The Facile One-Pot Synthesis of Shell Cross-Linked Micelles in Aqueous Solution at High Solids

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Following pioneering work by Wooley and co-workers in 1996, there has been increasing interest in shell cross-linked (SCL) micelles.[1] In particular, recent efforts have focused on the synthesis of SCL micelles that have either hollow cores or hydrophilic cores. Hollow SCL micelles have been prepared by chemical degradation of the core-forming block,[2,3] whereas hydrophilic-core SCL micelles have been synthesized either by chemical modification[4,5] or by using core-forming blocks which have tunable hydrophilic/hydrophobic character.[6] In addition, increasing attention is being given to SCL micelles prepared from copolymers synthesized by atom transfer radical polymerization (ATRP),[2b,5] a relatively new example of living free-radical polymerization chemistry developed by Matyjaszewski and others.[7,8] At Sussex we have developed ATRP for the efficient polymerization of hydrophilic monomers in water at room temperature.[8] In our SCL micelle studies, we have recently demonstrated that ABC triblock copolymers offer great advantages over conventional AB diblock copolymers, since the former allow inner-shell cross-linking to be carried out at high solids (>10 w/v%) without any intermicelle cross-linking.[9]

Herein we describe the synthesis of a new hydrophilic ABC triblock copolymer via ATRP which undergoes micellization *reversibly*, allowing the facile synthesis of SCL micelles with tunably hydrophilic cores. Furthermore, the ATRP protocol is sufficiently robust and versatile to enable us to carry out high-yielding, one-pot syntheses of these SCL micelles at high solids in water, with concomitant efficient removal of the ATRP catalyst using silica chromatography.

The ABC triblock copolymer was prepared from a poly(propylene oxide) [PPO−Br] macro-initiator (1), which was used to polymerize 2-(dimethylamino)ethyl methacrylate [DMA] and methoxy-capped oligo(ethylene glycol) methacrylate [OEGMA] in turn, using 1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA) and Cu(I)Cl (PPO−Br:CuCl:HMTETA = 1:1:1 molar ratio) as a catalyst, see Figure 1a. The PPO−Br macro-initiator was prepared by reacting monohydroxy-terminated PPO, (M_w/M_n = 1.06, M_n = 1940 by ^{1}H NMR) with 2-bromoisobutyryl bromide in the presence of triethylamine. The successive GPC traces for each step (Supporting Information, Figure 1) support the synthesis of well-defined PPO−DMA−OEGMA triblock copolymers.

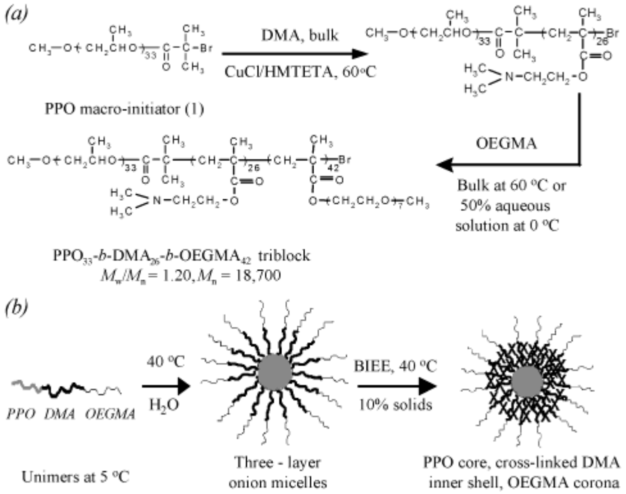

Figure 1. Reaction scheme for: (a) the synthesis of the PPO_{33}-DMA_{26}−$OEGMA_{42}$ triblock copolymer via ATRP; (b) the one-pot synthesis of shell cross-linked micelles at high solids using this triblock copolymer.

Dynamic and static light scattering (DLS, SLS) studies[10] (Supporting Information, Figure 2) confirmed that the PPO_{33}−DMA_{26}−$OEGMA_{42}$ triblock copolymer is molecularly dissolved in cold water at pH 8.50 and 5 °C but undergoes micellar self-assembly on raising the temperature above the LCST of the PPO block (estimated to be around 15 °C). For a 1.0 w/v% triblock copolymer solution at room temperature these micelles have highly hydrated PPO cores; progressive dehydration occurs on warming to 40 °C, leading to smaller, more compact micelles with an intensity-average hydrodynamic diameter $\langle D_h \rangle$ of 20 nm. At 60−70 °C, the inner shell of DMA residues becomes hydrophobic,[11] and the three-layer onion micelles are now stabilized solely by the OEGMA chains in the outer layer. The overall hydrophilic/hydrophobic balance of the copolymer also changes, leading to an increase in the micelle hydrodynamic diameter to 72 nm at 75 °C, and a 100-fold increase in the light-scattering intensity, suggesting a large increase in the micelle aggregation number. Polydispersity indexes (μ_2/Γ^2) calculated by cumulants analysis was less than 0.12 for the micelles formed at various temperatures; the micelles are spherical since the average characteristic line widths (Γ/q^2) are independent of the angle of detection.

These subtle changes in the relative degrees of hydration of the three blocks are confirmed by in situ ^{1}H NMR spectroscopy studies (see Supporting Information, Figure 3). In the unimer regime at 5 °C, the signal due to the methyl groups of the PPO block appears as a sharp doublet at δ 0.9. At 40 °C, this signal broadens and becomes less intense. This is consistent with the formation of micelles with PPO cores. The PPO chains must retain some degree of hydration, since the PPO signal does not disappear. Similar observations have been reported for the temperature-induced micellization of many other block copolymers.[6,9] Above 40 °C, several signals due to the DMA residues (at δ 2.1−2.3 and δ 2.5−2.6) broaden and become less intense, indicating increasing dehydration of the central DMA block at higher temperatures.

Initially several PPO−DMA−OEGMA triblock copolymers were prepared and characterized in terms of their mean degrees

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of polymerization, molecular weight distributions, and aqueous solution properties. GPC analyses (THF eluent, PMMA standards) typically gave polydispersities of around 1.20 for these triblocks, with little or no evidence for PPO macro-initiator contamination. On the basis of these initial results, one particular block composition was targeted for the *one-pot* synthesis of SCL micelles depicted in Figure 1. First, DMA was polymerized to high conversion (>99%) in the bulk at 60 °C using the PPO macro-initiator. On cooling to 0 °C, an aqueous solution of OEGMA monomer was added, forming the target triblock copolymer at a solution concentration of 64.0 w/v%. At this point, the viscous reaction solution was diluted with water to 10.0 w/v% and heated to 40 °C to induce micellar self-assembly. A bifunctional quaternizing agent, 1,2-bis(2-iodoethoxy)ethane [BIEE; BIEE/DMA molar ratio = 0.30], was then added to cross-link the DMA residues located in the inner shell of the micelles. This shell cross-linking reaction was carried out at 40 °C and pH 8.5 for at least 72 h. On cooling to room temperature, this aqueous micellar solution was purified using silica chromatography to remove the blue Cu(II) catalyst, yielding a colorless aqueous solution. The degree of quaternization was estimated to be 54% by ^{1}H NMR (the peak integral of the remaining unquaternized DMA residues at δ 2.1−2.3 was compared to that at δ 3.3−3.8 due to the PPO and OEGMA signals). The actual degree of cross-linking is almost certainly lower than this estimated degree of quaternization because it is unlikely that both iodoalkyl groups of every BIEE molecule react with the DMA residues; in addition, some degree of intrachain quaternization most likely occurs.

DLS studies at 20 °C indicated the existence of water-swollen SCL micelles with an intensity-average diameter of 39 nm and a polydispersity index (μ_2/Γ^2) of 0.15 by cumulants analysis. On cooling to 5 °C, the light-scattering intensity and hydrodynamic diameter remains essentially constant, indicating that the micellar structure has been successfully “locked in”. Static light scattering (SLS) studies[10] of the micellar solutions indicated a mean radius of gyration of 22 nm and a micellar mass of approximately 3.73×10^6 g mol^{-1}. Given that M_w of the original PPO$_{33}$−*b*-DMA$_{26}$−*b*-OEGMA$_{42}$ triblock copolymer is estimated to be 25 000 (and assuming that the actual degree of cross-linking is 54%), this indicates a mean micelle aggregation number of approximately 150. On heating the SCL micelles to 40 and 75 °C, the $\langle D_h \rangle$ of these micelles decreased only slightly from 39 nm to approximately 37 and 36 nm, respectively. However, for SCL micelles prepared with a target degree of cross-linking of 30%, the $\langle D_h \rangle$ decreased from 41 nm at 20 °C to 36 and 33 nm at 40 and 75 °C, respectively. (Supporting Information, Table 1 and Figure 4). The deswelling of the SCL micelles is due to progressive dehydration of the micelle cores. Variable-temperature ^{1}H NMR studies confirmed this interpretation (see Supporting Information Figure 3). On lowering the temperature from 40 to 5 °C, a well-resolved doublet due to the PPO block reappears, due to the reversible rehydration of the micelle cores. Clearly, such reversible swelling behavior offers considerable scope for the use of these new “nanogels” as delivery vehicles for controlled-release applications. A typical transmission electron micrograph of the dried SCL micelles shown in Figure 2 suggested a spherical, polydisperse morphology; the approximate number-average particle diameter is around 30−40 nm. Allowing for hydration and polydispersity effects, and given that the PPO core is liquidlike and probably spreads on the surface of the TEM grid, this value is reasonably consistent with that obtained from DLS.

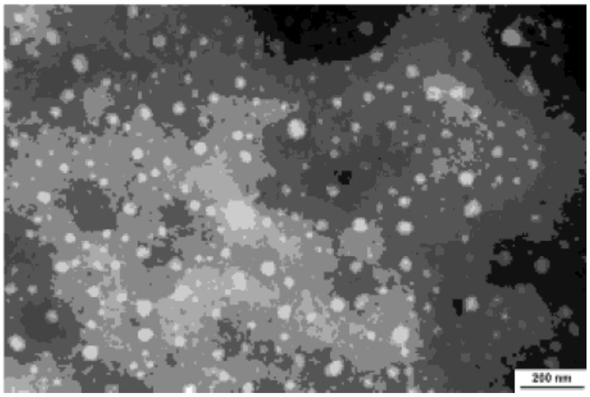

Figure 2. Typical transmission electron micrograph of shell cross-linked micelles (negatively stained with phosphotungstic acid) prepared via the one-pot synthetic route outlined in Figure 1.

SCL micelles have also been prepared with variable target degrees of shell cross-linking over a range of concentrations and temperatures (see Supporting Information, Table 1).

In summary, novel SCL micelles with tunable hydrophilic cores based on PPO−DMA−OEGMA triblock copolymers are readily prepared in one-pot syntheses at high solids via ATRP. Moreover, a wide range of SCL micelles (i.e., tunable micelle structures with variable degrees of swelling) can be prepared from the *same triblock copolymer*, simply by varying the synthesis temperature, copolymer concentration and the target degree of cross-linking. We believe that these one-pot syntheses enhance the commercial viability of SCL micelle technology.

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Supporting Information Available: Detailed experimental procedures for synthesis of PPO−Br, the block copolymer, and SCL micelles; GPC traces of each step during the synthesis of triblock copolymer; temperature dependence of scattering light intensity, and $\langle D_h \rangle$ of micelles; ^{1}H NMR spectra of the PPO−DMA−OEGMA triblock copolymer, PPO-core micelles and SCL micelles; temperature dependence of scattering-light intensity and $\langle D_h \rangle$ of SCL micelles; summary table of DLS data vs temperature. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Dynamic light scattering was performed using a Brookhaven BI-200SM model and 9000AT correlator using a solid-state laser (50 mW, λ = 532 nm). DLS was conducted at scattering angles of 15−150° using both cumulants and CONTIN software. The *dn*/d*c* of the one-pot synthesized SCL micelles was determined to be 0.133 (λ = 633.0 nm) at 20 °C, using an Optilab DSP Interferometric refractometer. Static light scattering was performed on a DAWN DSP Laser Photometer, with a 5 mW He−Ne laser (λ = 632.8 nm) and 18 detectors at different angles.

(11) DMA homopolymer with a degree of polymerization (DP) of 26 has a cloud point of about 45 °C at pH 8.5.(Butun, V. Ph.D. Thesis, University of Sussex, UK, 1999) However, when the DMA block is attached to a highly hydrophilic OEGMA block, its LCST (cloud-point) increased to 60−70 °C. (Bailey, L. Ph.D. Thesis, University of Sussex, UK, 2001).