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Synthesis and aqueous solution properties of a well-defined thermo-responsive schizophrenic diblock copolymer

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We report only the second example of a thermo-responsive 'schizophrenic' diblock copolymer surfactant: unlike the original (meth)acrylamide-based example reported by Laschewsky and co-workers (*J. Am. Chem. Soc.*, 2002, 124, 3787), this new methacrylate-based diblock copolymer is near-monodisperse, readily synthesized in high yield and exhibits a broad temperature range between the two micelle transitions.

In 1998 we reported the first example[1] of an AB diblock copolymer that could form two types of micelles (A-core micelles or B-core micelles) solely in aqueous media. In later papers[2–4] we described second and third generation examples, including a pH-responsive diblock copolymer, and the phrase 'schizophrenic' was coined to describe the behavior of this remarkable new class of polymeric surfactants. With the pH-responsive diblock copolymer, one block comprised a weak polybase and the other block comprised a weak polyacid: at low pH the neutral, hydrophobic polyacid formed the micelle cores and at high pH the deprotonated polybase formed the inverted micelle cores. The aqueous solution behavior of this pH-responsive copolymer was extensively studied[4] using dynamic light scattering, ^{1}H NMR spectroscopy, aqueous electrophoresis and surface tensiometry.

Very recently, Laschewsky and co-workers reported[5,6] an important and interesting extension of our earlier studies: an entirely thermo-responsive schizophrenic diblock copolymer. This new copolymer, which was prepared by radical addition fragmentation transfer [RAFT] chemistry,[7] comprised a methacrylamide-based sulfobetaine monomer and *N*-isopropylacrylamide (NIPAM). However, only relatively poor yields of diblock copolymer were achieved: the NIPAM monomer was polymerized first but conversion was only allowed to reach 27%, apparently so as to ensure reasonable blocking efficiency with the sulfobetaine monomer. Furthermore, the authors stated:[5] 'our strategy…implies neither that blocks with low polydispersities are made nor that the efficiency of grafting of the second block is close to quantitative'. Some sulfobetaine homopolymer (and monomer) contamination of the crude diblock copolymer was obtained and purification required repeated precipitation followed by dialysis. Despite these synthetic difficulties, Laschewsky and co-workers demonstrated that the purified diblock copolymer, which had a polydispersity of 1.35,[6] exhibited the expected thermo-responsive behavior. A lower critical micelle temperature was observed at around 20 °C, which is close to the cloud point of the sulfobetaine homopolymer. The upper critical micelle temperature occurred at approximately 34 °C, which is near the cloud point of 32 °C reported for polyNIPAM.[8]

Herein we report only the second example of a thermo-responsive 'schizophrenic' diblock copolymer. Unlike the example reported by Laschewsky's group, this new tertiary amine methacrylate-based diblock copolymer is near-monodisperse and can be synthesized efficiently by the block copolymerization of 2-(dimethylamino)ethyl methacrylate [DMA] and 2-(*N*-morpholino)ethyl methacrylate [MEMA] via group transfer polymerization (GTP),[9,10] followed by selective quaternization[11] of the more reactive DMA residues using 1,3-propane sultone (see Fig. 1).

Two DMA–MEMA diblock copolymer precursors were prepared: the first had a DMA content of 35 mol% and an M_n of 35,000 and the second contained 51 mol% and had an M_n of 31,300. Both these diblocks had very low polydispersities ($M_w/M_n \leq 1.10$) as judged by THF GPC (*vs.* PMMA standards). After reaction with 1,3-propane sultone under mild conditions,† the resulting two sulfobetaine-based diblock copolymers [SBMA–MEMA] **1** and **2** had M_n values of approximately 44,000 and 42,500, respectively. We emphasize that both the final yield and purity of these diblock copolymers was very high; full details of both the multi-gram scale GTP synthesis and the selective quaternization of the DMA residues using 1,3-propane sultone have already been published elsewhere and are not repeated here.[10,11] In principle, the same SBMA–MEMA diblocks can also be prepared directly by sequential monomer addition using Atom Transfer Radical Polymerization [ATRP] in protic media. We note that, since the SBMA monomer is commercially available, this alternative ATRP route means that post-polymerization quaternization with the highly toxic 1,3-propane sultone reagent may be avoided, if desired.

The dilute aqueous solution properties of the two GTP-synthesized SBMA–MEMA diblock copolymers were assessed using turbidimetry, dynamic light scattering and ^{1}H NMR spectroscopy, respectively. It is well known that pure water is a marginal solvent for the SBMA homopolymer at ambient temperature.[12] In general, the attractive electrostatic forces between the polysulfobetaine chains can be attenuated either by adding salt or by raising the temperature to increase the thermal energy of the system.[12–14] In contrast, MEMA homopolymer exhibits the typical inverse temperature solubility behavior often observed for neutral water-soluble polymers; its cloud point varies from 34 °C to 49 °C at pH 8, depending on its degree of polymerization.[10] This inverse temperature solubility behavior occurs because increased thermal energies lead to disruption of the hydrogen bonds that are responsible for the initial dissolution of the polymer chains. Thus the aqueous solution properties of the thermo-responsive diblock copolymer are governed by the complementary temperature dependences of the electrostatic forces for the SBMA block and hydrogen bonding forces for the MEMA block, respectively.

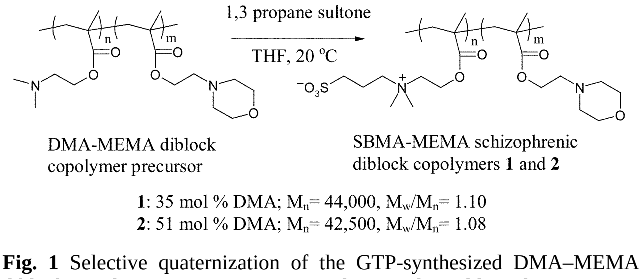

Fig. 1 Selective quaternization of the GTP-synthesized DMA–MEMA diblock copolymer using 1,3 propane sultone under mild conditions to give the thermo-responsive SBMA–MEMA diblock copolymers **1** and **2**.

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As expected, both SBMA–MEMA diblock copolymers dissolved molecularly in doubly-distilled, de-ionized water at 30–40 °C. On cooling these copolymer solutions to below 20 °C, SBMA-core micelles were obtained, due to the increased electrostatic attractive forces for this block. In contrast, MEMA-core micelles were formed on raising the temperature above 50 °C. A typical scattered light *vs.* temperature plot is shown in Fig. 2 for a 1.0 w/v% aqueous solution of copolymer **2** at around neutral pH. Here low levels of scattered light indicate molecular dissolution and increased scattering indicates the formation of colloidal aggregates (micelles). Variable temperature dynamic light scattering studies (Brookhaven instrument, 125 mW laser operating at 532 nm, fixed scattering angle of 90°) of an aqueous solution of copolymer **2** enabled the micelle dimensions to be determined. The SBMA-core micelles obtained at 4 °C had an intensity-average diameter of approximately 50 nm and were somewhat polydisperse (polydispersity, μ_2/Γ^2 = 0.45) (see Fig. 2). In contrast, near-monodisperse MEMA-core micelles with intensity-average diameters of approximately 39–45 nm (μ_2/Γ^2 = 0.09–0.10) were obtained at elevated temperature (55–65 °C). Similar observations were obtained for copolymer **1**.

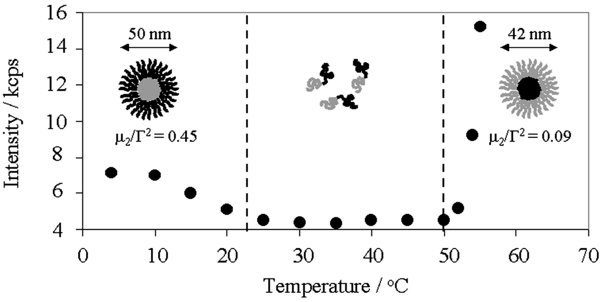

Fig. 2 Intensity of scattered light measured by DLS for a 1.0 w/v% aqueous solution of SBMA–MEMA diblock copolymer **2** at different temperatures.

^{1}H NMR spectra recorded at various temperatures for copolymer **1** in D_2O at around pH 6.5 are shown in Fig. 3. At 30 °C this diblock copolymer is molecularly dissolved and all the signals due to both blocks are visible,[11c] whereas at 3 °C the signals *b*, *h*, *i*, *j* and *k* attributed to the SBMA residues become broadened and are somewhat suppressed relative to the MEMA signals. Conversely, at 70 °C the MEMA signals *d*, *e* and *f* are significantly attenuated relative to signals *b* and *k*, indicating that the MEMA block forms the de-solvated, less mobile micelle cores under these conditions. Thus the ^{1}H NMR spectra are consistent with the two types of micelles anticipated on the basis of chemical intuition. Qualitatively, it appears that the micelle cores formed by the neutral MEMA block are more hydrophobic than those formed by the ionic sulfobetaine block; Laschewsky and co-workers drew similar conclusions regarding their methacrylamide-based diblock copolymer.[5]

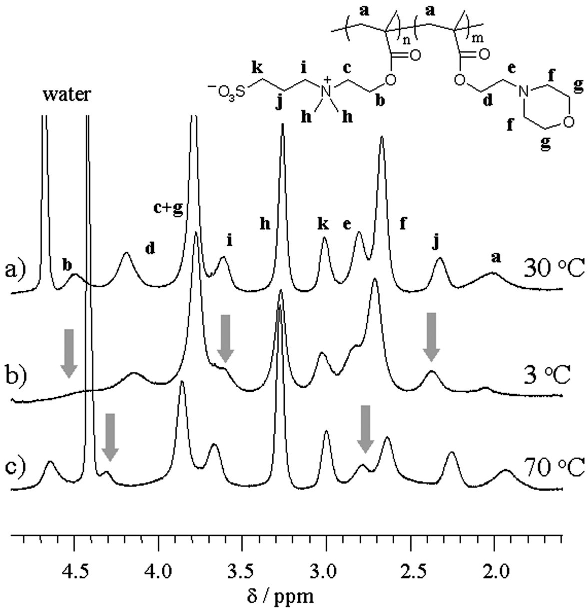

Fig. 3 ^{1}H NMR spectra of the SBMA–MEMA diblock copolymer in D_2O at pH 6.5 recorded at (a) 30, (b) 3 and (c) 70 °C.

In summary, only the second example of a schizophrenic thermo-responsive diblock copolymer is reported. Unlike the (meth)acrylamide-based copolymer described by Laschewsky and co-workers, these new methacrylate-based SBMA–MEMA copolymers are near-monodisperse, have well-defined block architectures and can be conveniently synthesized in much higher yield by GTP. Molecular dissolution occurs in dilute aqueous solution at 30–40 °C; polydisperse, hydrated SBMA-core micelles are formed below a lower critical micelle temperature of approximately 20 °C and near-monodisperse, relatively dehydrated MEMA-core micelles are formed above an upper critical micelle temperature of about 50 °C. Potential applications for this new class of polymeric surfactants are currently being explored in our laboratory.

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Notes and references

† DMA homopolymer is much more reactive towards quaternization than MEMA homopolymer (see ref. 11). Thus, provided that the 1,3-propane sultone is not used in excess (*i.e.* if the molar ratio of 1,3-propane sultone to DMA residues is no greater than unity) this reagent reacts selectively with the DMA block, leaving the MEMA residues untouched. Very high degrees of quaternization (up to 98%, as judged by ^{1}H NMR) are achieved at ambient temperature in THF. We have previously shown that no chain scission occurs under these mild conditions and hence the narrow molecular distribution of the precursor polymer is preserved in the final sulfobetaine polymer (see ref. 14).

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