Synthesis and Characterization of Novel "Schizophrenic" Water-Soluble Triblock Copolymers and Shell Cross-Linked Micelles

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Received September 21, 2005; Revised Manuscript Received November 19, 2005

ABSTRACT: A series of novel "schizophrenic" ABC triblock copolymers, 2-(diethylamino)ethyl methacrylate-*b*-2-(dimethylamino)ethyl methacrylate-*b*-2-(*N*-morpholino)ethyl methacrylate [PDEA−PDMA−PMEMA], has been synthesized by using group transfer polymerization. These triblock copolymers dissolved molecularly in aqueous solution at low pH (<6.6) due to protonation of all tertiary amine residues of the three blocks and formed three-layer "onionlike" micelles at pH 7.6 by PDEA block forming the micelle cores, PDMA block forming the inner shells, and PMEMA forming the coronas. On the other hand, by the addition of Na_2SO_4 to the molecularly soluble polymer solution at pH 6.5 the neutral PMEMA-block became hydrophobic due to the salting-out effect and another three-layer "onionlike" micellization occurred, comprising PMEMA cores, PDMA inner shells, and PDEA coronas. DLS studies indicated nearly-monodisperse micelles in both cases. The intensity-average radii of the PMEMA−core and the PDEA−core micelles were 10.1 nm (polydispersity index, $\mu_2/\Gamma^2 = 0.10$) and 12.9 nm ($\mu_2/\Gamma^2 = 0.08$), respectively. It was also observed that these triblock copolymers formed PMEMA−core micellization in *n*-hexane. Finally, two types of novel shell cross-linked micelles (PDEA−core in aqueous media and PMEMA−core in *n*-hexane) were also prepared from these remarkable PDEA−PDMA−PMEMA triblock copolymers by cross-linking the inner PDMA shell of the micelles. In shell cross-linking of both micelles, the outer PDEA or PMEMA shell acted as steric stabilizer and prevented intermicelle aggregation even when the cross-linking chemistry was carried out at high polymer concentrations.

Introduction

Since 1998 numerous examples of novel water-soluble diblock copolymers that exhibit so-called "schizophrenic" character have been reported.[1−14] That is, the copolymer chains can self-assemble in dilute aqueous solution in the absence of any organic cosolvent to form *two* distinct micelle structures. In each case, the individual blocks can be independently tuned to become either hydrophilic or hydrophobic by subtle adjustment of the solution temperature, solution pH or ionic strength. The original report in this new sub-field involved a tertiary amine methacrylate-based AB diblock copolymer, 2-(diethylamino)ethyl methacrylate-*b*-2-(*N*-morpholino)ethyl methacrylate [PDEA−PMEMA],[1,2] synthesized by using group transfer polymerization that was both pH- and salt-responsive, allowing the formation of either PMEMA−core micelles or PDEA−core micelles in aqueous solution with the diameter of 26 and 33 nm, respectively.

The synthesis of a second "schizophrenic" diblock copolymer, poly(propylene oxide)-*b*-2-(diethylamino)ethyl methacrylate [PPO−PDEA] was reported using atom transfer radical polymerization (ATRP) chemistry.[3] While the PDEA block has pH-sensitive water-solubility the PPO block exhibits inverse temperature solubility behavior. The PPO−PDEA diblock dissolved molecularly at 5 °C at pH 6, with the PDEA block in its protonated, cationic form. When the solution pH was adjusted to pH 8.5, PDEA−core micelles were formed at 5 °C. Alternatively, warming the original solution at pH 6 up to 40 °C led to PPO−core micelles.

Later on, various novel zwitterionic diblock copolymers, (4-vinylbenzoic acid)-*b*-DEA [PVBA−PDEA],[4] PVBA−PMEMA,[5] 2-(dimethylamino)ethyl methacrylate-*b*-methacrylic acid [PDMA−PMAA],[6] PMAA−PDEA,[7] succinyl ethyl methacrylate-*b*-DEA [PSEMA−PDEA][8,] and MAA-*b*-methoxy-capped oligo(ethylene glycol) methacrylate [PMAA−OEGMA],[9] were also reported having "schizophrenic" character merely by adjusting the solution pH and temperature. In the cases of PMAA−core micelles, it was not possible to obtain conclusive spectroscopic evidence.[9,7]

There are a few reports on the purely thermoresponsive "schizophrenic" diblock copolymers, (*N*-isopropylacrylamide)-*b*-(sulfobetaine methacrylamide) [PNIPAM−PSBMAM],[10,11] selectively betainized PDMA−PMEMA diblock copolymer [PSBMA−PMEMA][12] and selectively betainized DMA-*b*-N,N′-diethyl acrylamide[13] which forms A−core micelles below the lower consolute solution temperature (LCST) and B−core micelles above the consolute solution temperature (UCST).

Only one ABC type block copolymer was reported as "schizophrenic" triblock copolymer in the literature.[14] A PEO-based macroinitiator was used to first polymerize 2-(diethylamino)ethyl methacrylate (DEA) and then 2-hydroxyethyl methacrylate (HEMA) in a one-pot synthesis via ATRP. The resulting PEO−PDEA-PHEMA triblock copolymer precursors were converted into the corresponding PEO−PDEA−PSEMA zwitterionic triblock copolymers by esterification of the hydroxy groups on the HEMA block using succinic anhydride. A "trinity" of micellar aggregates was formed by these PEO−PDEA−PSEMA triblock copolymers in aqueous solution simply by adjusting the solution pH at ambient temperature.[14] Three types of micelles were formed in aqueous solution: (i) the hydrogen-bonded PSEMA/PEO−core micelles at low pH, (ii) the PDEA−core micelles in alkaline, and (iii) the PSEMA/PDEA interpolyelectrolyte-core micelles formed at around the IEP. In all micellizations of PEO−PDEA−PSEMA triblock copolymer, there were two layers (core and corona).

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10.1021/ma052052k CCC: $33.50
Published on Web 01/13/2006

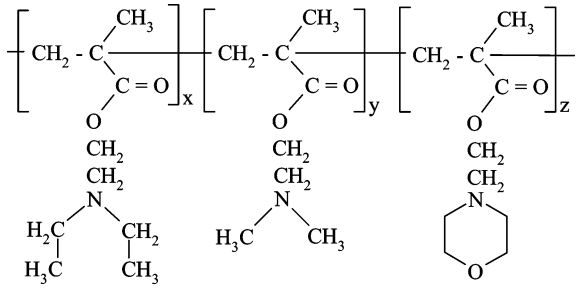

Figure 1. Chemical structure of the PDEA−PDMA−PMEMA triblock copolymer synthesized by using group transfer polymerization.

Here in we report a novel ABC type triblock copolymer [PDEA−PDMA−PMEMA, see Figure 1] having "schizophrenic" character which forms "onion" micelles [A−core micelles and C−core micelles, with solvated double blocks containing cross-linkable inner shell, depending on aqueous solution conditions] (see Figure 2). In each micellization, both A block and C block can be independently tuned to become either hydrophilic or hydrophobic by subtle adjustment of the solution pH and ionic strength. In addition, as far as we are aware, there is no report in the literature about ABC type "schizophrenic" triblock copolymers having a cross-linkable middle hydrophilic block in both A−core and C−core "onion" micelles.

Experimental Section

General Protocols. Group transfer polymerization (GTP) was used to synthesize tertiary amine methacrylate based triblock copolymers with narrow molecular weight distributions and well-controlled molecular weights and comonomer compositions in THF at 20 °C. All chemicals were purchased from Aldrich, unless otherwise stated. All glassware and transfer needles were dried by storing in an oven overnight at 140 °C before use. All reactions were carried out under dry nitrogen. To eliminate surface moisture, all glassware was directly assembled from the oven, flamed out under high vacuum (10^{-4}−10^{-5} Torr) and allowed to cool to room temperature. Nitrogen was passed through both a silica column and a P_2O_5 drying column prior to use.

Tetrahydrofuran (THF; Fisher) was initially dried over sodium wire and refluxed over potassium for 3 days before use. The dried THF was stored over 4 Å molecular sieves at room temperature and transferred into the reaction vessel via cannula. MEMA (SP2), DMA, and DEA were each passed in turn through a basic alumina column to remove the hydroquinone methyl ether inhibitor and stirred over calcium hydride, the less volatile 2,2-diphenyl-1-picrylhydrazyl hydrate (DPPH) inhibitor was added, and then the reaction was stored at −20 °C. The monomers were each distilled under reduced pressure before transferring into the reaction vessel by cannula under a dry nitrogen atmosphere. 1-Methoxy-1-trimethylsiloxy-2-methyl-1-propane (MTS) was distilled and stored at −20 °C in a graduated Schlenk flask under dry nitrogen prior to use. Tetra-*n*-butylammonium bibenzoate (TBABB) was prepared by the method of Dicker et al.[15] and stored under dry nitrogen.

Table 1. Copolymer Compositions, Number Average Molecular Weights (M_n), Polydispersities (PD), and Polymerization Degrees (DP) for the PDEA−PDMA−PMEMA Triblock Copolymers

sample code	M_n (GPC)	M_w/M_n (GPC)	M_n (NMR)	DP (theory)	DP (NMR)
VB396	19 300	1.10	24 600	30/60/30	34/67/39
VB395	21 500	1.13	22 300	25/60/30	27/66/35

Synthesis of Tertiary Amine Methacrylate Triblock Copolymers. To synthesize a triblock copolymer by group transfer polymerization (GTP), the solid TBABB catalyst (approximately 100 mg) was added from a sidearm under a nitrogen purge into a 250 mL three-necked round-bottom flask. THF (approximately 150 mL) was then transferred into the flask via cannula before the addition of MTS (0.45 mL). This solution was stirred for 15 min, and then monomer (13.0 mL of DEA) was added by cannula. In the meantime, a contact thermocouple was attached to the side of the reaction vessel to monitor the exotherm during the addition of monomer. It was observed that the reaction temperature typically increased by 6 °C, which depends on monomer/solvent ratio. The reaction mixture was stirred until the solution temperature returned to room temperature (approximately 40 min). Then a 0.5 mL aliquot of the reaction mixture was extracted via syringe for GPC and NMR analysis. To produce an AB diblock copolymer (PDEA−PDMA), after a 0.5 mL aliquot was extracted from the polymerizing DEA reaction mixture (as described above), the second monomer (DMA, 15.0 mL) was added via cannula and a second exotherm was recorded (9.2 °C). The reaction mixture was stirred at room temperature until the exotherm had abated (approximately 40 min).

Finally, to produce an ABC triblock copolymer (PDEA−PDMA−PMEMA), after a 0.5 mL aliquot was extracted from the polymerizing PDEA−PDMA reaction mixture (as described above) and the third monomer (MEMA, 10.0 mL) was added via cannula and a third exotherm was recorded (5.7 °C). The reaction mixture was, again, stirred at room temperature until the exotherm had abated (approximately 50 min).

After extraction of a 0.5 mL aliquot for GPC analysis, the reaction was terminated with methanol (2 mL) prior to recovery using a rotary evaporator. The resulting triblock copolymer was dried on a vacuum line at room temperature for 24 h after removing PDEA and PDEA−PDMA contaminations as described below. The DP's of the resulting PDEA−PDMA−PMEMA triblock copolymer were calculated from ^{1}H NMR spectra as being 34 (PDEA), 67 (PDMA) and 39 (PMEMA), respectively. All copolymerizations gave very high yields (>98%). A summary of the two synthesized triblock copolymers, including their NMR and GPC data, are listed in Table 1.

Synthesis of SCL Micelles. $PDEA_{34}$−$PDMA_{67}$−$PMEMA_{39}$ triblock copolymer (2.0 g) was molecularly dissolved in 200 mL

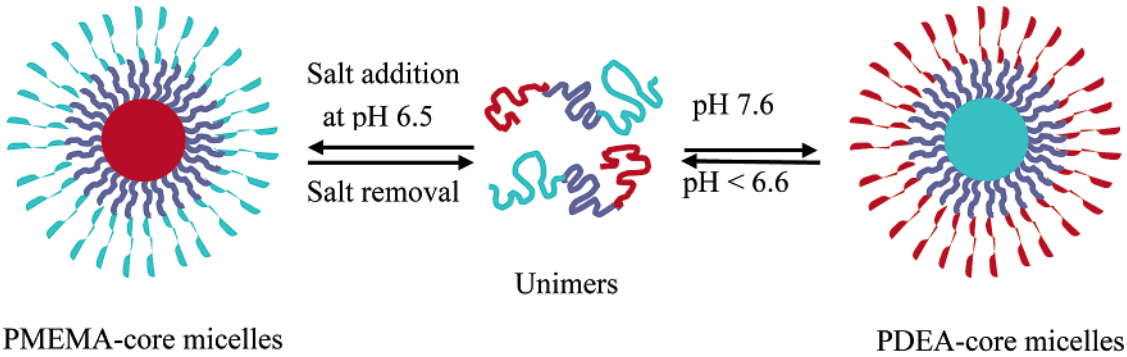

Figure 2. Schematic representation of the "schizophrenic" behavior exhibited by a PDEA−PDMA−PMEMA triblock copolymer in dilute aqueous solution: Three-layer "onion" micelles with PDEA−core are formed above pH 7.5, whereas PMEMA−core "onion" micelles can be formed at around pH 6.5 on addition of sufficient electrolyte. In both cases, the DMA block remains as solvated inner shell.

of water by adjusting solution pH to 2.2 using 2.0 M HCl. The solution pH was increased to pH 7.6 by the dropwise addition of 1.0 M KOH solution while the solution was being stirred with the speed of 1250 rpm. Both dynamic light scattering (DLS) measurements and proton NMR studies indicated PDEA−core micelle formation with the radius of 12.9 nm ($\mu_2/\Gamma^2 = 0.08$). Inner shell cross-linking was achieved at pH 7.6 at room temperature for 3 days using bifunctional cross-linker (260 μL), 1,2-bis(2-iodoethoxy)ethane [BIEE; 25 mol % based on DMA residues].[16]

The synthesis of PMEMA−core SCL micelles was carried out in *n*-hexane by using THF as cosolvent. $PDEA_{34}$−$PDMA_{67}$−$PMEMA_{39}$ triblock copolymer (0.5 g) was first dissolved molecularly in THF (6.0 mL) before addition of *n*-hexane (44.0 mL) to form PMEMA−core micelles at 50 °C. DLS measurements indicated that the radius of the micelle was 15.4 nm ($\mu_2/\Gamma^2 = 0.08$) at 50 °C. The inner shell (PDMA block) was cross-linked with the same cross-linker [BIEE; 65 μL, 25 mol % based on DMA residues] by stirring the solution for 3 days at 50 °C. The resulting shell cross-linked micelles were characterized by using DLS.

Copolymer Characterizations. Gel Permeation Chromatography (THF Eluent). Molecular weights and molecular weight distributions of all polymers were determined by using gel permeation chromatography (GPC). The GPC consisted of a Viscotek LC pump, a refractive index detector, two mixed "E" and mixed "D" columns (from Polymer Labs), and calibration was carried out using PMMA calibration standards (from Polymer Labs), with M_n ranging from 680 to 218 600 g mol^{-1}. The GPC eluent was HPLC grade THF stabilized with BHT, at a flow rate of 1.0 mL min^{-1}.

Nuclear Magnetic Resonance Spectroscopy (NMR). The degrees of polymerizations (DP) of all copolymers and all triblock copolymer compositions were investigated using a Bruker 300 MHz Avance NMR instrument. All spectra were recorded in $CDCl_3$ solvent. The methoxy signal at δ 3.6−3.7 due to the MTS initiator fragment was used to estimate the actual DP of the first PDEA block.[17] Treating this PDEA block as an end group, the block copolymer compositions were determined by comparing appropriate integrals assigned to the different comonomers. ^{1}H NMR studies with Bruker 300 and 400 MHz Avance NMR instruments were also carried out to characterize micellization behavior of the triblock copolymers in D_2O by adjusting the solution pH with DCl and NaOD and in *n*-hexane by using $CDCl_3$ as cosolvent.

Dynamic Light Scattering Studies. To determine the hydrodynamic radius and the polydispersity index (PDI = μ_2/Γ^2) of the triblock copolymer micelles and both SCL micelles Dynamic Light Scattering (DLS) studies were conducted using an ALV/CGS-3 compact goniometer system (Malvern, U.K.) equipped with a 22 mW He−Ne laser operating at λ_o 632.8 nm, an avalanche photodiode detector with high quantum efficiency, and an ALV/LSE−5003 multiple tau digital correlator electronics system. All measurements were performed on copolymer solutions having concentrations between 0.1% and 1.0% (w/v) at 20 °C for aqueous solution and at 20, 30, and 50 °C for THF/*n*-hexane solutions using a fixed scattering angle of 90°, and the data were fitted using second-order cumulants analysis.

Results and Discussion

Triblock Copolymer Syntheses and Characterizations. The PDEA−PDMA−PMEMA triblock copolymers were successfully synthesized in high yield using GTP and characterized by using GPC and ^{1}H NMR spectroscopy. The number-average molecular weights (M_n) and the polydispersities (PD) of the copolymers were determined by GPC and are summarized in Table 1. The GPC chromatograms of each step in the synthesis of a PDEA−PDMA−PMEMA triblock copolymer (VB396) are given in Figure 3. As GPC indicated little homopolymer and diblock copolymer contaminations, the PDEA−PDMA−PMEMA triblock copolymers were precipitated from THF into cold *n*-hexane to remove the contaminants. Liquid nitrogen was used to cool *n*-hexane. Typically, copolymer (30 g) was dissolved in minimum amount of THF (50 mL) and then poured into cold *n*-hexane (800 mL). The precipitated block copolymer was washed with cold *n*-hexane twice before drying under vacuum at room temperature for 24 h. M_n's and polydispersities of the triblock copolymer were determined by GPC and are summarized in Table 1.

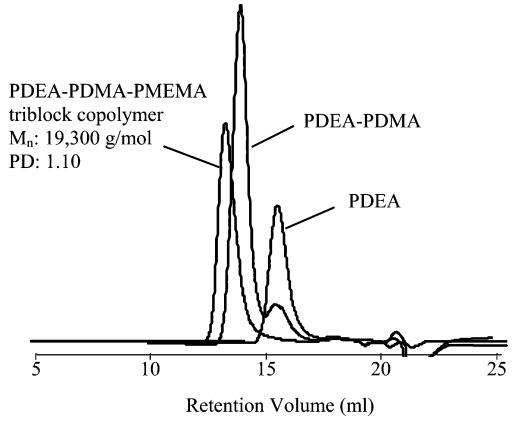

Figure 3. GPC chromatograms of each step in the synthesis of PDEA−PDMA−PMEMA triblock copolymer (VB396): (a) PDEA; (b) PDEA−PDMA; (c) PDEA−PDMA−PMEMA triblock copolymer (after removal of the PDEA and PDEA−PDMA contaminants).

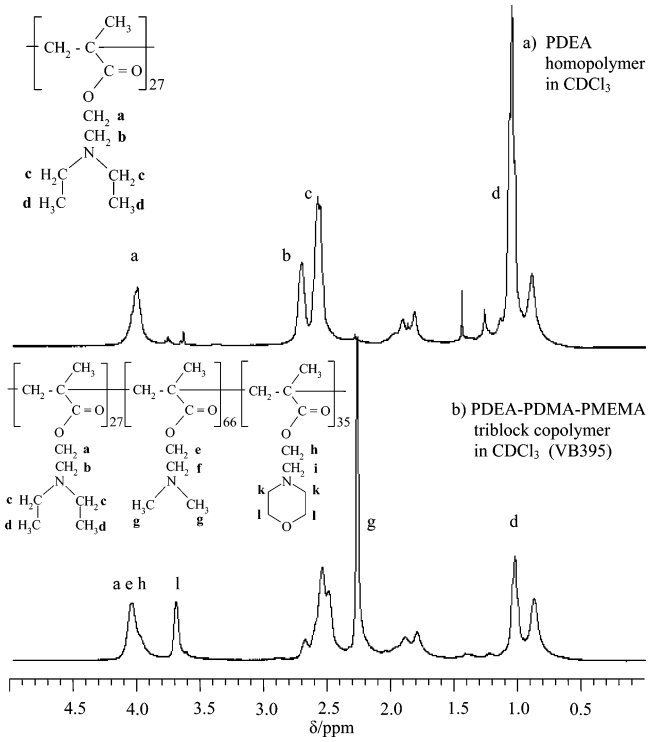

Figure 4. Proton NMR spectra of a PDEA homopolymer (before addition of DMA and MEMA monomers) and a PDEA−PDMA−PMEMA triblock copolymer (VB395) in $CDCl_3$.

Typical ^{1}H NMR spectra of both PDEA homopolymer (just before addition of second and third monomers) and the triblock copolymer (PDEA−PDMA−PMEMA, VB395) are shown in Figure 4, recorded in $CDCl_3$ with the relevant signals labeled. Absolute DP's and the block compositions were determined by comparing well-defined peak integrals assigned to the different comonomers. The absolute DP of the PDEA homopolymer was estimated to be 27 by comparing the peak integrals of the three methoxy protons at δ 3.6−3.7 due to the terminal MMA residues derived from the MTS initiator with the oxymethylene

protons of the PDEA residues at δ 4.0 (see upper spectrum in Figure 4).[17] Treating this PDEA block as an "end group", inspection of the lower ^{1}H NMR ($CDCl_3$) spectrum in Figure 4 for the triblock copolymer indicated average degrees of polymerization for the PDMA and PMEMA blocks of 66 and 35, respectively [by comparing the peak integrals of the oxymethylene protons of all PDEA, PDMA, and PMEMA residues at δ 4.0−4.1 with both the peak integral of the six dimethylamino protons in the PDMA residues at δ 2.2−2.3 and the peak integrals of $-CH_2-O-CH_2-$ protons in morpholino rings of the PMEMA residues at δ 3.7]. The observed small increases in DP compared to theoretical values are almost certainly due to the imperfect MTS initiator efficiency (around 90% in such polymerizations) and the removal of the homopolymer contamination from the triblock copolymers, which results in a decrease in the mean DPs. In general, good agreement was observed between the theoretical and determined M_n's, DP's and comonomer compositions from the NMR/GPC values (see Table 1). Both triblock copolymers had low PD's (<1.13), which is typical of polymers synthesized via GTP.

Aqueous Solution Behavior of the Triblock Copolymer. The PDMA and PMEMA homopolymers are both weak polybases and they are water-soluble at both neutral and acidic pH at room temperature but less soluble at pH > 10. They exhibit inverse temperature−solubility behavior, and their pK_a values are 7.0 and 4.9, respectively, as reported in our previous studies.[17] Above pH 8, the cloud points of PDMA homopolymers range from 32 to 46 °C depending on molecular weight. On the other hand, the PMEMA chains are soluble in their nonprotonated, neutral form, above pH 6. Depending on molecular weight, the cloud points of PMEMA homopolymers range from 34 to 54 °C at pH 7.

However, when they are not protonated, in neutral form, they precipitate from neutral or basic aqueous solution above 32 °C depending on their molecular weights. As reported before,[17] PMEMA homopolymer is more soluble than PDMA homopolymer at high pH and 20 °C. It was also reported that PMEMA homopolymer in its neutral form can also easily be precipitated (salted out) at room temperature from aqueous solution above pH 6 on addition of electrolytes such as Na_2SO_4, and K_2CO_3 and so on. Under the same conditions, PDMA homopolymer remains solvated up to pH 8 due to protonation of the tertiary amine residues. On the other hand, PDEA homopolymer dissolves as a cationic polyelectrolyte in acidic solution (pH < 6.6) due to protonation of its tertiary amine residues. Precipitation from aqueous solution occurs when the solution pH exceeds the pK_a of 7.3 for PDEA homopolymer, because the average degree of protonation drops below a critical value and the chains become hydrophobic. In contrast, PMEMA and PDMA homopolymers remain water-soluble at room temperature in mildly alkaline media in the absence of electrolyte.

In view of these observations, we realized that the subtle variation of the hydrophilic/hydrophobic balance of the PDEA−PDMA−PMEMA triblock copolymer provided a unique opportunity to prepare *two* distinct three-layer "onionlike" micelle structures from the same triblock copolymer in aqueous solution: (i) PDEA−core micelles by the PDMA block forming hydrated inner shell and the PMEMA block forming the hydrated corona and (ii) PMEMA−core micelles by the PDMA block forming the solvated inner shell and the PDEA block forming the solvated corona (see Figure 2).

Salt-Induced Formation of Three-Layer "Onion" Micelles with PMEMA-Core. The PDEA−PDMA−PMEMA triblock copolymer dissolved molecularly in dilute HCl (or in dilute DCl for ^{1}H NMR studies) at pH 2.2. Careful addition of KOH solution (or KOD for ^{1}H NMR studies) to this acidic solution at 20 °C produced a final pH of 6.5. Proton NMR studies and DLS studies confirmed that the triblock copolymer was molecularly soluble (unimers) under these conditions (see Table 2). The pH 6.5 solution was divided into two parts (I and II). When Na_2SO_4 was added into polymer solution I, ^{1}H NMR studies confirmed that both blocks of PDEA and PDMA remain solvated due to protonation of tertiary amine residues under these conditions (note the prominent signals at 1.4, 3.3 for DEA and at 3.0 for DMA residues), whereas the signals due to the PMEMA block at 2.6−2.8 and 3.7 are suppressed (compare parts a and b of Figure 5). This is consistent with the PMEMA block forming the nonsolvated micelle cores, which is entirely expected given its low tolerance to added electrolyte, PDMA block forming the hydrated inner shells and PDEA block forming the solvated micelle coronas.

Table 2. Summary of the Dynamic Light Scattering Data for Unimers, PDEA−Core Micelles, and PMEMA−Core Micelles of PDEA−PDMA−PMEMA Triblock Copolymers at Different Solution pH and the Electrolyte Concentration at 20 °C[a]

	Na_2SO_4	VB396		VB395		
	concn	radius		radius		
pH	(mol/L)	(nm)	PD	(nm)	PD	
2.2		1.1	0.05	1.2	0.11	molecularly soluble
3.5		1.5	0.15	1.4	0.12	molecularly soluble
6.5		2.5	0.20	2.6	0.22	molecularly soluble
6.5	1.0	10.1	0.10	11.0	0.11	PMEMA−core micelles
7.6		12.9	0.08			PDEA−core micelles
8.0				13.8	0.10	
>9						precipitation

[a] All DLS measurements were carried out by using 1.0% triblock copolymer solutions.

pH-Induced Formation of Three-Layer "Onion" Micelles with PDEA—Core. If the pH of the solution II of the PDEA−PDMA−PMEMA triblock copolymer was increased from 6.5 to 7.6 by careful addition of KOH solution (or KOD for NMR studies) at 20 °C in the absence of electrolyte the PDEA block is substantially deprotonated and therefore hydrophobic, whereas the both blocks of PDMA and PMEMA remain hydrated under these conditions (see Figure 5). Thus, three-layer "onion" micelles comprising PDEA cores, PDMA inner shells and PMEMA coronas are expected. DLS and ^{1}H NMR studies confirmed this to be the case. A macroscopic precipitation occurs with the further increase on pH (pH > 9), since deprotonation of the tertiary amine residues of PDMA causes a decrease on the hydrophilic character of the PDMA block.

The ^{1}H NMR spectra in Figure 5 represents the $PDEA_{27}-PDMA_{66}-PMEMA_{35}$ triblock copolymer (VB395) in D_2O. By comparing parts a and c of Figure 5, it is clear that the signal due to the DEA residues at δ 3.4 and δ 1.4 is suppressed (indicating lower mobility and decreased salvation for this block), whereas signals due to the PDMA block at δ 2.4 and PMEMA block at 3.7−3.8 are still prominent.

Figure 6 shows DLS distribution functions of the $PDEA_{34}-PDMA_{67}-PMEMA_{39}$ triblock copolymer in aqueous solution (1.0%). DLS studies indicated molecular dissolution at low pH (pH < 6.6), with micellar self-assembly occurring either at around pH 7.6 or at around pH 6.5 by the addition of salt (see Figure 6 and Table 2). If the solution pH decreased from 6.5 to 2.2 by the addition of HCl, the radius of the unimer decreased from 2.5 to 1.1 nm. As reported by Pradny and Sevcik, the protonated tertiary amine group forms a cyclic structure with the carbonyl group in the side chain due to hydrogen bonding. This unusual decrease on the size of fully protonated triblock

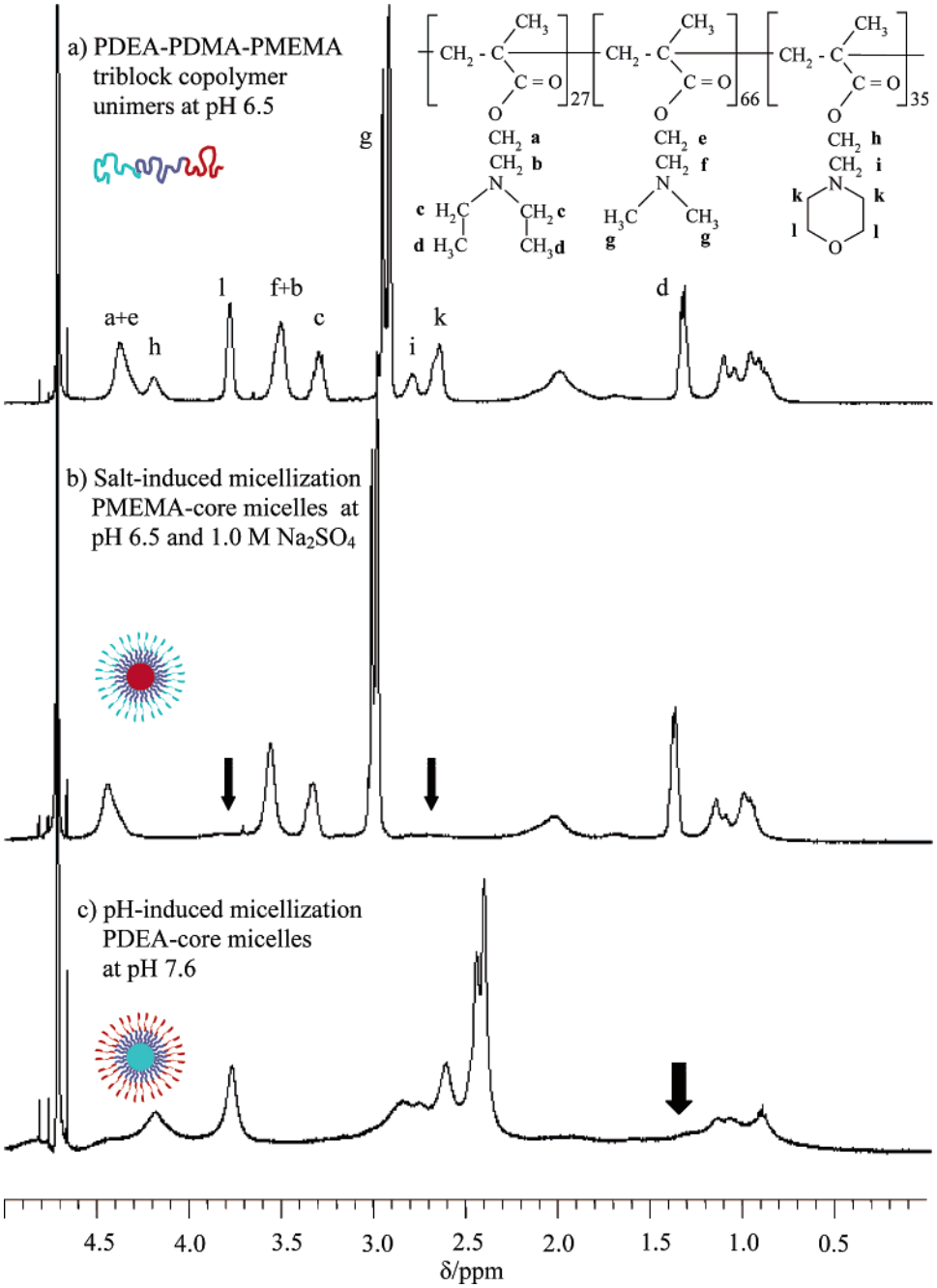

Figure 5. ^{1}H NMR spectra of a PDEA−PDMA−PMEMA triblock copolymer (VB395) in D_2O: (a) unimers at pH 6.5; (b) PMEMA−core micelles at pH 6.5 in the presence of 1.0 M Na_2SO_4; (c) PDEA−core micelles at pH 7.6 without addition of electrolyte. DCl and NaOD were used to adjust the solution pH.

copolymer chain at low pH is presumably due to an increase on such intramolecular cyclization in tertiary amine residues. This intramolecular cyclization may lower the repulsion between cationic quaternary amine residues and cause a decrease on the size of triblock copolymer coils.[18]

Figure 6c indicated three-layer "onionlike" nearly monodisperse PDEA−core micelle formation at pH 7.6 and 20 °C. The intensity-average radii of the PDEA−core micelles were measured to be 12.9 nm ($\mu_2/\Gamma^2 = 0.08$) for $PDEA_{34}$−$PDMA_{67}$−$PMEMA_{39}$ at pH 7.6 (see Figure 6c) and 13.8 nm ($\mu_2/\Gamma^2 = 0.10$) for $PDEA_{27}$−$PDMA_{66}$−$PMEMA_{35}$ at pH 8.0 (see Table 2). This pH-induced micellization is completely reversible. Addition of acid led to reprotonation of the PDEA residues, leading to the formation of unimers below pH 6.6 at 20 °C (see Table 2). Alternatively, by use of this unimer solution at pH 6.5, second type three-layer "onionlike" micelles ($\mu_2/\Gamma^2 = 0.10$) were obtained by the addition of Na_2SO_4 (1.0 M) due to selective salting out of the PMEMA block. In this case, the micellization occurred by PMEMA block forming the dehydrated micelle cores, PDMA block forming the hydrated inner shell and PDEA block locating in the corona. In both micellizations, the middle PDMA block remains soluble as hydrated inner shell (see Figure 6d). Careful control of the solution pH was essential. If the solution pH was too low, all three blocks would become soluble as cationic polyelectrolytes. Conversely, if the solution pH was too high, the PDEA block would become desolvated in addition to the PMEMA block in the presence of salt, and macroscopic precipitation would occur. A solution pH of 6.0 to 6.6 was found to be a suitable compromise for the formation of PMEMA−core "onion" micelles. All three blocks are soluble under these conditions, but given the difference in pK_a values, both the PDEA and the PDMA blocks are protonated and the PMEMA

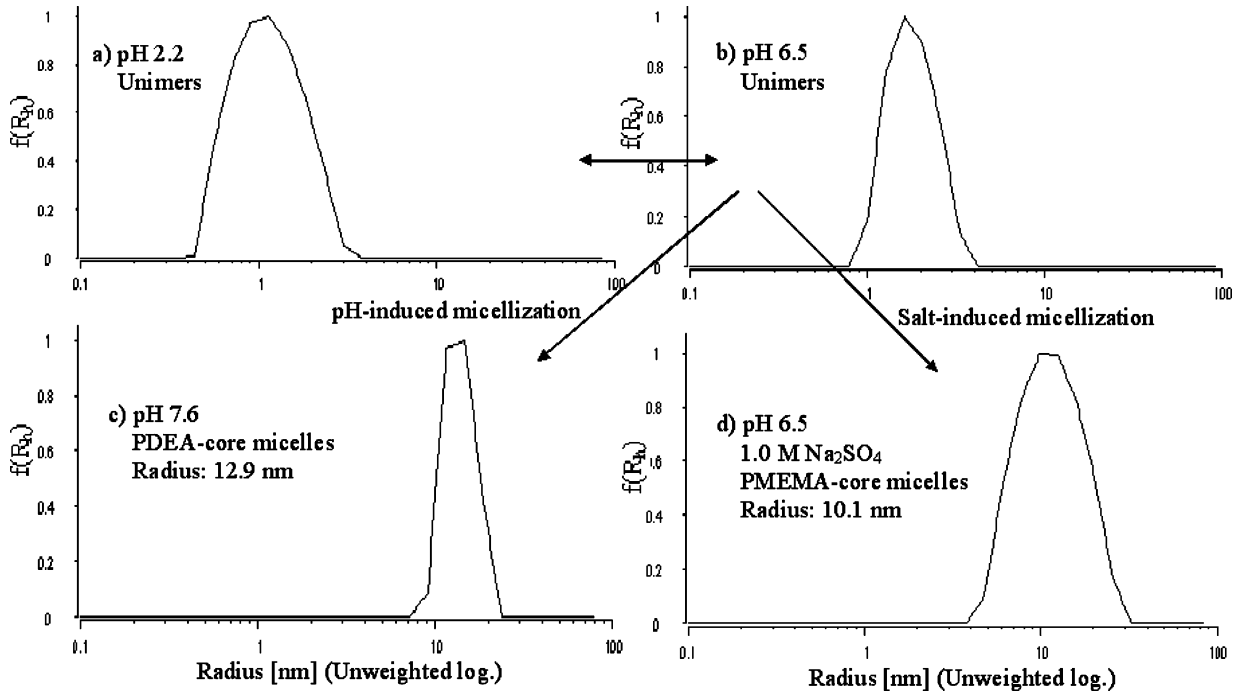

Figure 6. Hydrodynamic radius distribution for the $PDEA_{34}-PDMA_{67}-PMEMA_{39}$ triblock copolymer (VB396, 0.5%) at 20 °C: (a) Unimers at pH 2.2; (b) unimers at pH 6.5; (c) PDEA−core micellization at pH 7.6; (d) PMEMA−core micellization in the presence of Na_2SO_4 (1.0 M) at pH 6.5.

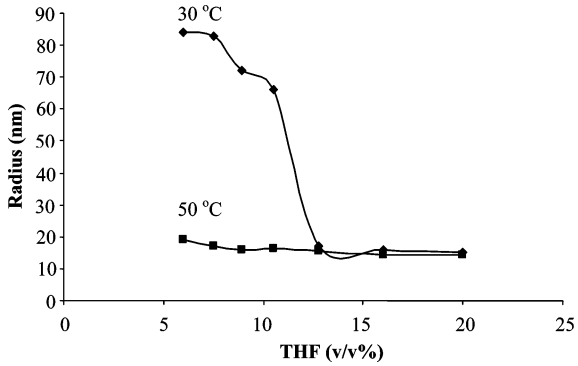

Figure 7. Variation of hydrodynamic radius of PMEMA−core micelles in *n*-hexane as a function of cosolvent content (THF) at 30 and 50 °C.

block is nonprotonated. Under these conditions, DLS studies indicated the formation of colloidally stable, nearly-monodisperse PMEMA−core "onion" micelles, with intensity-average radius of 10.1 nm for the $PDEA_{34}-PDMA_{67}-PMEMA_{39}$ triblock copolymer and 11.0 nm for the $PDEA_{27}-PDMA_{66}-PMEMA_{35}$ triblock copolymer (see Table 2 and Figure 6).

Nonaqueous Solution Behavior of the Triblock Copolymer. PDEA−PDMA−PMEMA triblock copolymer is molecularly soluble in many organic solvents such as in THF and in chloroform but forms PMEMA−core micelles in *n*-alkanes. While the PDEA−PDMA segment of the triblock copolymer is soluble in *n*-alkanes, the PMEMA block is not soluble in such solvents. Thus, a $PDEA_{34}-PDMA_{67}-PMEMA_{39}$ triblock copolymer (0.05 g) was molecularly dissolved in a minimum amount of THF (2.0 mL) (or in $CDCl_3$ for NMR study) and diluted with *n*-hexane for DLS studies. The THF content was varied from 20 to 6 vol % by addition of *n*-hexane. Figure 7 shows DLS distribution functions on the change of the radii of the micelles by varying cosolvent content at both 30 and 50 °C. It confirmed that the micelle diameters depended on both the solution temperature and the amount of cosolvent (THF). At 50 °C, the radius of the micelles slightly increased from 14 to 19 nm ($\mu_2/\Gamma^2 < 0.10$) with a decrease on THF/*n*-hexane ratios. At 30 °C, if the THF content of the solvent mixture was more than 13 vol % the radii of the micelles were similar to the radii of the micelles at 50 °C. If THF content is less than 13 vol %, the micelle diameter increases dramatically. This might be due to a decrease on the solubility of DMA block in hexane with lowering temperature and cosolvent content of the solvent mixture. On the other hand, the PDI of the micelles were inversely depended on the solution temperature (Table 4). DLS studies also indicated that the PDEA−PDMA−PMEMA triblock copolymer formed fairly compact, relatively well-defined micelles ($\mu_2/\Gamma^2 = 0.08-0.11$) not only in aqueous media at 20

Table 3. Summary of the Dynamic Light Scattering Data on 1.0% Aqueous Solutions of the PDEA−PDMA−PMEMA Triblock Copolymer (VB396) at Different pH Values before and after Shell Cross-Linking of the Solvated Inner Shell (PDMA block) at Room Temperature

	pH	radius (nm)	PD	solubility and morphology
before shell cross-linking	2.2	1.1	0.05	molecularly soluble (unimers)
	7.6	12.9	0.08	PDEA-core micelles
	>9.0			precipitation
after shell cross-linking	7.6	18.2	0.11	PDEA-core SCL micelles
	2.2	20.1	0.10	swollen SCL micelles
	11.0	18.4	0.11	SCL micelles, no precipitation

Table 4. Hydrodynamic Radii and PDI Values of the Precursor PDEA−PDMA−PMEMA Triblock Copolymer (VB396, 1.0% w/v solution) in Different Ratios of THF/*n*-Hexane Solvent Mixtures and at Different Temperatures before and after Shell Cross-Linking of the Solvated Inner Shell (PDMA Block) at 50 °C

	THF/ hexane (v/v%)	50 °C radius (nm)	50 °C PD	30 °C radius (nm)	30 °C PD	20 °C radius (nm)	20 °C PD	
before shell cross-linking	12/88	15.4	0.08	20.7	0.11	67.0	0.23	PMEMA−core micelles
	90/10	3.5	0.36	3.6	0.41	3.3	0.42	unimers
after shell cross-linking	12/88	25.0	0.14	26.1	0.14	24.0	0.13	PMEMA−core SCL micelles
	90/10	28.7	0.20	26.4	0.22	25.4	0.22	PMEMA−core SCL micelles

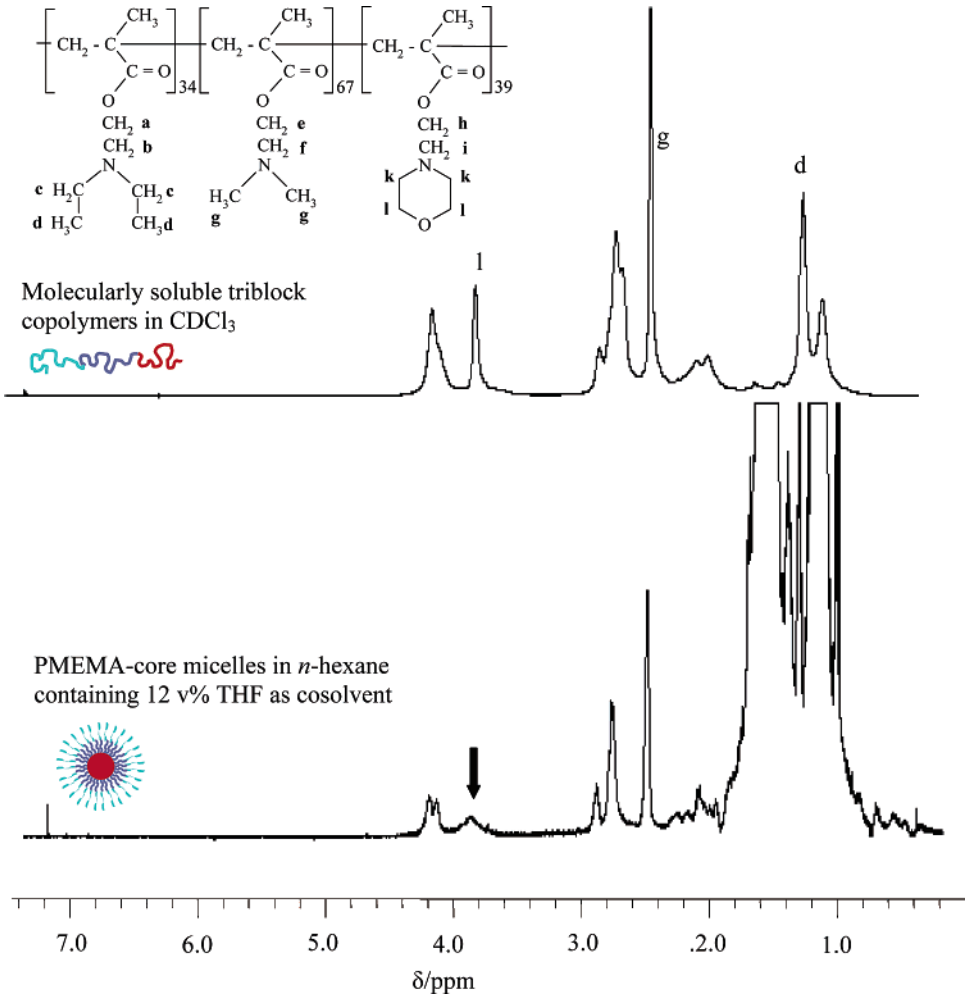

Figure 8. ^{1}H NMR spectra of a 0.5% PDEA−PDMA−PMEMA triblock copolymer (VB396): (a) unimers in $CDCl_3$; (b) PMEMA−core micelles in $CDCl_3$/*n*-hexane mixture (volume ratio: 1/10).

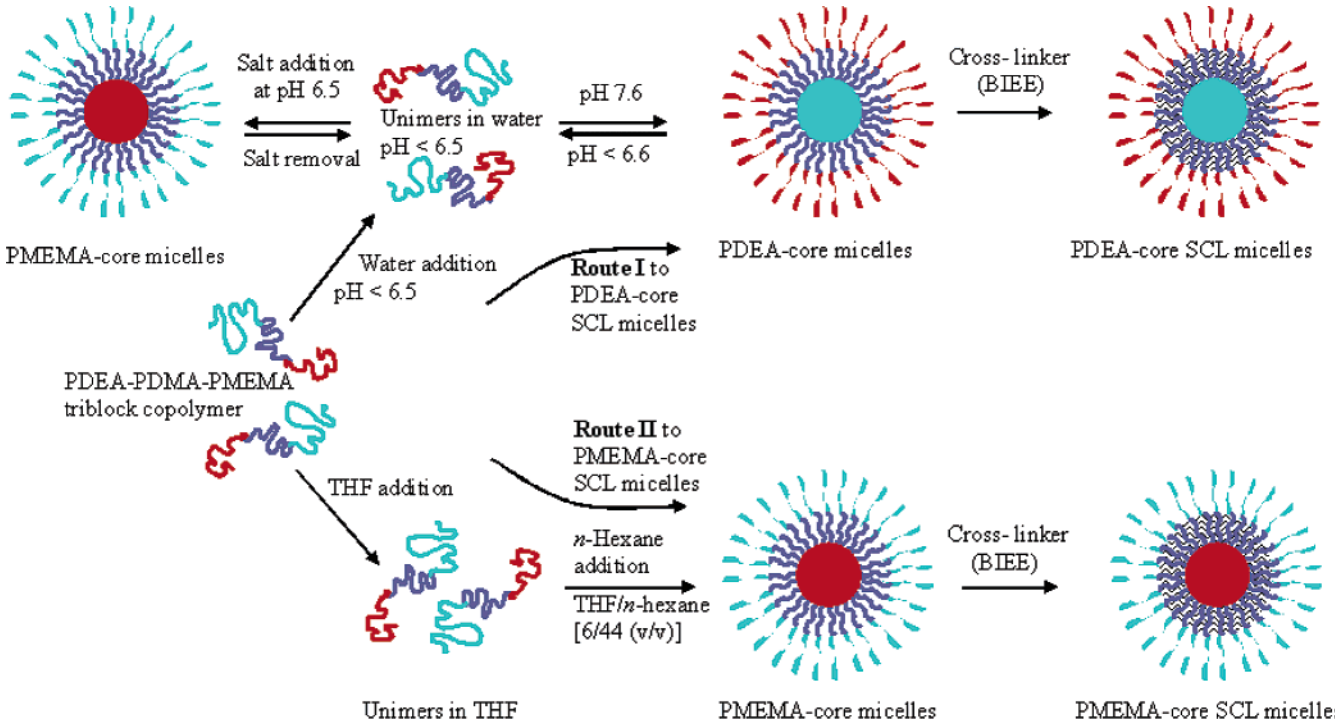

Figure 9. Schematic representation of the syntheses of both PDEA−core SCL micelles in aqueous solution and PMEMA−core SCL micelles in *n*-hexane by using the same precursor PDEA−PDMA−PMEMA triblock copolymer and the same bifunctional cross-linker: PDEA−core SCL micelles were synthesized at pH 7.6 (route I), whereas PMEMA−core SCL micelles were synthesized in *n*-hexane by using THF (12.0 vol %) as cosolvent (route II). In both cases, 50 mol % of the tertiary amine residues of the solvated DMA block was aimed to be cross-linked.

°C but also in *n*-hexane at 30 and 50 °C (see Figure 6, parts c and d), whereas it formed relatively large, polydisperse micelles ($\mu_2/\Gamma^2 = 0.23$) in *n*-hexane at 20 °C (see Table 4).

^{1}H NMR studies indicated desolvation of the PMEMA block of the triblock copolymer (note that the signals due to the PMEMA block at 3.9−4.0 are suppressed; compare the two spectra in Figure 8) and supported DLS studies by PMEMA block forming desolvated micelle cores. As can be seen from Figure 5 and Figure 8, ^{1}H NMR studies on the micellar systems lead to valuable information of the micellar structures.

Shell Cross-Linked Micelle (SCL) Syntheses. During past decade, there has been increasing interest in SCL micelles with either hydrophobic cores or hydrophilic cores.[16,19−26] These fascinating supramolecular structures combine the properties of micelles, microgels, nanoparticles, and dendrimers, and various applications such as drug delivery, sequestration of metabolites, picker oil in water systems, and entrapment of environmental pollutants have been suggested. In peticular, recent efforts have focused on the synthesis of SCL micelles from ABC type triblock copolymers, since shell cross-linking can be carried out at high solids with little or no intermicellar cross-linking which increased commercial interest.[25,26] Here in, only the first example of a "schizophrenic" ABC triblock copolymer with shell cross-linkable solvated middle block is reported. Two novel types of SCL micelles were successfully synthesized from the same PDEA−PDMA−PMEMA triblock copolymer by cross-linking of the tertiary amine residues in the inner shell (the PDMA block) of both PDEA−core and PMEMA−core "onion" micelles: (i) PDEA−core SCL micelles and (ii) PMEMA−core SCL micelles.

For the synthesis of PDEA−core SCL micelles, after preparation of the "onion" type PDEA−core micelles of the $PDEA_{34}$−$PDMA_{67}$−$PMEMA_{39}$ triblock copolymer (1.0%, 200 mL) with the radius of 12.9 nm ($\mu_2/\Gamma^2 = 0.08$) at pH 7.6, shell cross-linking of the inner PDMA shell was achieved by using 1,2-bis(2-iodoethoxy)ethane (BIEE, 0.25 mol per mol of DMA residues) at 20 °C (see route I in Figure 9). BIEE reacts selectively with the DMA residues on adjacent block copolymer chains to "lock in" the micellar structure.[16,23−26] The resulting SCL micelles had a mean hydrodynamic diameter of 18.2 nm ($\mu_2/\Gamma^2 = 0.11$) at pH 7.6 (see Figure 10). The SCL micelles have a spherical morphology, a high degree of dispersion (i.e., essentially no intermicelle cross-linking occurs).

It is worth that the precursor $PDEA_{34}$−$PDMA_{67}$−$PMEMA_{39}$ triblock copolymer dissolved as unimers at acidic solution (no Tyndall scattering, see Figure 11), formed PDEA−core micelles between pH 7.3−8.5 and precipitated above pH 8.5 at room temperature (see Figure 5, 6 and 11). For the PDEA−core SCL micelles prepared from 1.0% aqueous solution of $PDEA_{34}$−$PDMA_{67}$−$PMEMA_{39}$, the solution pH was adjusted to both pH 2.2 and pH 11.0 using HCl and KOH solutions (2.0 M). If no shell cross-linking had occurred, not only dissociation into individual triblock copolymer chains in acidic pH but also precipitation of the triblock copolymer at high pH values would be expected (see Table 3 and Figure 11). However, both DLS studies and visual inspection confirmed the continued presence of Tyndall scattering characteristics of micellar solutions and hence indicated successful covalent stabilization (see Figures 10 and 11). The resulting SCL micelles had spherical morphology at a wide pH range from pH 2 to pH 11, with a mean number-average particle radii of 18.2 nm at pH 7.6, 20.1 nm at pH 2.2, and 18.4 nm at pH 11.0 and an average polydispersity index of 0.11 (see Table 3 and Figure 10). Because of quaternization of tertiary amine residues of the PDMA block

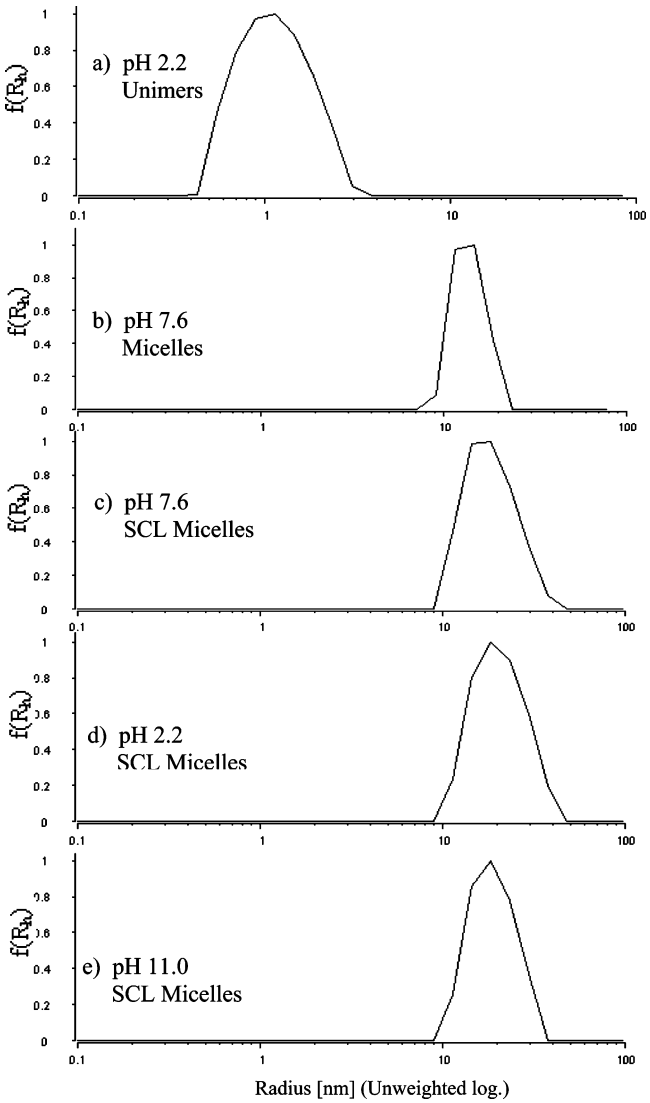

Figure 10. DLS hydrodynamic radius distribution functions for $PDEA_{34}$−$PDMA_{67}$−$PMEMA_{39}$ triblock copolymer (VB396, 1.0%) in aqueous solution at different pH and 20 °C, before and after shell cross-linking of the inner shell, PDMA block: (a) unimers at pH 2.2; (b) PDEA−core micelles at pH 7.6; (c) SCL micelles at pH 7.60 after cross-linking of the inner PDMA shell; (d) SCL micelles at pH 2.2; (e) SCL micelles at pH 11.0.

via cross-linking, ion−dipole attractions between quaternary residues and water kept the SCL micelles in solution without precipitation at pH 11.0. As can be seen from Table 3 and Figure 10, when solution pH was decreased to 2.2 the radius of the SCL micelle slightly increases from 18.2 to 20.1 nm due to electrostatic repulsion between cationic protonated tertiary amine residues of the triblock copolymer as expected. It is worth that this pH-induced (de)swelling behavior is completely reversible.

For the PMEMA−core SCL micelle syntheses (see route II in Figure 9), 50 mol % of the tertiary amine residues of the inner PDMA shell of the PMEMA−core micelles having a radius of 15.4 nm ($\mu_2/\Gamma^2 = 0.08$) was cross-linked with the same cross-linker (BIEE) in THF/*n*-hexane mixture at 50 °C (see Table 4). The intensity-average radius and PDI of the resulting PMEMA−core SCL micelles were determined by DLS studies at 50 °C and found to be 25 nm and 0.14, respectively. The SCL micelles had a spherical morphology and a high degree of dispersion (i.e., essentially no intermicelle cross-linking occurs).

As can be seen in Table 4, when the triblock copolymer dissolved in THF/*n*-hexane mixture containing 10 vol %

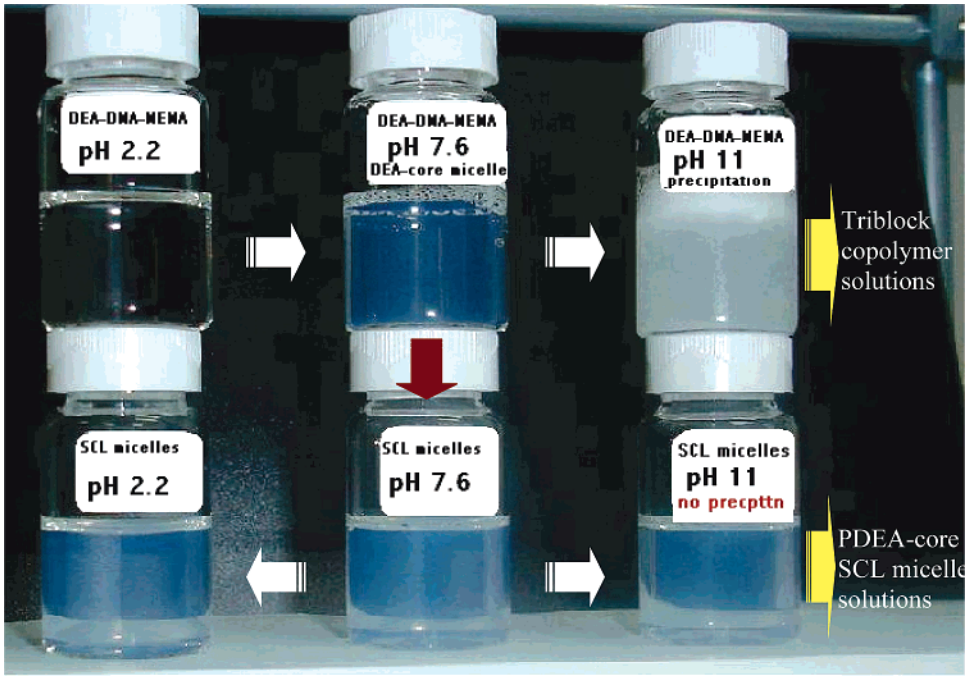

Figure 11. Digital photographic images of precursor $PDEA_{34}-PDMA_{67}-PMEMA_{39}$ triblock copolymer solutions and SCL micelle solutions at different pH.

n-hexane the polymer was molecularly soluble as DLS studies indicated. If the ratio of THF/*n*-hexane was reversed (THF/*n*-hexane ratio: 12/88 v/v %) PMEMA−core micellization occurred (see Table 4). It is clear evidence that after shell cross-linking the micelle diameter did not change even high THF content in the solvent mixture. It is remarkable that the radius of precursor PMEMA−core micelle increases from 15.4 to 67.0 nm when the solution temperature decreased from 50 to 20 °C. In contrast, after shell cross-linking of the DMA residues, the radius of resulting SCL micelles was almost independent from both temperature and THF/*n*-hexane ratios. The intensity-average radius of the PMEMA−core SCL micelles was around 25 nm in different ratios of THF and *n*-hexane and at different temperatures as measured by DLS (see Table 4).

ABC triblock copolymers provided an advantage to prepare shell cross-linked micelles at high solids as reported before.[25,26] The synthesis of SCL micelles using PDEA−PDMA−PMEMA triblock copolymer was also attempted at 10% w/v in aqueous solution at pH 7.5. The DLS indicated successful cross-linking with no intermicellar cross-linking. Further SCL micelle syntheses will be studied in detail in the near future by varying the degree of cross-linking from 10 to 50 mol % of the tertiary amine residues in the inner shell of both PDEA−core micelles in aqueous solution and PMEMA−core micelles in *n*-hexane. These novel SCL micelles might have attraction for potential applications such as in nanosize drug delivery applications since tunable hydrophilicity/hydrophobicity of the A or C block depending on solution pH, electrolyte concentration and the type of organic solvent should allow "triggered release" of both hydrophobic and hydrophilic drugs.

Conclusions

In summary, group transfer polymerization was successfully used to prepare novel "schizophrenic" water-soluble triblock copolymers of narrow molecular weight distribution (<1.13) based on tertiary amine methacrylates. The PDEA−PDMA−PMEMA triblock copolymers were well characterized by using GPC and ^{1}H NMR spectroscopy.

We have demonstrated for the first time that a novel "schizophrenic" PDEA−PDMA−PMEMA triblock copolymer can form micelles with nonsolvated cores comprising either the PDEA block or the PMEMA block in aqueous media. Unlike two-layer micellizations of the PEO−PDEA−PSEMA triblock copolymers described by Armes and co-workers [PEO−PDEA−PSEMA forms the hydrogen-bonded PSEMA/PEO−core micelles at low pH, PDEA−core micelles in alkaline and the PSEMA/PDEA interpolyelectrolyte−core micelles at around the IEP], these new tertiary amine methacrylate-based triblock copolymers formed two distinct three-layer "onionlike" micelles in aqueous solution: (i) PMEMA−core micelles, by PDMA block forming the hydrated inner shell and PDEA block locating in the coronas, and (ii) PDEA−core micelles, by PDMA block forming the inner shell and PMEMA block locating in the coronas. In addition to formation of two distinct three-layer "onion" micellization in aqueous media, it was also possible to get PMEMA−core "onion" micelles in *n*-hexane by using a cosolvent such as THF. In all cases, the micellizations were fully reversible. It is remarkable that this highly unusual behavior can be observed at room temperature merely by judicious control of the solution pH and the electrolyte concentration.

Only the first example of a "schizophrenic" ABC triblock copolymer with shell cross-linkable solvated middle block is reported here. Shell cross-linking of the inner shell PDMA block of both "onion" micelles (PDEA−core micelles in aqueous solution and PMEMA−core micelles in *n*-hexane) was achieved by using BIEE. The PDEA−core SCL micelles had a spherical morphology at a wide pH range. The PMEMA−core SCL micelles also had a spherical morphology at a wide temperature range.

Acknowledgment. Eskişehir Osmangazi University (ESOGU) is thanked for financial support. This work was supported by the commission of scientific research projects of ESOGU (GR/200319040). Turkish Academy of Science is also thanked for an encouragement award for science scholarship.

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MA052052K