

Synthesis of Shell Cross-Linked Micelles with Tunable Hydrophilic/Hydrophobic Cores

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Wooley and co-workers recently reported^{1–5} the synthesis of shell cross-linked “knedel” (SCK) micelles and suggested that these supramolecular structures “appear to be a hybrid between dendrimers, hollow spheres, latex particles, and block copolymer micelles.” Various applications, in areas as diverse as solubilization, catalysis, fillers, coatings, and delivery were proposed for these fascinating new materials.¹ Although the synthesis of SCK micelles is relatively straightforward, two problems are apparent. First, the shell cross-linking reaction must be carried out at relatively high dilution in order to avoid intermicellar cross-linking. More importantly, the SCK micelles described by Wooley and co-workers have only hydrophobic micellar cores, typically based on polystyrene or polyisoprene. If these “nanocapsules” were to be used as delivery vehicles, an explicit release mechanism would be desirable.

Herein we report the synthesis of SCK micelles with temperature-variable core hydrophilicity. This is achieved by reacting partially quaternized 2-(dimethylamino)ethyl methacrylate-*N*-(morpholino)ethyl methacrylate (DMAEMA–MEMA) diblock copolymer micelles with a bifunctional quaternizing agent, 1,2-bis-(2-iodoethoxy)ethane, in aqueous solution at 60 °C. On cooling to 25 °C, the hydrophobic MEMA micelle cores become hydrated. Thus, these new SCK micelles differ from those reported by Wooley’s group in that the micelle core can be reversibly hydrated or dehydrated, depending on the solution temperature and/or electrolyte concentration. This ability to control the degree of hydration of the micelle cores suggests possible uptake/release applications.

Block Copolymer Synthesis. The DMAEMA–MEMA diblock copolymer was synthesized using group transfer polymerization as described previously.^{6,7} DMAEMA monomer was polymerized first and quantitative yields were obtained for both monomers. The overall M_n and M_w/M_n of the block copolymer was 36000 and 1.10, respectively.⁸ The DMAEMA content of the block copolymer was 35 mol %, as determined by proton NMR spectroscopy.⁹ Partial *selective* quaternization of the DMAEMA

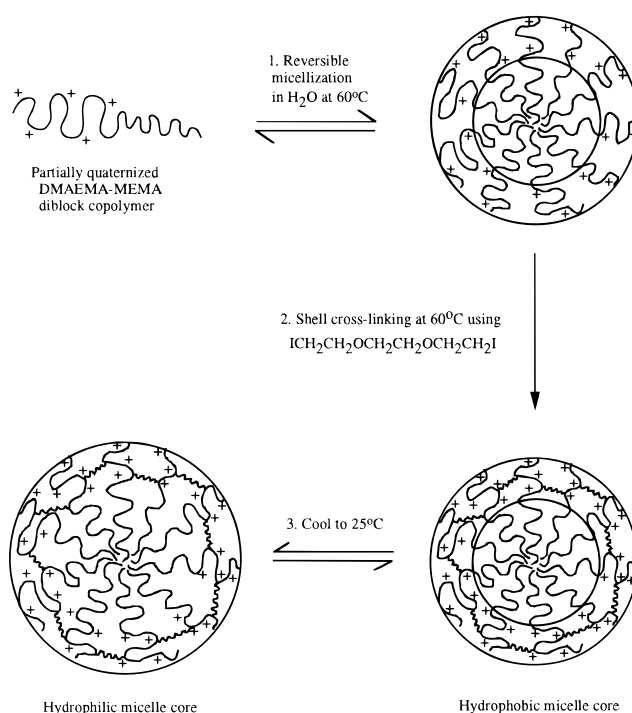


Figure 1. Reaction scheme for the synthesis of SCK micelles using a partially quaternized DMAEMA–MEMA block copolymer.

residues was achieved using methyl iodide in THF (25 °C for 1 h). Proton NMR spectroscopy indicated a degree of quaternization of 30% for the DMAEMA block. Control experiments with DMAEMA and MEMA homopolymers confirmed that the MEMA block did not react under these conditions.⁹ Quaternization allows discrimination between the DMAEMA and MEMA block sequences in aqueous media, since the partially quaternized DMAEMA block no longer exhibits inverse temperature–solubility behavior. The derivatized block copolymer undergoes reversible micellization in aqueous media on raising the solution temperature above the cloud point of the MEMA block. SCK micelles are then readily prepared by selective cross-linking of the unquaternized DMAEMA residues in the micellar corona (see Figure 1).

Shell Cross-Linking of the Block Copolymer Micelles. A 0.50 wt % aqueous solution of the partially quaternized DMAEMA–MEMA block copolymer in 0.10 M Na₂SO₄ at pH 10 was heated to 60 °C. Under these conditions the MEMA block becomes dehydrated and forms the nonsolvated micelle core, with the partially quaternized DMAEMA block forming the solvated corona. This is confirmed by variable temperature NMR studies; proton signals due to the MEMA block are significantly reduced in intensity relative to the DMAEMA signals at 60 °C (compare the NMR spectra in Figure 2A and B). Dynamic light-scattering studies¹¹ at 60 °C indicated an intensity-average micelle diameter of 36 nm. Shell cross-linking of the unquaternized DMAEMA residues was achieved by adding 1,2-bis-(2-iodoethoxy)ethane

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(8) Gel permeation chromatography data were obtained under the following conditions: THF eluent, PMMA standards, refractive index detector, flow rate 1.0 mL min^{−1}.

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(10) Proton NMR spectra were recorded using a 250 MHz spectrometer in either CDCl₃ or D₂O. In certain experiments the solution pH was adjusted using either DCl or NaOD. The block copolymer composition was calculated by comparing the peak integral at δ 2.2–2.3 due to the six dimethylamino protons of the DMAEMA residues to that due to the four methylene protons of the MEMA residues at δ 3.6–3.9.

(11) Dynamic light-scattering studies were carried out between 25 °C and 60 °C using a Malvern 4700 instrument (80 mW argon ion laser, CONTIN software) on 0.3 to 0.6% block copolymer solutions at 90°. Polydispersities (variances) as low as 0.06 were obtained for the micelles prior to shell cross-linking. After shell cross-linking, polydispersities of 0.11 to 0.20 were obtained.

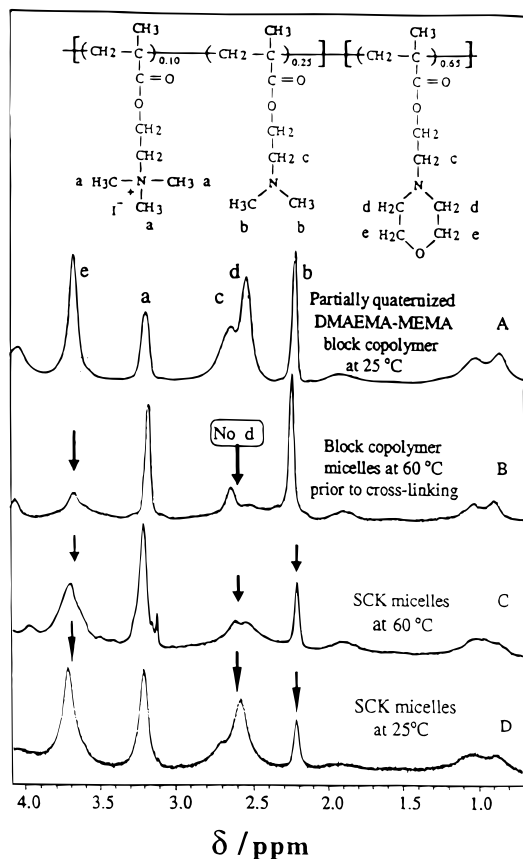


Figure 2. Variable temperature proton NMR studies of a partially quaternized DMAEMA–MEMA block copolymer [35 mol % DMAEMA, M_n 36000, 30% quaternized using methyl iodide; 1.0% copolymer in D_2O at pH 10]: (a) unimers at 25 °C; (b) micelles at 60 °C in the presence of 0.10 M Na_2SO_4 ; (c) shell cross-linked micelles at 60 °C in the presence of 0.25 M Na_2SO_4 ; (d) SCK micelles on cooling to 25 °C in the presence of 0.25 M Na_2SO_4 .

(0.40 mol per mole of unquaternized DMAEMA residues) to the micellar solution at 60 °C.

Verification of the SCK Micelle Structure. At 60 °C the intensity-average micelle diameter after the shell cross-linking reaction was 28 nm. However, after this reaction solution was cooled to 25 °C, dynamic light-scattering studies indicated an intensity-average diameter of ca. 30 nm, which confirms SCK micelle formation. If shell cross-linking had been unsuccessful, no micelles could exist at 25 °C since the MEMA block is hydrophilic at this temperature and micelle dissociation would occur. The small increase in micelle diameter on cooling the solution to 25 °C suggests some degree of swelling as a result of the ingress of water into the now-hydrophilic MEMA core. A proton NMR spectrum of these SCK micelles recorded in D_2O at 60 °C and 0.25 M Na_2SO_4 indicated that shell cross-linking was incomplete since there is a residual signal due to the unquaternized DMAEMA residues at δ 2.2–2.3 (see Figure 2C). Comparison of this peak integral with that due to the quaternized DMAEMA residues at δ 3.1–3.3 indicated that around 30% of the DMAEMA residues remained unquaternized after shell cross-linking. Allowing for the original degree of quaternization of 30%, we estimate an upper limit of 14% for the degree of shell cross-linking. However, the actual degree of shell cross-linking is somewhat lower; a significant proportion of the $-CH_2I$ groups of the cross-linking agent probably remains unreacted, and also some degree of intrachain reaction is likely.

Examination of a dilute suspension of the SCK micelles by TEM confirmed their uniform particle size and spherical morphology and indicated a number-average micelle diameter of approximately 20 nm. Allowing for dehydration and polydis-

persity effects, this value is in reasonable agreement with the intensity-average diameter obtained from dynamic light-scattering.

Although the effect of temperature on the SCK micelle diameter described above is relatively small, it was both reproducible and reversible. Significantly larger changes in micelle diameter were observed on varying the solution pH. Thus, SCK micelles of 30 nm at 25 °C and pH 10 swelled to 38 nm at pH 2 on addition of HCl. This is presumably due to extensive protonation of the MEMA core. Such pH-induced micelle swelling is reversible; returning to pH 10 by the addition of NaOH produced micelles of 31 nm. Finally, heating a micellar solution at pH 2 from 25 °C to 60 °C apparently leads to micelle de-swelling, since the intensity-average micelle diameter decreases from 38 to 32 nm. This is surprising since the non-cross-linked, partially quaternized DMAEMA–MEMA block copolymer remains soluble as unimers under the same conditions, which suggests that temperature-induced dehydration of the MEMA chains does not occur at pH 2. Work is in progress in order to clarify these observations.

Variable temperature NMR spectra recorded for the partially quaternized DMAEMA–MEMA block copolymer in D_2O (pH 10, 0.25 M Na_2SO_4) are shown in Figure 2. At 25 °C the NMR signals due to both the DMAEMA block (δ 3.1–3.3) and the MEMA block (at δ 3.6–3.9 and δ 2.5–2.7) are evident, as expected (see Figure 2A). At 60 °C, both MEMA signals are substantially reduced in intensity relative to the DMAEMA signal (see Figure 2B). This indicates that the MEMA block becomes much less solvated under these conditions, which is consistent with extensive dehydration of the micelle core. A similar NMR spectrum was obtained after shell cross-linking although, since the overall degree of quaternization is now higher, the signal at δ 3.1–3.3 due to the three methyl groups of the quaternized DMAEMA residues increases relative to that at δ 2.2–2.3 due to the two methyl groups of the unquaternized DMAEMA residues (see Figure 2C). On cooling the solution to 25 °C, the MEMA signals at δ 3.6–3.9 and δ 2.5–2.7 regain their original intensities; this confirms hydration of the micelle cores (see Figure 2D). Temperature cycling confirmed that core (de)hydration was reversible. The effect of adding electrolyte (1.0 M Na_2SO_4) at 25 °C and pH 10 was also examined. Under these conditions the two NMR signals due to the MEMA block are again suppressed (not shown), indicating substantial dehydration of the SCK micelle cores at 25 °C due to the high salt concentration. This effect is also reversible; removal of the salt via dialysis restores these MEMA signals in the NMR spectrum.

The MEMA block's low tolerance of added electrolyte also allows the preparation of SCK micelles *without* partial quaternization of the DMAEMA–MEMA precursor block. Sufficient discrimination between the DMAEMA and MEMA blocks can be achieved by carefully controlling the solution pH and electrolyte concentration. Thus, a 0.40% aqueous solution of an *unquaternized* DMAEMA–MEMA block copolymer (48 mol % DMAEMA; overall block copolymer M_n 21500) in 0.30 M Na_2SO_4 at pH 7.5 was heated to 55 °C. NMR studies (not shown) confirmed that the MEMA block formed the nonsolvated micellar core, with the partially protonated DMAEMA block forming the solvated corona. Dynamic light-scattering studies at 50 °C indicated an intensity-average micelle diameter of 23 nm. Shell cross-linking was achieved by adding 1,2-bis-(2-iodoethoxy)ethane to this micellar solution at 55 °C. Thus, judicious selection of the aqueous solution conditions allows a more efficient synthesis of SCK micelles since the quaternization step may be omitted if desired.

In summary, novel SCK micelles based on tertiary amine methacrylate block copolymers have been synthesized using a bifunctional quaternizing reagent in aqueous media. The cores of these new SCK micelles can be reversibly hydrated or dehydrated depending on the solution temperature or salt concentration.