres prefer the surfaces completely or are incorporated to some extent within the interior of the larger assemblies; certainly, the fact that many PMCL domains clearly protrude from the larger spheres suggests the former. It is also not obvious from the images whether the larger spherical assemblies are solid or actually vesicle-like. However, the hydrophobic chains are not long enough to allow the larger micelles to be both solid and spherical; they could be disk-like, however, in analogy to the flattened parent segmented worms. The visible worms in Figure 5 are fully consistent with the expected EO cylindrical micelles (Figure 6); for example, the average diameter of the worms protruding from the spotted structures is about 11.5 ± 2.5 nm, consistent with that of the wormlike micelles formed from pristine EO(2-5) micelles (12.9 ± 2.1 nm). The fact that these cylinders protrude from the larger spherical assemblies is fascinating in its own right, suggesting that these micelles nucleate at the initial site of PMCL block cleavage.

On the basis of the degradation process suggested above, we propose the following mechanism for the evolution of the micelle structures, illustrated schematically in Figure 7. After the initial PMCL cleavage at or near the μ-EOC juncture, the cores of the segmented wormlike micelles must accommodate PMCL homopolymer inclusions. These appear as spherical features in the cryoTEM images (Figure 5). The unperturbed μ-EOC triblocks and those with short PMCL chains resulting from degradation serve to stabilize the resultant structures by lowering the interfacial tension between the free PMCL chains and the
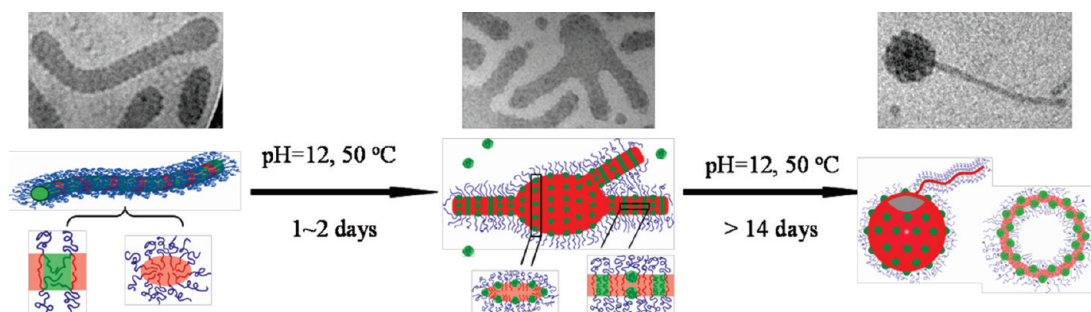

Figure 6. CryoTEM image obtained from a dilute dispersion (1 wt %) of EO(2-5) in water. Scale bar indicates 100 nm.

Figure 7. Schematic cartoons illustrating the morphological transition of μ-EOC micelles during the hydrolytic degradation.

PEE from the EO diblocks. The cryoTEM images in Figure 5a,b suggest that the initially flat worms expand laterally to give sheets. The presence of EO diblock is apparent from the wormlike micelles that protrude from these sheet-like structures. This indicates that some of the EO diblock in the micelles can be extruded from the sheets and adopt its native form. We posit that the structures observed after both 14 and 28 days are the result of either the sheets folding into small nanostructured vesicles we have previously observed in μ-EOF systems or disk-like micelles with structured cores. In either case, as noted above, they are too large to be spherical raspberry micelles.

SUMMARY

We have demonstrated a remarkable multicompartment micelle to multicompartment micelle morphology transition upon pH-induced chemical degradation of a sacrificial block. The evolution of μ-EOC multicompartment micelles from segmented wormlike structures to raspberry-like vesicles or disks upon the cleavage of PMCL chains in pH 12 buffer at 50 °C is clearly revealed by cryoTEM. Most of the PMCL chains are cleaved at or near the juncture with the E and O blocks, producing EO diblocks (some with shorter PMCL blocks) and significant amounts of PMCL homopolymer. The striking morphology change is driven by minimization of the unfavorable interfacial energy between three immiscible blocks, under the release of the constraint that the PMCL chains are connected to the other two. This work illustrates the potential for stimulus-induced micelle-to-micelle transitions.

EXPERIMENTAL METHODS

μ-EOC Micelle Solution Preparation. Micelle solutions of μ-EOC(2-5-14) were prepared by a dialysis technique. In a typical procedure, 0.15 g of the μ-EOC terpolymer was dissolved in 15 mL of tetrahydrofuran (THF), and subsequently 30 mL of distilled water was added to the polymer/THF solution using a syringe pump at a rate of 5 mL/h with gentle stirring. The solution started to become turbid at 20−30 vol % water. The addition of water continued until the water content reached 67 vol %. The micelle solution was subsequently placed into a dialysis tube (Spectra/Por, molecular weight cutoff = 2 kDa) and dialyzed against distilled water to remove THF. Distilled water was changed twice a day for 5 days. After dialysis, the polymer/water concentration was adjusted to be 0.5 wt % by evaporation of water under N_2 purge and stirred for at least 1 week at room temperature prior to further analysis.

Hydrolytic Degradation of μ-EOC Micelles. The hydrolytic cleavage of the PMCL chains from the μ-EOC micelles was investigated as follows. Two milliliters of the μ-EOC micelle solution was filtered through a 0.45 μm hydrophilic filter into a dust-free 0.5 in. diameter glass tube and mixed with 1 mL of pH 12 (pH 11.3 at 50 °C) Na_2HPO_4/NaOH buffer solution (Fluka). The tube was filled with Ar by three vacuum-refill cycles to remove air. Subsequently, the tube was sealed off and left in an oil bath at 50 °C with gentle stirring. After the prescribed time, the micelle solution was characterized by cryogenic transmission electron microscopy. Then 1.5 mL of micelle solution was lyophilized and analyzed by size exclusion chromatography (SEC) and proton nuclear magnetic resonance spectroscopy (^{1}H NMR) without purification.

Molecular Characterization. SEC measurements were carried out on a Hewlett-Packard 1100 series liquid chromatograph fitted with a Hewlett-Packard 1047A refractive index detector and three PLgel columns. The calibration curve was obtained using both poly(styrene) and poly(γ-methyl-ε-caprolactone) standards. Chloroform was used as an eluent at a flow rate of 1 mL/min at 35 °C. ^{1}H NMR spectra were recorded on a Varian INOVA-500 spectrometer at room temperature. All samples were dissolved in $CDCl_3$.

Cryogenic Transmission Electron Microscopy (cryoTEM). The cryoTEM samples were prepared in a controlled environment vitrification system (CEVS) at room temperature under saturated water.[30] An aliquot of the micelle solution was placed onto a lacey carbon-supported TEM grid. Excess solution was blotted with a filter paper, resulting in films with thicknesses of ca. 100−300 nm on the grid. After allowing at least 15 s for relaxation of the films, the grid was quickly plunged into a reservoir of liquid ethane cooled by liquid nitrogen. Vitrified specimens were stored in liquid nitrogen prior to transferring and mounting on a cryogenic sample holder (Gatan 626) and then were examined with a JEOL 1210 TEM operated at an acceleration voltage of 120 kV at about −178 °C. Images were recorded on a Gatan 724 multiscan CCD camera and processed with Digital Micrographs version 3.3.1. Phase contrast was enhanced by acquiring images at an underfocus.

Supporting Information Available: ^{1}H NMR data for hydrolytically degraded μ-EOC(2-5-14), and cryoTEM images of both hydrolytically degraded μ-EOC(2-5-14) micelles and the micelles formed in neutral water. This material is available free of charge via the Internet at http://pubs.acs.org.

REFERENCES AND NOTES

1. Laschewsky, A. Polymerized Micelles with Compartments. *Curr. Opin. Colloid Interface Sci.* **2003**, *8*, 274–281.
2. Fang, B.; Walther, A.; Wolf, A.; Xu, Y.; Yuan, Y.; Müller, A. H. E. Undulated Multicompartment Cylinders by the Controlled and Directed Stacking of Polymer Micelles with a Compartmentalized Corona. *Angew. Chem., Int. Ed.* **2009**, *48*, 2877–2880.
3. Walther, A.; Müller, A. H. E. Formation of Hydrophobic Bridges between Multicompartment Micelles of Miktoarm Star Terpolymers in Water. *Chem. Commun.* **2009**, 1127–1129.
4. Schacher, F.; Walther, A.; Ruppel, M.; Drechsler, M.; Müller, A. H. E. Multicompartment Core Micelles of Triblock Terpolymers in Organic Media. *Macromolecules* **2009**, *42*, 3540–3548.
5. Kubowicz, S.; Baussard, J. F.; Lutz, J, F.; Thünemann, A. F.; von Berlepsch, H.; Laschewsky, A. Multicompartment Micelles Formed by Self-Assembly of Linear ABC Triblock Copolymers in Aqueous Medium. *Angew. Chem., Int. Ed.* **2005**, *44*, 5262–5265.
6. Lutz, J. F.; Laschewsky, A. Multicompartment Micelles: Has the Long-Standing Dream Become a Reality? *Macromol. Chem. Phys.* **2005**, *206*, 813–817.
7. Skrabania, K.; Laschewsky, A.; von Berlepsch, H.; Böttcher, C. Synthesis and Micellar Self-Assembly of Ternary Hydrophilic-Lipophilic-Fluorophilic Block Copolymers with a Linear PEO Chain. *Langmuir* **2009**, *25*, 7594–7601.
8. von Berlepsch, H.; Böttcher, C.; Skrabania, K.; Laschewsky, A. Complex Domain Architecture of Multicompartment Micelles from a Linear ABC Triblock Copolymer Revealed by Cryogenic Electron Microscopy. *Chem. Commun.* **2009**, 2290–2292.
9. Li, Z.; Kesselman, E.; Talmon, Y.; Hillmyer, M. A.; Lodge, T. P. Multicompartment Micelles from ABC Miktoarm Stars in Water. *Science* **2004**, *306*, 98–101.
10. Zhou, Z.; Li, Z.; Ren, Y.; Hillmyer, M. A.; Lodge, T. P. Micellar Shape Change and Internal Segregation Induced by Chemical Modification of a Tryptych Block Copolymer Surfactant. *J. Am. Chem. Soc.* **2003**, *125*, 10182–10183.
11. Li, Z.; Hillmyer, M. A.; Lodge, T. P. Laterally Nanostructured Vesicels, Polygonal Bilayer Sheets, and Segmented Wormlike Micelles. *Nano Lett.* **2006**, *6*, 1245–1249.
12. Li, Z.; Hillmyer, M. A.; Lodge, T. P. Morphologies of Multicompartment Micelles Formed by ABC Miktoarm Star Terpolymers. *Langmuir* **2006**, *22*, 9409–9417.
13. Liu, C.; Hillmyer, M. A.; Lodge, T. P. Evolution of Multicompartment Micelles to Mixed Corona Micelles Using Solvent Mixtures. *Langmuir* **2008**, *24*, 12001–12008.
14. Li, Z.; Hillmyer, M. A.; Lodge, T. P. Control of Structure in Multicompartment Micelles by Blending μ-ABC Star Terpolymers with AB Diblock Copolymers. *Macromolecules* **2006**, *39*, 765–771.
15. Ringsdorf, H.; Lehmann, P.; Weberskirch, R. Multicompartmentation—A Concept for the Molecular Architecture of Life. *Book of Abstracts*; 217th National Meeting of the American Chemical Society, Anaheim, CA, March 21−25, 1999, BTEC-001.
16. Lodge, T. P.; Rasdal, A.; Li, Z.; Hillmyer, M. A. Simultaneous, Segregated Storage of Two Agents in a Multicompartment Micelle. *J. Am. Chem. Soc.* **2005**, *127*, 17608–17609.
17. Rodríguez-Hernández, J.; Chécot, F.; Gnanou, Y.; Lecommandoux, S. Toward 'Smart' Nano-Objects by Self-Assembly of Block Copolymers in Solution. *Prog. Polym. Sci.* **2005**, *30*, 691–724.
18. Li, M.; Keller, P. Stimuli-Responsive Polymer Vesicles. *Soft Matter* **2009**, *5*, 927–937.
19. Park, T. G.; Jeong, J. H.; Kim, S. W. Current Status of Polymeric Gene Delivery Systems. *Adv. Drug Delivery Rev.* **2006**, *58*, 467–486.
20. Amir, R. J.; Zhong, S.; Pochan, D. J.; Hawker, C. J. Enzymatically Triggered Self-Assembly of Block Copolymers. *J. Am. Chem. Soc.* **2009**, *131*, 13949–13951.
21. Klaikherd, A.; Nagamani, C.; Thayumanavan, S. Multi-stimuli Sensitive Amphiphilic Block Copolymer Assemblies. *J. Am. Chem. Soc.* **2009**, *131*, 4830–4838.
22. Goodwin, A. P.; Mynar, J. L.; Ma, Y.; Fleming, G. R.; Fréchet, J. M. J. Synthetic Micelle Sensitive to IR Light *via* a Two-Photon Process. *J. Am. Chem. Soc.* **2005**, *127*, 9952–9953.
23. Liu, C.; Hillmyer, M. A.; Lodge, T. P. Multicompartment Micelles from pH-Responsive Miktoarm Star Block Terpolymers. *Langmuir* **2009**, *25*, 13718–13725.
24. Saito, N.; Liu, C.; Lodge, T. P.; Hillmyer, M. A. Mulitcompartment Micelles from Polyester-Containing ABC Miktoarm Star Terpolymers. *Macromolecules* **2008**, *41*, 8815–8822.
25. Liggins, R. T.; Burt, H. M. Polyether-Polyester Diblock Copolymers for the Preparation of Paclitaxel Loaded Polymeric Micelle Formulations. *Adv. Drug Delivery Rev.* **2002**, *54*, 191–202.
26. Geng, Y.; Discher, D. E. Hydrolytic Degradation of Poly(ethylene oxide)-*block*-Polycaprolactone Worm Micelles. *J. Am. Chem. Soc.* **2005**, *127*, 12780–12781.
27. Kabanov, A. V.; Batrakova, E. V.; Alakhov, V. Y. Pluronic Block Copolymers as Novel Polymer Therapeutics for Drug and Gene Delivery. *J. Controlled Release* **2002**, *82*, 189–212.
28. Li, Z.; Hillmyer, M. A.; Lodge, T. P. Synthesis and Characterization of Triptych μ-ABC Star Triblock Copolymers. *Macromolecules* **2004**, *37*, 8933–8940.
29. Zupancich, J. A.; Bates, F. S.; Hillmyer, M. A. Aqueous Dispersions of Poly(ethylene oxide)-*b*-Poly(γ-methyl-ε-caprolactone) Block Copolymers. *Macromolecules* **2006**, *39*, 4286–4288.
30. Bellare, J. R.; Davis, H. T.; Scriven, L. E.; Talmon, Y. Controlled Environment Vitrification System—An Improved Sample Preparation Technique. *J. Electron Microsc.* **1988**, *10*, 87–111.