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Synthesis of Shell Cross-Linked Micelles at High Solids in Aqueous Media

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Recently both Wooley and co-workers[1−5] and also Liu and co-workers[6−8] have reported the synthesis of shell cross-linked “knedel” (SCK) micelles. These fascinating supramolecular structures have properties which are intermediate between micelles, microgels, nanoparticles, and dendrimers, and numerous applications have been suggested. However, one major drawback in the synthesis of conventional SCK micelles is that shell cross-linking must be carried out at high dilution (typically 0.1−0.5% solids) in order to avoid extensive intermicellar cross-linking. Unless this problem is addressed, it is unlikely that the synthesis of SCK micelles on an industrial scale will be commercially viable, even for speciality applications.

In 1998 we described the synthesis of SCK micelles with tunable core hydrophilicity.[9] An aqueous micellar solution of partially quaternized poly[2-(dimethylamino)ethyl methacrylate-*block*-2-(*N*-morpholino)ethyl methacrylate] (DMA−MEMA) was reacted with a bifunctional cross-linker, 1,2-bis(2-iodoethoxy)ethane (BIEE), in aqueous solution at 60 °C. Under these conditions the MEMA block is above its cloud point and forms the micelle core. On cooling to 20 °C, the hydrophobic MEMA micelle cores become hydrated. Thus, the cores of these SCK micelles can be reversibly hydrated or dehydrated, depending on the solution temperature.

Herein we report the first synthesis of well-defined SCK micelles in relatively concentrated solution (10% solids). This is achieved in aqueous media using a poly[ethylene oxide-*block*-2-(dimethylamino)ethyl methacrylate-*block*-2-(*N*-morpholino)ethyl methacrylate] (PEO−DMA−MEMA) triblock copolymer (see Figure 1a).[10] Aqueous GPC studies (using PEO standards) indicated that the original PEO block had a low polydispersity ($M_w/M_n < 1.10$) and a number-average molecular weight of approximately 2,000, which corresponds to a degree of polymerization of 45 ethylene oxide residues. Treating this PEO block as an “end group”, inspection of the ^{1}H NMR ($CDCl_3$) spectrum of the triblock copolymer indicated average degrees of polymerization for the DMA and MEMA blocks of 57 and 62, respectively. Thus, the overall number-average molecular weight (M_n) of this triblock copolymer [PEO−DMA−MEMA(1)] was calculated to be 23 600. GPC studies (THF eluent) of the triblock copolymer indicated a polydispersity (M_w/M_n) of 1.33. The PEO−DMA−MEMA triblock copolymer can be molecularly dissolved in water at 20 °C but the chains undergo self-assembly to form a three-layer “onion” micelle in the presence of Na_2SO_4. This electrolyte selectively “salts out” the MEMA block, with the hydrated DMA residues forming the inner shell and the PEO residues forming the outer shell (see Figure 1b). This structure is supported by ^{1}H NMR studies; the signals associated with the MEMA residues disappear, whereas those due to the PEO and DMA residues remain. The hydrodynamic diameter of the diluted “onion” micelles is around 68 nm by dynamic light scattering.

Inner shell cross-linking was achieved in 1.0 M Na_2SO_4 at 20 °C for 3−7 days using 1,2-bis(2-iodoethoxy)ethane [BIEE; 6−20 mol % based on DMA residues]. This reagent selectively quaternizes the more reactive DMA residues in the presence of the sterically hindered MEMA residues.[9] The PEO block in the outer layer of the SCK micelle is sufficiently long to prevent the DMA

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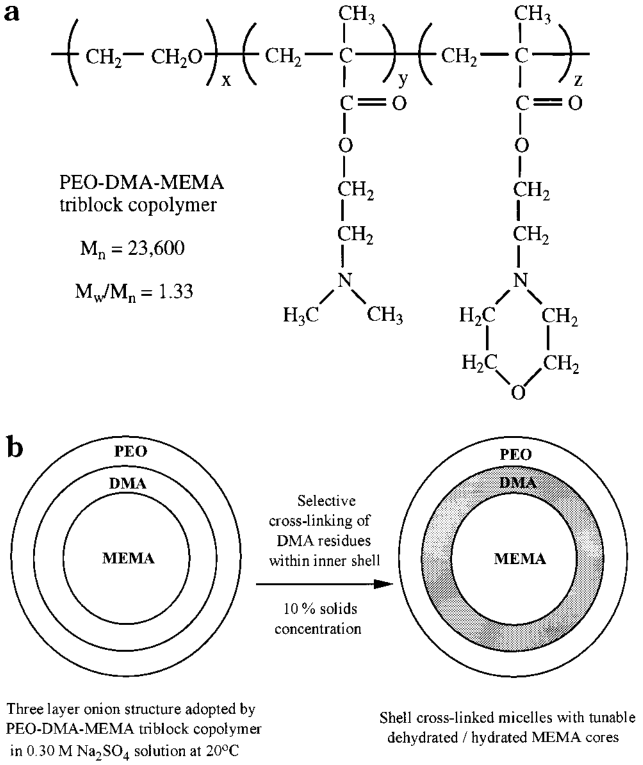

Figure 1. (a) Chemical structure of the PEO–DMA–MEMA triblock copolymer. (b) Schematic formation of SCK micelles at high solids using the PEO–DMA–MEMA triblock copolymer.

residues of one SCK micelle coming into contact with those in a neighboring SCK micelle. As micelles approach each other in solution, inter-mixing of the PEO chains in the respective outer shells is unfavorable both entropically (due to restricted conformations) and enthalpically (PEO–water interactions are more favorable than PEO–PEO interactions since water is a good solvent for PEO). Thus, even at high copolymer concentrations, cross-linking of the DMA residues occurs exclusively *within* micelles and aggregation via inter-micelle cross-linking is prevented by the well-known "steric stabilization" mechanism.[11] In a control experiment, shell cross-linking of an analogous DMA–MEMA diblock copolymer at 10% solids led to macroscopic gelation due to intermicellar cross-linking. This serves to illustrate the importance of the outer shell of PEO chains for the preparation of well-defined shell cross-linked micelles at high solids. It is also noteworthy that these PEO chains may confer "stealth" properties on these SCK micelles, which could be beneficial in drug delivery applications.[12]

Shell cross-linking was verified as follows. After exposure to BIEE for several days at 20 °C, the 10% micellar solution was diluted 10-fold and adjusted to pH 2 using HCl. If no shell cross-linking had occurred, dissolution of the micelles into the individual triblock copolymer chains would be expected since the MEMA block becomes hydrophilic under these conditions (this was confirmed by control experiments with no BIEE). However, dynamic light scattering studies indicated the continued presence of the micelles, which confirmed that shell cross-linking had been successful. In one series of experiments conducted with a similar triblock copolymer of higher molecular weight [PEO–DMA–MEMA(2)],[13] the BIEE concentration was systematically increased from 3 to 30 mol % (based on DMA residues) and shell cross-linking was carried out in D_2O to facilitate NMR studies. Aliquots of the SCK micelles were periodically extracted, diluted with D_2O, and analyzed by dynamic light scattering. It was found that robust, if somewhat polydisperse, SCK micelles of approximately 90 nm were obtained even at 6 mol % BIEE. This value is significantly lower than the minimum degree of cross-linking of 10% reported by Ding and Liu for the UV-induced cross-linking of cinnamoyl-based residues.[6] In practice, the true degree of shell cross-linking will almost certainly be less than 6% because (1) it is improbable that both iodoalkyl groups of every BIEE molecule react with DMA residues and (2) some degree of intrachain quaternization most likely occurs.

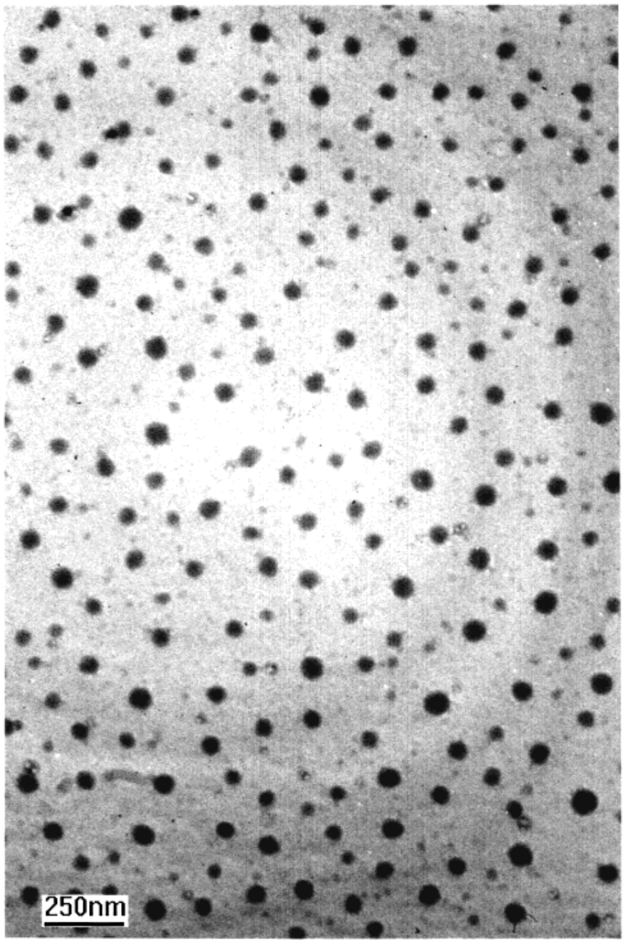

Figure 2. Representative transmission electron micrograph of a dilute suspension of SCK micelles originally prepared using the PEO–DMA–MEMA(1) triblock copolymer at 10% solids in aqueous media at 20 °C.

Unfortunately, overlapping peak integrals prevented estimation of the degree of quaternization of the DMA residues by ^{1}H NMR spectroscopy. However, NMR proved very useful for monitoring the extent of hydration of the MEMA residues in the cores of the SCK micelles on varying the electrolyte concentration and/or solution temperature. For example, in the presence of 1.0 M Na_2SO_4 at 20 °C, the NMR signals at δ 2.5 and δ 3.6 due to the MEMA residues disappeared. These signals reappeared after dialysis and/or dilution.

Static light scattering (SLS) studies of diluted SCK micelles prepared using PEO–DMA–MEMA(1) gave a high quality Zimm plot which yielded a radius of gyration of 21 ± 2 nm and a micelle mass of approximately 11.5×10^6 g mol^{-1}. Given that the weight-

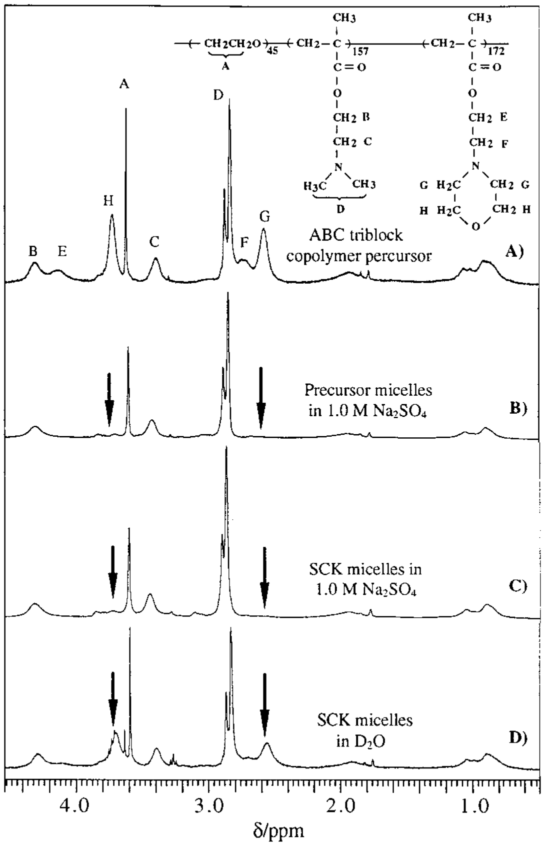

Figure 3. ^1H NMR spectra in D_2O at 20 °C: (a) triblock copolymer PEO−DMA−MEMA(2); (b) the same copolymer in the presence of 1.0 M Na_2SO_4 (note the absence of any signals due to the MEMA residues, indicating that this block forms the core of the onion micelles, as expected); (c) SCK micelles prepared from this copolymer at 10% solids in the presence of 1.0 M Na_2SO_4; (d) the same SCK micelles in the absence of Na_2SO_4 (note the reappearance of the MEMA signals at δ 2.5 and δ 3.6, indicating rehydration of the micelle core).

average molecular weight (M_w) of the original triblock copolymer is estimated to be 31 400 (and assuming that the target degree of cross-linking of 20% was achieved) this indicates a micelle aggregation number of approximately 340. A transmission electron micrograph of a dilute suspension of SCK micelles prepared at 10% solids using PEO−DMA−MEMA(1) is shown in Figure 2. The particles have a spherical morphology, a high degree of dispersion (i.e., essentially no inter-micelle cross-linking occurs), and a mean number-average particle diameter of around 40 nm. This size is somewhat smaller than the hydrodynamic diameter of 68 nm obtained from dynamic light scattering studies. Some discrepancy would be expected due to solvation effects, but the relatively large difference observed may also reflect the polydisperse nature of these particles.

Other ABC triblock copolymers gave similar results. In particular, a copolymer[14] comprising ethylene oxide, DMA, and *tert*-butylaminoethyl methacrylate (BAEMA) residues dissolved molecularly in water at 4 °C but formed "BAEMA-core" micelles on warming to 20 °C. Thus, one advantage of this copolymer is that micellization can be induced without addition of electrolyte. Shell cross-linking at 20 °C was achieved with BIEE at 10% solids with minimal inter-micelle cross-linking, as judged by dynamic light scattering. We anticipate that, at some critical copolymer concentration between 20 and 50%, there should be a phase transition from spherical to nonspherical micelles (i.e., wormlike or rodlike particles). Shell cross-linking under these conditions is expected to lead to new anisotropic supramolecular structures with interesting rheological properties.[15]

In summary, these preliminary "proof of concept" experiments verify that sterically stabilized SCK micelles with tunable core hydrophilicity can be readily prepared at high solids in aqueous media using ABC triblock copolymers. This is an important advance which suggests that SCK micelles, perhaps hitherto regarded as an academic curiosity, may be amenable to commercial exploitation.

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(14) The average degrees of polymerization for this triblock copolymer were 45 for PEO, 49 for DMA, and 71 for BAEMA.

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