Synthesis and Aqueous Solution Behavior of a pH-Responsive Schizophrenic Diblock Copolymer

Shiyong Liu and Steven P. Armes*

School of Chemistry, Physics and Environmental Science, University of Sussex, Falmer, Brighton, East Sussex, BN1 9QJ, United Kingdom

A novel zwitterionic poly[4-vinylbenzoic acid-*block*-2-*N*-(morpholino)ethyl methacrylate] (VBA$_{63}$-*b*-MEMA$_{123}$) diblock copolymer was synthesized via atom transfer radical polymerization using protecting group chemistry for the acidic residues. The acidic VBA block has a pK_a of 7.1, which is higher than that of the conjugate acid of the MEMA block (pK_a = 4.9). This has important consequences for the aqueous solution properties of this zwitterionic diblock copolymer. For example, unlike other zwitterionic diblock copolymers such as poly[methacrylic acid-*block*-2-(dimethylamino)ethyl methacrylate], precipitation does not occur at the isoelectric point (IEP) of around pH 6.2. This is most likely due to the relatively low degree of charge density on both the VBA and MEMA blocks at this pH. The VBA$_{63}$−MEMA$_{123}$ copolymer exhibits interesting "schizophrenic" micellization behavior. Below pH 6, VBA-core micelles are formed, while above pH 6, the diblock copolymer can be dissolved as unimers. In the presence of sufficient Na$_2$SO$_4$ or at elevated temperature, well-defined MEMA-core micelles are formed in alkaline media. Thus, if dissolved in the presence of 0.80 M Na$_2$SO$_4$, the zwitterionic diblock copolymer can be switched from VBA-core micelles to MEMA-core micelles (and vice versa) simply by manipulating the solution pH. At intermediate pH around the IEP precipitation occurs, in contrast to the solution behavior in the absence of salt. The most likely explanation is that the weakly hydrophilic copolymer is simply "salted out" under these conditions. Alternatively, the added electrolyte leads to a higher charge density on the copolymer chains and precipitation occurs due to polyelectrolyte complexation. Both the VBA-core micelles and the "inverted" MEMA-core micelles have been characterized at different solution pHs, ionic strengths, and temperatures using potentiometric titration, aqueous electrophoresis, dynamic and static light scattering, and ^{1}H NMR spectroscopy measurements, respectively.

Introduction

AB diblock copolymers undergo micellar self-assembly in solvents that are selective for one of the blocks.[1−5] Like conventional surfactants, which form micelles and reverse micelles in aqueous and nonaqueous media, block copolymers can form both conventional micelles and so-called "inverted" micelles by choosing appropriate selective solvents for each block. Recently, we reported that certain new hydrophilic AB diblock copolymers can self-assemble in purely aqueous media to form both conventional micelles (with the A block forming the micellar core) and inverted micelles (with the B block forming the micellar core).[6−8] We have described these diblock copolymers as having "schizophrenic" character in a recent publication.[8] To date, only two well-documented examples of schizophrenic diblocks have been reported. The first "proof-of-concept" example was poly[2-(*N*-morpholino)ethyl methacrylate-*block*-2-(diethylamino)ethyl methacrylate] (MEMA-*b*-DEA). Here both blocks are weak polybases, and the block

copolymer was synthesized by group transfer polymerization (GTP).[6,7] Formation of micelles with DEA cores was achieved merely by adjusting the solution pH, while the formation of the inverted MEMA-core micelles was obtained on addition of electrolyte, which selectively "salted out" the MEMA block. Both types of micelles were stable at room temperature. The second example comprised a thermoresponsive poly(propylene oxide) (PPO) block and a pH-responsive DEA block; this copolymer was synthesized by atom transfer radical polymerization (ATRP) using a PPO macroinitiator and dissolved molecularly in cold water at pH 6.5. DEA-core micelles were formed at 5 °C in mildly alkaline solution (pH 8.5), and PPO-core micelles were obtained at pH 6.5 at elevated temperatures (40−70 °C).[8] Thus neither micellar state was stable at ambient temperature, which is rather inconvenient for both characterization studies and also for potential industrial applications.

Zwitterionic polymers, or polyampholytes, possess both positive and negative charge and are therefore interesting synthetic analogues for proteins. Although there is considerable literature on the synthesis and aqueous solution properties of zwitterionic statistical copolymers,[9] there have been relatively few reports of the synthesis of polyampholytes with block copolymer architectures. Examples include poly(2-vinyl pyridine-*block*-acrylic acid),[10] poly(2-vinyl pyridine-*block*-sodium 4-styrenesulfonate),[11] poly[*p*-(*N*,*N*-dimethylamino)styrene-*block*-methacrylic

* To whom correspondence should be addressed. Tel: UK + 1273-678650. Fax: UK + 1273-677196. E-mail: S.P.Armes@sussex.ac.uk.
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acid],[12] poly(1-methyl-4-vinylpyridinium chloride-*block*-methacrylic acid),[13] and probably the most extensively studied, poly(2-(dimethylamino)ethyl methacrylate-*block*-methacrylic acid) (DMA-*b*-MAA).[14−22] In the latter example, the DMA and MAA blocks are generally hydrophilic over the whole pH range and behave as a weak polybase and polyacid, respectively. At low pH, the DMA block is cationic and the MAA block is neutral, whereas at high pH the MAA block is anionic and the DMA block is neutral. At intermediate pH, both DMA and MAA units can be charged, thus leading to a zwitterionic diblock copolymer. At the isoelectric point (IEP), the cationic charges on the DMA block just balance the anionic charges on the MAA block; thus the diblock polymer precipitates due to polyelectrolyte complexation. In contrast, no precipitation is observed for a *statistical* DMA−MAA copolymer around the IEP region.

For a diblock copolymer comprising a neutral block and a basic block, such as poly(ethylene oxide-*block*-2-vinyl pyridine) (PEO-*b*-P2VP), molecular dissolution occurs at low pH and micelles are formed above pH 4.8, because the P2VP block is then deprotonated and hence insoluble in water.[23] Since there is little (if any) interaction between the PEO and P2VP blocks, the driving force for micellization is the hydrophobic interactions between the P2VP blocks. However, for a zwitterionic diblock copolymer, the electrostatic attraction between the oppositely charged blocks is expected to be an additional driving force for precipitation, aggregation, or micellization. Depending on its block composition, solution pH, and ionic strength, the DMA−MAA diblock copolymer is molecularly dissolved, is insoluble, or forms large, loose aggregates with a hydrodynamic diameter D_h of around 400−500 nm due to the hydrophilic nature of both blocks.[19] It was claimed that MAA-core micelles are formed at low pH and DMA-core micelles are formed at high pH, although these aggregates appear to be too large to be "true" micelles. At intermediate pH, precipitation was observed at around the IEP, as expected.

Herein we describe a new zwitterionic AB diblock copolymer, poly[4-vinylbenzoic acid-*block*-2-(*N*-morpholino)ethyl methacrylate)] (VBA-*b*-MEMA), which can self-assemble in purely aqueous solution to form both VBA-core micelles and MEMA-core micelles, depending on the subtle interplay between solution pH, ionic strength, and temperature. The aqueous solution properties of this VBA-*b*-MEMA diblock copolymer and its schizophrenic micellization behavior have been characterized using hydrogen ion titration, aqueous electrophoresis, dynamic and static light scattering, and ^{1}H NMR spectroscopy, respectively.

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Experimental Section

Materials. 4-Vinylbenzoic acid was synthesized from 4-carboxybenzyltriphenyl phosphonium bromide in 90% yield using Wittig chemistry according to a literature procedure.[24] 2-(*N*-Morpholino)ethyl methacrylate (Polysciences Inc.) was passed through a basic alumina column and then vacuum distilled over CaH$_2$ and stored at −20 °C prior to use. Copper(I) chloride, copper-(I) bromide, *N,N,N′,N′*-pentamethyldiethylenetriamine (PM-DETA), 2,2′-bipyridine (bpy), 1,1,4,7,10,10-hexamethyltriethyl-enetetramine (HMTETA), and all other chemicals were purchased from Aldrich and used without further purification.

4-Vinylbenzoyl Chloride. To a stirred mixture of thionyl chloride (56 mL) and 4-*tert*-butylpyrocatecol (20 mg) under nitrogen in an ice bath was added 4-vinylbenzoic acid (26.2 g, 177 mmol) in small portions. The reaction temperature was maintained at below 10 °C for 4 h and at 40 °C for 2 h to afford a homogeneous solution. After removal of unreacted thionyl chloride, distillation gave 27.5 g of 4-vinylbenzoyl chloride as a colorless liquid at 66−69 °C (0.2 mmHg).[25]

Tert-Butyl 4-Vinylbenzoate. *t*-Butyl 4-vinylbenzoate (*t*-BuVBA) was synthesized by reacting 4-vinylbenzoyl chloride (13.3 g, 79.9 mmol) with 100 mL of *tert*-butyl alcohol in dry diethyl ether (30 mL) in the presence of potassium *tert*-butoxide (180 mmol).[25]

Preparation of Poly(*tert*-butyl 4-vinylbenzoate) Macroinitiator. For a typical polymerization of *tert*-butyl 4-vinylbenzoate via ATRP, Cu^{I}Br (143 mg, 1 mmol) was added to a dry, round-bottomed flask equipped with a stir bar. After sealing with a rubber septum, the flask was degassed and backfilled with nitrogen three times. Anisole (8 mL) and *tert*-butyl 4-vinylbenzoate (15.0 g, 74 mmol) were added, both of which were deoxygenated and added via syringes that had been prepurged with nitrogen. The PMDETA ligand (173 mg, 1 mmol) was added, and the copper complex was observed. Methyl 2-bromopropionate (MBrP) (167 mg, 1.00 mmol) was added to the flask, which was placed in a temperature-controlled oil bath at 95 °C; after 3 h, the flask was frozen with liquid nitrogen, and then the contents were dissolved in dichloromethane. ^{1}H NMR analysis indicated a monomer conversion of 67%. The polymer was purified by passing through an alumina column; after partial solvent evaporation, it was then precipitated into excess methanol. The polymer was then dried under vacuum at room temperature. The mean degree of polymerization of the *t*-BuVBA macroinitiator was determined to be 63 using ^{1}H NMR spectroscopy by comparing the integrated signal intensities at δ 4.1 (due to the methyl groups from the initiator fragment) and δ 6.3−7.8 (due to the aromatic protons of the monomer residues). Gel permeation chromatography (GPC) analysis using (poly(methyl methacrylate) (PMMA) standards, tetrahydrofuran (THF) eluent and a refractive index detector showed that this *t*-BuVBA macroinitiator had a number-average molecular weight (M_n) of 12 800 and an M_w/M_n of 1.09.

Preparation of VBA-*b*-MEMA Diblock Copolymer. MEMA was polymerized using the above *t*-BuVBA macroinitiator in 1,2-dichlorobenzene at 95 °C using Cu^{I}Cl and HMTETA as the catalyst and ligand, respectively. Up to 60% conversion was obtained after 40 min. The resulting crude *t*-BuVBA-*b*-MEMA diblock copolymer was purified by passing the reaction solution through a neutral alumina column, prior to precipitation into a 10-fold excess of *n*-hexane. The degree of polymerization of the MEMA block was determined to be 123 by ^{1}H NMR spectroscopy (see Figure 5), indicating a mean block composition of 66 mol % MEMA. GPC analysis (PMMA standards, THF eluent, refractive index detector) of this protected diblock copolymer gave an M_n of 33 700 and an M_w/M_n of 1.08, which is typical of copolymers prepared by ATRP. Selective hydrolysis of the *tert*-butyl groups was readily achieved by refluxing the diblock copolymer in a 10% v/v HCl/dioxane solution for 10 h at 85 °C. This reaction mixture was precipitated into acetone to isolate the resulting zwitterionic VBA-*b*-MEMA diblock copolymer. VBA homopolymer

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was prepared by hydrolyzing the *t*-BuVBA macroinitiator under similar conditions and then purified by precipitation into acetone.

Characterization. Dynamic light scattering (DLS) studies were performed on a Brookhaven Instruments Corp. BI-200SM goniometer equipped with a BI-9000AT digital correlator using a solid-state laser (125 mW, $\lambda = 532$ nm) with a scattering angle ranging from 90° to 20°. The intensity-average hydrodynamic diameter, $\langle D_h \rangle$, and polydispersity of the micelles were obtained by a cumulants analysis of the experimental correlation function.[26,27]

Static light scattering (SLS) studies were performed using a DAWN DSP laser photometer, equipped with a 5 mW He−Ne laser ($\lambda = 633$ nm) and 18 photodiode detectors at scattering angles ranging from 22.5° to 147°. In static light scattering, the angular dependence of the excess absolute time-averaged scattered light intensity, known as the Rayleigh ratio $R_{vv}(q)$, of a very dilute polymer solutions led to the apparent weight-average molar mass $(M_w)_{app}$ and the root-mean-square *z*-average radius of gyration $\langle R_g^2 \rangle_z^{1/2}$ (or written as $\langle R_g \rangle$), where *q* is the scattering vector.[26,27] In the presence of 0.80 M Na$_2$SO$_4$, the d*n*/d*c* values of diblock copolymer solutions comprising MEMA-core micelles at pH 10 and VBA-core micelles at pH 2 were determined to be 0.145 and 0.120 mL/g at 20 °C using an Optilab DSP Interferometric refractometer ($\lambda = 633$ nm).

Aqueous electrophoresis measurements were carried out using a Malvern ZetaMaster instrument. Zeta potentials were calculated from mobilities using the Henry equation and determined as a function of solution pH in the presence of 0.02 M NaCl at 25 °C. The solution pH was adjusted by addition of either dilute HCl or NaOH.
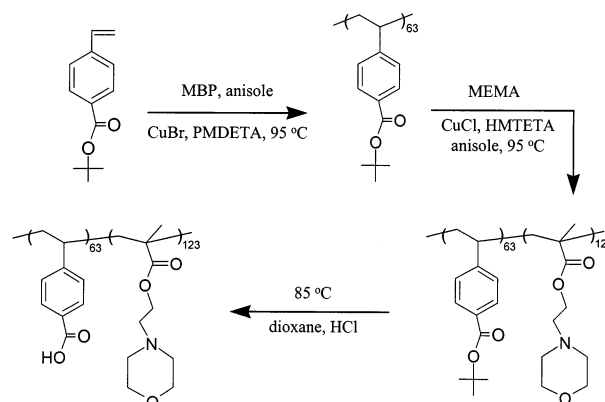
Hydrogen Ion Titration. The VBA homopolymer was first dissolved in dilute NaOH (pH 12) at 0.68 g/L. This polymer solution was titrated by the dropwise addition of 0.1 M HCl, and the solution pH was monitored with a Corning Check-Mite pH meter (precalibrated with pH 4, 7, and 10 buffer solutions).

^{1}H NMR spectra were recorded on 10.0 g L^{-1} copolymer solutions in D$_2$O using a Bruker Avance DPX 300 MHz spectrometer.

Results and Discussion

Initial attempts to polymerize sodium 4-vinylbenzoate in aqueous media by ATRP followed by adding MEMA monomer proved to be unsuccessful, due to the large amount of unwanted VBA homopolymer impurity. This contamination became apparent when characterizing the aqueous solution properties of the diblock copolymer since a cloudy, rather than micellar, solution was observed at low pH. Fortunately, the protected *t*-BuVBA$_{63}$−MEMA$_{123}$ diblock copolymer precursor was successfully synthesized by nonaqueous ATRP via a macroinitiator route using *tert*-butyl groups to mask the carboxylic acid functionality of the VBA block. These protecting groups were readily cleaved by acidic hydrolysis to produce the final target VBA−MEMA diblock copolymer (see Figure 1).

Figure 2 shows the GPC chromatograms of the *t*-BuVBA$_{63}$ macroinitiator and the *t*-BuVBA$_{63}$-*b*-MEMA$_{123}$ diblock copolymer. Clearly there is a shift to higher molecular weight, indicating chain extension of the *t*-BuVBA macroinitiator by the MEMA monomer. Also, there is almost no residual peak due to the macroinitiator, indicating relatively high initiator efficiency. It seems that isolation and purification of the *t*-BuVBA macroinitiator at relatively low conversion (67%) is sufficient to suppress the undesirable side reactions that usually occur under monomer-starved conditions with ATRP and hence allows the target well-defined diblock copolymer to be obtained.[28]

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Figure 1. The ATRP synthesis of the poly[4-vinylbenzoic acid-*block*-2-(*N*-morpholino)ethyl methacrylate] (VBA$_{63}$-*b*-MEMA$_{123}$) diblock copolymer using *tert*-butyl protecting groups to mask the acidic block.
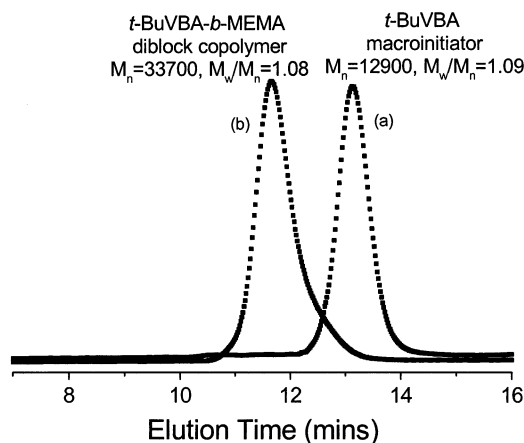
Figure 2. Gel permeation chromatograms (PMMA standards, THF eluent, refractive index detector) of (a) the *t*-BuVBA macroinitiator and (b) the *t*-BuVBA-*b*-MEMA diblock copolymer precursor.

To assess the possibility of hydrolysis of the MEMA block during hydrolysis of the *t*-BuVBA block, MEMA homopolymer was subjected to the same hydrolysis conditions as those used to remove the *tert*-butyl groups, and there was almost no detectable MEMA hydrolysis by ^{1}H NMR spectroscopy. This control experiment confirmed the structural integrity of the final VBA$_{63}$-*b*-MEMA$_{123}$ diblock copolymer.

We have previously reported that MEMA homopolymer is a weak polybase with a pK_b of approximately 9.1 (and a corresponding conjugate acid with a pK_a of 4.9).[6,7,29] It is molecularly soluble over a wide pH range, either as a weak cationic polyelectrolyte in acidic media or as an uncharged polymer at neutral or alkaline pH. Under the latter conditions, MEMA homopolymer can precipitate at 32−53 °C, depending on its molecular weight. The aqueous solubility of MEMA homopolymer at neutral or basic pH is also salt-sensitive: it can be salted out relatively easily from aqueous solution on addition of electrolytes such as Na$_2$SO$_4$ and K$_2$CO$_3$. However, MEMA homopolymer can be redissolved as a cationic polyelectrolyte by addition of acid even at high salt concentration (or elevated temperature) due to protonation of the morpholine groups.
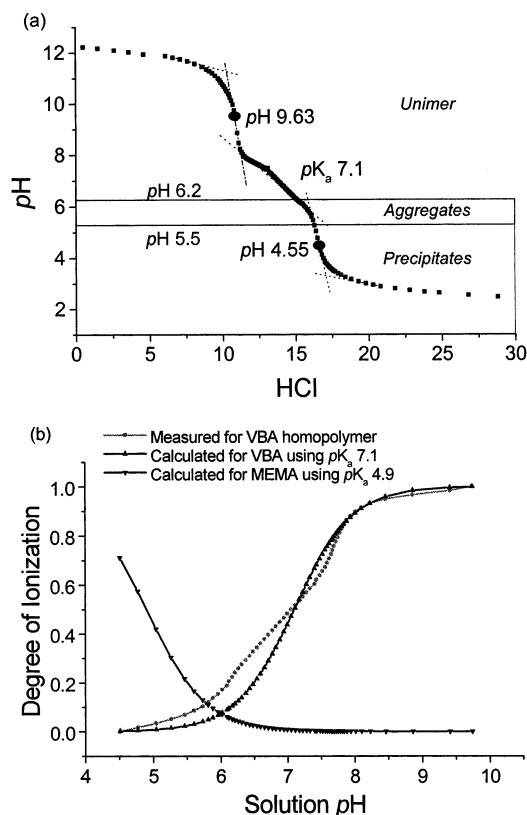
Figure 3a shows the titration curve for the VBA homopolymer in dilute aqueous solution, where the *x* axis represents the amount of HCl added. Analysis of these

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Figure 3. (a) Experimental titration curve obtained for a 0.68 g/L aqueous solution of VBA homopolymer using 0.10 M HCl. (b) The variation of the degree of ionization of the VBA homopolymer (measured and calculated) and the degree of protonation of the MEMA homopolymer (calculated) as a function of solution pH.

data gave a pK_a of 7.1 for the VBA homopolymer.[30] Dynamic light scattering studies revealed that VBA homopolymer is not soluble below pH 5.5. Above pH 6.2, VBA homopolymer is molecularly dissolved, while from pH 5.5 to 6.2, it forms colloidal aggregates of around 60–100 nm. This is probably due to the intermolecular hydrogen bonding between aromatic carboxyl groups at low degrees of ionization. Figure 3b shows the variation of degree of ionization (or protonation) of the VBA and MEMA blocks with solution pH. The calculated and measured curves for the VBA homopolymer agree reasonably well given that we have not considered the possible effect of local charge density in suppressing ionization.[14]

It was anticipated that the VBA-*b*-MEMA diblock copolymer would form VBA-core micelles[30] at low pH and MEMA-core micelles at high pH in the presence of salt (or at elevated temperature).[6,7] Hence supramolecular self-assembly in aqueous solution could be switched from micelles to inverted micelles simply by changing the solution pH, salt concentration, or temperature. Moreover, given the zwitterionic nature of the VBA-*b*-MEMA diblock, an IEP was expected. However, because the pK_a of the VBA block is higher than that of the conjugate acid of the MEMA block (see Figure 3b), the charge density of both blocks is unusually low at the IEP. Presumably, this accounts for the surprising solubility of this zwitterionic diblock copolymer at its IEP; this is in striking contrast to literature examples such as DMA–MAA diblock copolymers, which invariably precipitate at around the IEP region.[14–22]

(30) Note that this pK_a differs from that reported previously by Gabaston and co-workers [Gabaston, L. I.; Furlong, S. A.; Jackson, R. A.; Armes, S. P. *Polymer* **1999**, *40*, 4505].
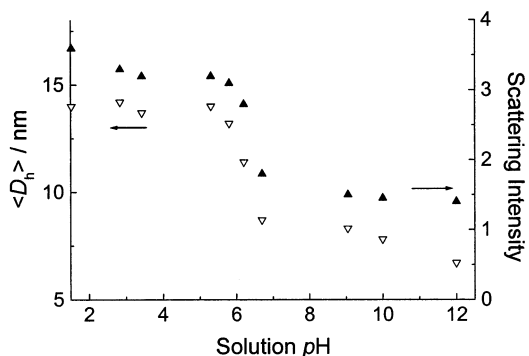

Figure 4. Variation of intensity-average hydrodynamic diameter $\langle D_h \rangle$ and scattering intensity (at 90°) as a function of pH for a 2.0 g/L aqueous solution of the VBA$_{63}$-*b*-MEMA$_{123}$ diblock copolymer.
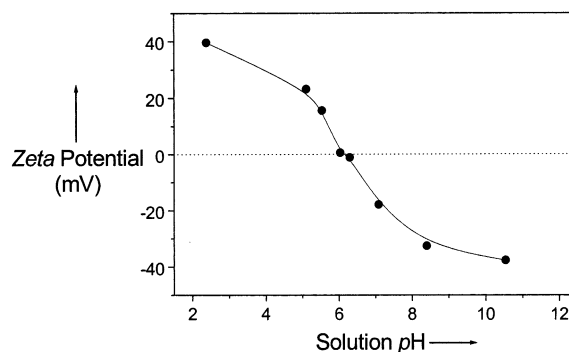
Figure 5. Zeta potential vs pH curve for a 0.20 g/L aqueous solution of the VBA$_{63}$-*b*-MEMA$_{123}$ zwitterionic diblock copolymer at 20 °C.

Figure 4 shows the variation of intensity-average hydrodynamic diameter $\langle D_h \rangle$ and scattering intensity on adjusting the pH of a 0.20 g/L solution of the VBA$_{63}$-*b*-MEMA$_{123}$ diblock copolymer. Above pH 6.5, the diblock copolymer dissolves molecularly as unimers, with a $\langle D_h \rangle$ of around 6–8 nm and very low scattering intensity. Below pH 5.5, well-defined VBA-core micelles are formed due to the insolubility of the VBA block and the scattering intensity increases considerably. These micelles have a $\langle D_h \rangle$ of 14 nm and a fairly low polydispersity index (μ_2/Γ^2) of 0.10. Unexpectedly, this copolymer solution remains optically clear over the whole pH range; even the scattering intensity does not show any abrupt changes in the IEP region. The IEP of a zwitterionic diblock copolymer can be theoretically predicted if the dissociation constants are assumed to be independent of the block composition. The actual IEP depends on both the block composition and the respective pK_a and pK_b values. The IEP for a VBA$_{63}$-*b*-MEMA$_{123}$ diblock copolymer is calculated to be at pH 6.16.[14] Figure 5 shows the variation of zeta potential with solution pH for the diblock copolymer. The zeta potential is close to zero at around pH 6.20, which is in excellent agreement with the calculated IEP. However, as noted above, no macroscopic precipitation is observed in this region.

According to Figure 3b, at pH 6.20, the degree of ionization of the VBA block is only 11% and the degree of protonation of the MEMA block is just 4.8%, that is, there are approximately six protonated MEMA residues and six ionized VBA residues per diblock copolymer chain. In contrast, for a DMA-*b*-MAA zwitterionic copolymer with a similar block composition, the degrees of ionization (or protonation) for each block at its IEP are more than 50%; thus polyelectrolyte complexation between the cationic and anionic blocks is strong enough to cause precipitation to occur. Returning to the VBA$_{66}$-*b*-MEMA$_{123}$ diblock
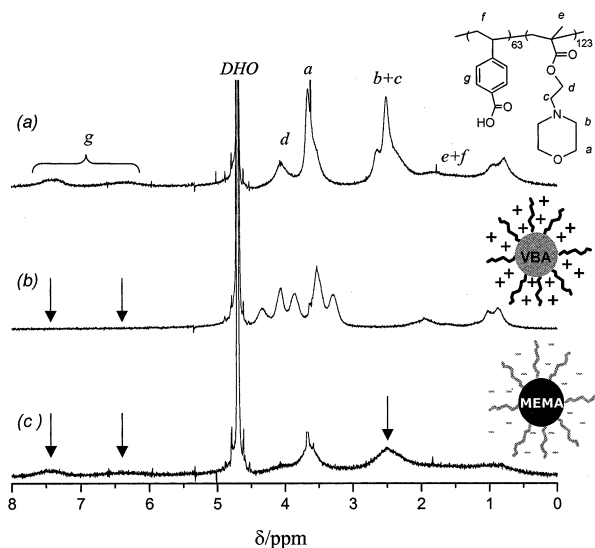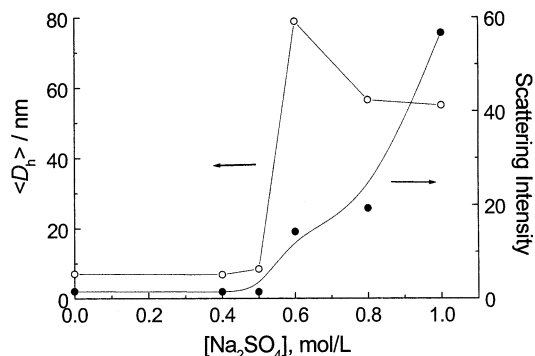
Figure 6. ^{1}H NMR spectra recorded for the VBA$_{63}$-*b*-MEMA$_{123}$ diblock copolymer: (a) at pH 10 in D$_2$O/NaOD; (b) at pH 4.5 in DCl/D$_2$O; (c) at pH 10 and 0.8 M Na$_2$SO$_4$ in D$_2$O/NaOD.
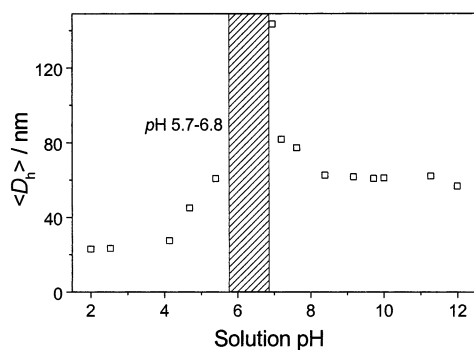

Figure 7. The variation of intensity-average hydrodynamic diameter $\langle D_h \rangle$ and scattering intensity (at 90°) as a function of Na$_2$SO$_4$ concentration for a 0.20 g/L aqueous solution of VBA$_{63}$-*b*-MEMA$_{123}$ diblock copolymer at pH 10.

Figure 8. The variation of intensity-average hydrodynamic diameter $\langle D_h \rangle$ and scattering intensity (at 90°) of VBA-core micelles obtained by the addition of Na$_2$SO$_4$ to a VBA$_{63}$-*b*-MEMA$_{123}$ diblock copolymer solution at pH 2.

copolymer, the degree of ionization of the VBA block increases above the IEP but the degree of protonation of the MEMA block decreases. Conversely, the degree of ionization of the VBA block decreases below the IEP but the degree of protonation of the MEMA block increases. In both cases, the hydrophilic character, and hence aqueous solubility, of the VBA (or MEMA) block increases and the electrostatic attraction between the two blocks is not sufficient to induce macroscopic precipitation.

The formation of VBA-core micelles can also be confirmed by ^{1}H NMR spectroscopy. Figure 6 shows ^{1}H NMR spectra of the VBA$_{63}$-*b*-MEMA$_{123}$ diblock under various conditions. In Figure 6a, the diblock copolymer is soluble as unimers at pH 10 and all the signals for the VBA and MEMA residues are observed, as expected. Compared to the ^{1}H NMR spectrum of the *t*-BuVBA-*b*-MEMA diblock copolymer precursor before hydrolysis (not shown), there are no longer any signals due to the *tert*-butyl groups at δ 1.5, indicating that the *t*-BuVBA residues have been completely hydrolyzed to yield VBA residues. In Figure 6b, all of the signals that are characteristic of the MEMA residues are visible at pH 4 but there are no aromatic signals (δ 6.5−7.8) corresponding to the VBA block; this indicates that VBA-core micelles are formed with cationic MEMA coronas.

MEMA homopolymer becomes insoluble at neutral or basic pH at elevated temperature or in the presence of salt.[6,7,29] Figure 7 shows the variation of $\langle D_h \rangle$ and scattering intensity on adding Na$_2$SO$_4$ to a 0.20 g L^{-1} aqueous solution of VBA$_{63}$-*b*-MEMA$_{123}$ diblock copolymer at pH 10. Below 0.5 M Na$_2$SO$_4$, a hydrodynamic diameter of about 6−8 nm and only low scattering intensity were detected by DLS, indicating that the block copolymer is molecularly dissolved under these conditions. Above 0.6 M Na$_2$SO$_4$, the scattering intensity increased abruptly; the $\langle D_h \rangle$ increased to 79 nm at 0.6 M Na$_2$SO$_4$ and then gradually decreased to 55 nm at 1.0 M Na$_2$SO$_4$ with a polydispersity index of 0.06. Thus near-monodisperse MEMA-core micelles are formed at high salt concentration, as expected. The increase of scattering intensity at higher salt concentration is accompanied with a reduction in micelle size, which suggests higher micellar densities, that is, denser packing of the chains within the micelles at higher salt concentration due to screening of the interchain repulsive forces within the micelle coronas. The ^{1}H NMR spectrum shown
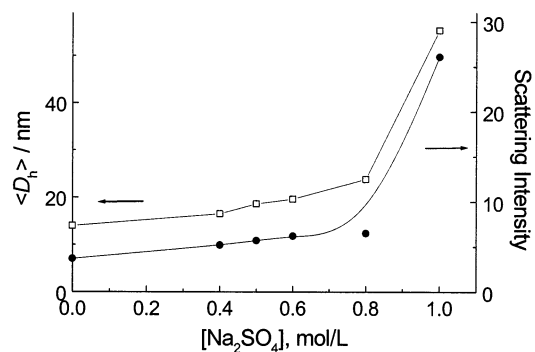
in Figure 6c confirms that the intensities of the signals assigned to the MEMA residues (δ 2.4−2.8, δ 3.5−3.9) are considerably attenuated while the aromatic signals corresponding to the VBA block at δ 6.3−7.8 remain visible; this indicates that MEMA-core micelles with anionic VBA coronas are formed at pH 10. Although suppressed, the MEMA signals do not completely disappear. This observation differs from that reported for salt-induced MEMA-core micelles formed from MEMA-*b*-DEA diblocks.[6,7] This is probably due to the differing degrees of hydrophilicity of the coronal chains in the two cases. A higher charge density is expected for the VBA chains compared to the DEA chains, which should in turn lead to less efficient coronal packing and hence looser, more hydrated micelle cores.

The MEMA-core micelles formed in the presence of added salt are much larger than the VBA-core micelles formed at low pH. Presumably, the block asymmetry contributes to this size difference, since the MEMA block is approximately twice as long as the VBA block; longer core-forming blocks lead to higher micelle aggregation numbers and hence larger micelles.[1−3] Furthermore, the presence of salt will make the insoluble block even more hydrophobic and the soluble block somewhat less hydrophilic. This shift in the overall hydrophilic−hydrophobic balance will inevitably lead to larger micelles. To illustrate this salt effect, a 0.20 g L^{-1} solution of the VBA-core micelles was initially molecularly dissolved at pH 10 and then adjusted to pH 2 to form a VBA-core micellar solution. DLS was used to study the change in micelle diameter caused by adding increasing amounts of Na$_2$SO$_4$. As shown in Figure 8, the VBA-core micelle diameter gradually increased from 14 to 24 nm as the Na$_2$SO$_4$ concentration was increased from zero to 0.8 M. Above 0.8 M, the micelle

Figure 9. The variation of intensity-average hydrodynamic diameter $\langle D_h \rangle$ and scattering intensity (at 90°) with solution pH for a 0.20 g/L aqueous solution of VBA_{63}-b-$MEMA_{123}$ diblock copolymer in the presence of 0.80 M Na_2SO_4.

Table 1. Dynamic and Static Light Scattering Characterization of VBA-Core Micelles and Inverted MEMA-Core Micelles Formed by the VBA_{63}-b-$MEMA_{123}$ Diblock Copolymer under Different Aqueous Solution Conditions

micelle parameters	VBA_{63}-b-$MEMA_{123}$ at pH 10, no Na_2SO_4	VBA-core micelles at pH 2 and 0.8 M Na_2SO_4	MEMA-core micelles at pH 10 and 0.8 M Na_2SO_4
$M_{w,\text{micelles}}$	4.54×10^4	4.81×10^5	1.36×10^7
$\langle R_g \rangle$/nm			25
$\langle R_h \rangle$/nm	4	14^a	33^a
$\langle R_g \rangle / \langle R_h \rangle$			0.76
N_{agg}	1−2	11	299
$\langle \rho \rangle$/(g/cm³)		0.070	0.15

^{a} The R_h values were obtained by extrapolation to zero angle.

diameter increased rapidly up to 55 nm, with a concomitant increase in scattering intensity. This is because the lateral electrostatic repulsions between the protonated, cationic MEMA chains in the micelle coronas become screened in the presence of sufficient electrolyte, leading to a large increase in the micelle aggregation number.

The results from Figure 4 and Figure 8 suggest that in the presence of sufficient electrolyte (>0.6 M Na_2SO_4), it is possible to switch between VBA-core micelles and MEMA-core micelles simply by adjusting the solution pH. One obvious question worthy of investigation is the following: is the transition from VBA-core micelles to MEMA-core micelles abrupt or is an intermediate state involved? Figure 9 depicts the variation in $\langle D_h \rangle$ with pH for the zwitterionic diblock copolymer in the presence of 0.8 M Na_2SO_4. VBA-core micelles are formed at pH 2 with a $\langle D_h \rangle$ of 24 nm, and this diameter increases up to 61 nm at pH 5.4. From pH 5.7 to 6.8, precipitation occurs. Above pH 6.8, the solution becomes optically clear again. DLS studies indicate an intensity-average diameter of about 143 nm at pH 7.0; considering the degree of polymerization of the VBA-b-MEMA diblock copolymer, colloidal aggregates are formed at pH 7 rather than well-defined micelles. The micelle diameter decreases monotonically with increasing solution pH, with MEMA-core micelles of 57 nm being formed at pH 12. Provided that the additional background salt formed during pH adjustment does not cause any salting-out effects, such pH-responsive micellization behavior is fully reversible.

SLS studies for the VBA-core and MEMA-core micelles, formed at pH 2 and pH 10 in the presence of 0.80 M Na_2SO_4, respectively, yielded weight-average micelle masses of approximately 4.81×10^5 and 1.36×10^7 g mol⁻¹ (see Table 1). On the basis of the weight-average molecular weight of VBA_{63}-b-$MEMA_{123}$ diblock copolymer determined

by SLS at pH 10 in the absence of salt (i.e., under conditions where it is assumed to be molecularly dissolved as unimers), the micelle aggregation numbers (N_{agg}) were estimated to be 11 and 299 for the VBA-core and MEMA-core micelles, respectively. This large difference in micelle aggregation number is attributed to the block asymmetry and is also consistent with the differences in hydrodynamic diameter for these two types of micelles (see Table 1), which indicate a 16-fold difference in micelle volume. Using the equation $\langle \rho \rangle = M_w/(4/3\pi N_a \langle R_h \rangle^3)$, the micelle densities, $\langle \rho \rangle$, of the VBA-core and MEMA-core micelles were estimated to be 0.070 and 0.15 g cm⁻³, respectively. Thus the MEMA-core micelles are somewhat more compact than the VBA-core micelles. The $\langle R_g \rangle / \langle R_h \rangle$ ratio for the MEMA-core micelles is 0.757, which is very close to the theoretical value of 0.774 for a hard sphere. The $\langle R_g \rangle$ value for the VBA-core micelles is close to the lower limit of around 10 nm for static light scattering, which prevents calculation of a reliable $\langle R_g \rangle / \langle R_h \rangle$ ratio. The two calculated micelle densities are much less than the solid-state density of 1.33 g cm⁻³ determined for the VBA−MEMA diblock copolymer by helium pycnometry. This indicates that both types of micelles are appreciably swollen, suggesting significant stretching of the coronal polyelectrolyte chains.

One intriguing feature of the effect of added electrolyte is the observation of precipitation of the VBA−MEMA diblock within the IEP region. The midpoint of the visually observed precipitation region is at pH 6.25, which can be taken as the approximate IEP. Bearing in mind that the effect of salt on the dissociation constants (pK_a's) of the VBA and MEMA blocks has been ignored, this is in fairly good agreement with the calculated IEP of pH 6.16. Given that the overall copolymer charge density remains very low, one obvious explanation for precipitation in the presence of salt is that the copolymer chains are simply salted out. Alternatively, the ionization/dissociation behavior of the VBA and MEMA blocks will be affected by the relatively high ionic strength imparted by the added electrolyte. Hoogeveen et al. reported that DMA homopolymer is a stronger polybase in the presence of salt.[31] This is because the electrolyte screens the charge density on the polymer chains; hence, at a given pH protonation occurs more easily. Thus the effective pK_b of the MEMA block increases (becomes more basic) and the effective pK_a of the VBA block decreases (becomes more acidic); that is, the MEMA block is more readily protonated and the VBA block is more easily ionized. Consequently the charge density on the copolymer chains at the IEP in the presence of salt will be higher than that obtained in the absence of salt. This increased charge density will aid the precipitation of the diblock copolymer from aqueous solution via polyelectrolyte complexation.

MEMA-core micelles are also formed at elevated temperature, since the MEMA block exhibits inverse temperature−solubility behavior in neutral/alkaline solution. Figure 10 shows the variation of scattering intensity and $\langle D_h \rangle$ as a function of temperature for the VBA_{63}-b-$MEMA_{123}$ copolymer at pH 10. Below 80 °C, there is no aggregation and the copolymer chains exist as unimers. MEMA-core micelles with a $\langle D_h \rangle$ of 50 nm are formed at or above 80 °C. The scattering intensity also increases, as expected. In the presence of salt, micelles are formed at lower temperatures. For example, in the presence of 0.40 M Na_2SO_4, the onset of aggregation occurs above 30 °C, with $\langle D_h \rangle$ gradually decreasing from 54 to 44 nm as the temperature is raised from 40 to 80 °C (see Figure 11). ¹H

(31) Hoogeveen, N. G.; Stuart, M. A. C.; Fleer, G. J.; Frank, W.; Arnold, M. *Macromol. Chem. Phys.* **1996**, *197*, 2553.
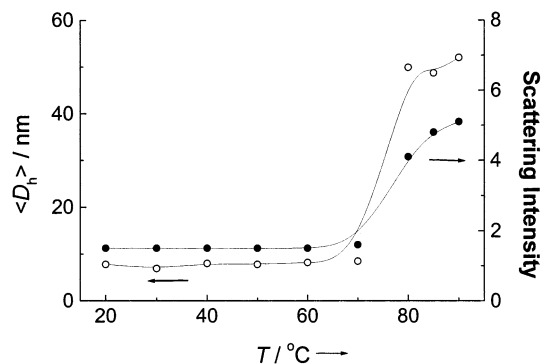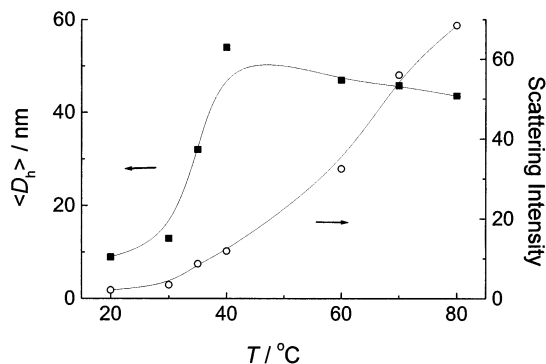
Figure 10. The variation of intensity-average hydrodynamic diameter $\langle D_h \rangle$ and scattering intensity (at 90°) with increasing temperature for a 0.20 g/L aqueous solution of the VBA$_{63}$-*b*-MEMA$_{123}$ diblock copolymer at pH 10.

NMR studies (not shown) confirmed that the MEMA signals were attenuated, indicating the formation of MEMA-core micelles at elevated temperatures. On cooling, micellar dissociation occurs and the original NMR spectrum was obtained.

Conclusions

In summary, a novel VBA$_{63}$-*b*-MEMA$_{123}$ zwitterionic diblock copolymer has been synthesized by ATRP using protecting group chemistry. The dilute aqueous solution properties of this diblock copolymer have been studied in some detail. This copolymer can form two types of micelles in aqueous solution at 20 °C simply by adjusting the solution pH. Unlike other zwitterionic diblock copolymers reported to date, precipitation does not occur at the IEP in the absence of salt. Presumably this is due to the relatively low charge density on the copolymer chains,

Figure 11. The variation of intensity-average hydrodynamic diameter $\langle D_h \rangle$ and scattering intensity (at 90°) as a function of temperature for a 0.20 g/L aqueous solution of the VBA$_{63}$-*b*-MEMA$_{123}$ diblock copolymer at pH 10 in the presence of 0.40 M Na$_2$SO$_4$.

which in turn is dictated by the pK_a values for the VBA and MEMA residues. In the presence of added salt, precipitation is observed at the IEP and both VBA-core and MEMA-core micelles are formed at 20 °C, as judged by ^{1}H NMR spectroscopy and laser light scattering studies. Thus this zwitterionic polymeric surfactant exhibits schizophrenic character. In the absence of salt, VBA-core micelles are formed in acidic solution at 20 °C but MEMA-core micelles are only formed at elevated temperatures (above the lower critical solution temperature of the neutral MEMA block).