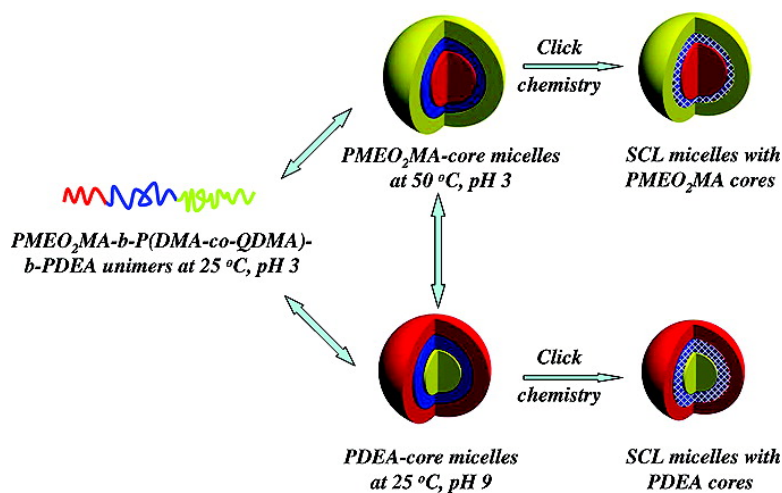


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Fabrication of Two Types of Shell-Cross-Linked Micelles with “Inverted” Structures in Aqueous Solution from Schizophrenic Water-Soluble ABC Triblock Copolymer via Click Chemistry

Xiaoze Jiang,[†] Guoying Zhang,[†] Ravin Narain,^{*,‡} and Shiyong Liu^{*,†}

CAS Key Laboratory of Soft Matter Chemistry, Department of Polymer Science and Engineering, Hefei National Laboratory for Physical Sciences at the Microscale, University of Science and Technology of China, Hefei, Anhui 230026, China, and Department of Chemistry and Biochemistry, Laurentian University, Sudbury, Ontario P3E 2C6, Canada

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A well-defined ABC triblock copolymer, poly(2-(2-methoxyethoxy)ethyl methacrylate)-*b*-poly(2-(dimethylamino)ethyl methacrylate)-*b*-poly(2-(diethylamino)ethyl methacrylate) (PMEO₂MA-*b*-PDMA-*b*-PDEA), was synthesized via sequential atom transfer radical polymerization using ethyl 2-bromoisobutyrate as the initiator. Reacting the triblock precursor with propargyl bromide in anhydrous tetrahydrofuran yielded PMEO₂MA-*b*-P(DMA-*co*-QDMA)-*b*-PDEA triblock copolymer with “clickable” moieties, where QDMA was quaternized DMA residues. PMEO₂MA-*b*-P(DMA-*co*-QDMA)-*b*-PDEA triblock copolymer exhibited “schizophrenic” micellization behavior in aqueous solution, forming three-layer onion-like PMEO₂MA-core and PDEA-core micelles upon proper adjustment of the solution pH and temperature. For temperature-induced formation of PMEO₂MA-core micelles at acidic pH, the critical micellization temperature can be tuned by incorporating oligo(ethylene glycol) methyl ether methacrylate (OEGMA; the mean degree of polymerization was 8–9) residues into the PMEO₂MA block, shifting from 38 to 43 °C as the OEGMA contents varied in the range of 0–10 mol %. In both types of micelles, the inner shell layer consisted of the middle P(DMA-*co*-QDMA) segment. Subsequently, cross-linking with tetra(ethylene glycol) diazide via click chemistry in the presence of copper catalysts led to the facile preparation of two types of shell-cross-linked (SCL) micelles with “inverted” structures in purely aqueous solution. The cores and coronas of SCL micelles exhibited multiresponsive swelling/shrinking and collapse/aggregation behavior, respectively. To the best of our knowledge, this represents the first report of the fabrication of two types of SCL micelles with inverted structures from a single schizophrenic water-soluble triblock copolymer in purely aqueous solution.

Introduction

Water-soluble double hydrophilic block copolymers (DHBCs) that exhibit so-called “schizophrenic” character have recently been widely investigated. These copolymer chains can self-assemble into two or more types of micelles with invertible structures in dilute aqueous solution in the absence of any organic cosolvent. The polymer segments can be tuned to become either hydrophilic or hydrophobic by a combination of the solution temperature, solution pH, and ionic strength.^{1–18} To provide structural versatility, many schizophrenic water-soluble triblock

copolymers were recently investigated instead of diblock copolymers.^{10,19–21}

Among the stimulus-responsive blocks, poly(*N*-isopropylacrylamide) (PNIPAM)^{3,4,8,10,21} and poly(propylene oxide) (PPO)^{2,7} have been used frequently as the thermoresponsive blocks. Furthermore, 2-(2-methoxyethoxy)ethyl methacrylate (MEO₂MA)^{22–24} has recently been used to form a new type of thermoresponsive block as the lower critical solution temperature (LCST) can be precisely adjusted by varying the comonomer composition with oligo(ethylene glycol) methacrylate (OEGMA; $M_n = 475$ g/mol). These novel copolymers can potentially find biomedical and biotechnology applications since they are mainly composed of biocompatible oligo(ethylene glycol) segments.

However, there is a fundamental problem with these self-assembled DHBC micelles. Their self-assembled structures can spontaneously dissociate at concentrations below their critical micelle concentration (cmc). Therefore, Armes and co-workers have applied the shell-cross-linking method to stabilize DHBC micellar structures.^{25–27} Furthermore, they have also investigated

* To whom correspondence should be addressed. (S.L.) E-mail: sliu@ustc.edu.cn. Phone: (86) 551-3607348. Fax: (86) 551-3607348. (R.N.) E-mail: rnarain@laurentian.ca. Phone: (705) 675-1151 (ext 2186). Fax: (705) 675-4844.

[†] University of Science and Technology of China.

[‡] Laurentian University.

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the preparation of shell-cross-linked (SCL) micelles from triblock copolymers at high solids, taking advantage of steric stabilization of the soluble block located in the outer coronas of three-layer "onion-like" micelles.^{28–30}

In the fabrication of SCL micelles reported by the Armes group, the bifunctional alkyl iodide 1,2-bis(2-iodoethoxy)ethane (BIEE)^{26,27,30,31} was frequently used as the cross-linker to cross-link tertiary amine at alkaline pH condition. However, its toxicity apparently limited its application. The group further developed a new method of cross-linking by electrolyte complexation for reducing toxicity.³² However, this structure was not as stable as covalently cross-linked micelles when the solution ionic strength was changed. Many other cross-linking methods were used such as cross-linking via carbodiimide coupling,^{33–38} amidation,^{39–42} or Michael addition^{29,31,43} under mild conditions.

However, these above-mentioned methods could only fix one type of self-assembled micellar aggregates. The fixation of other self-assembled structures normally needs organic solvent. One typical example is the fixation of self-assembled micelles with PMEMA cores from poly(2-(diethylamino)ethyl methacrylate)-*b*-poly(2-(dimethylamino)ethyl methacrylate)-*b*-poly(2-(*N*-morpholino)ethyl methacrylate) (PDEA-*b*-PDMA-*b*-PMEMA) triblock copolymer for which tetrahydrofuran (THF)/*n*-hexane should be used as cosolvents as reported by Büttin and co-workers.²⁰ Armes et al.⁴³ reported the synthesis of poly(2-(methacryloyloxy)phosphorylcholine)-*b*-poly(glycerol methacrylate)-*b*-poly(2-(diethylamino)ethyl methacrylate) (PMPC-*b*-PGMA-*b*-PDEA) to form PDEA-core SCL micelles in aqueous solution and another PMPC-core SCL micelle in THF/methanol

as cosolvents. The fabrication of two types of SCL micelles prepared directly from the same triblock copolymer in aqueous solution has not been reported. Therefore, there is a need to develop a more versatile, reliable, and robust strategy for the preparation of SCL micelles.

In the past few years, "click chemistry",^{44–50} as termed by Sharpless et al., has gained a great deal of attention due to its high specificity, quantitative yield, tolerance to a broad variety of functional groups, and applicability under mild reaction conditions. Recently, Wooley et al. have reported the fabrication of amphiphilic block copolymer SCL micelles from these self-assembled micelles containing clickable functional groups.^{51,52} To the best of our knowledge, there is no report concerning the fabrication of double hydrophilic block copolymer SCL micelles via click chemistry.

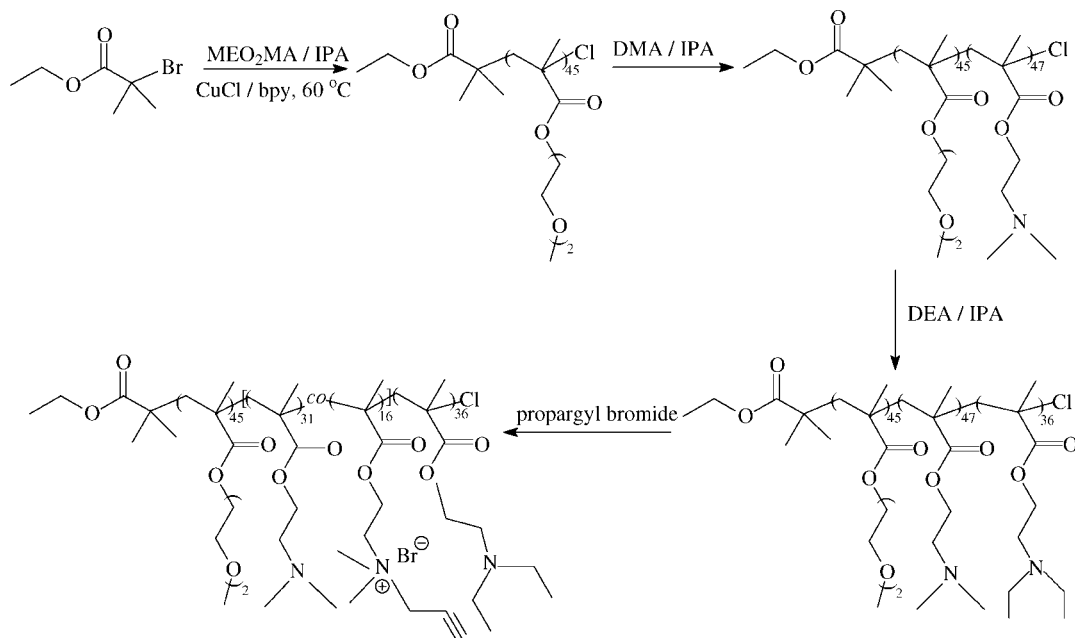
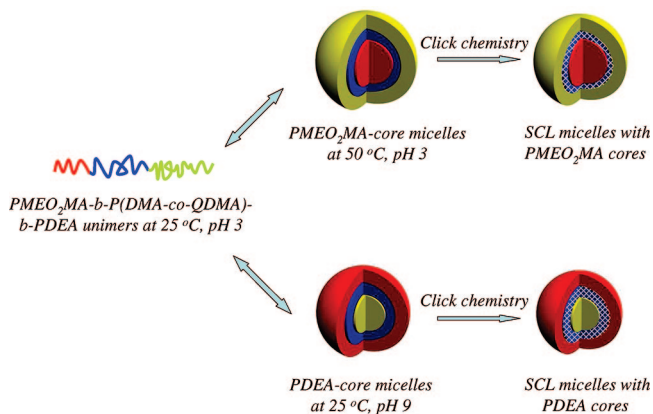
Herein we present an efficient synthesis of two types of SCL micelles with either pH- or temperature-sensitive cores from a novel PMEO₂MA-*b*-P(DMA-*co*-QDMA)-*b*-PDEA triblock copolymer. First, PMEO₂MA-*b*-PDMA-*b*-PDEA was prepared via atom transfer radical polymerization (ATRP) using the one-pot method. Subsequently, the DMA blocks were partially converted to a quaternized DMA (QDMA) block with click-cross-linkable moieties to form novel schizophrenic water-soluble PMEO₂MA-*b*-P(DMA-*co*-QDMA)-*b*-PDEA triblock copolymer. The pH- or temperature-induced micellization and subsequent shell cross-linking of the P(DMA-*co*-QDMA) inner shell with the tetra(ethylene glycol) diazide via click chemistry were studied in detail. The reversible pH- or temperature-responsive swelling/shrinking properties of these corresponding SCL micelles were investigated by a combination of laser light scattering (LLS) and transmission electron microscopy (TEM). Scheme 2 shows a representation of the preparation of two types of SCL micelles with "inverted" structures. This strategy represents the first report concerning the preparation of two types of SCL micelles with inverted structures via click chemistry starting from a well-defined schizophrenic water-soluble triblock copolymer in purely aqueous solution.

Experimental Section

Materials. OEGMA ($M_n = 475$ g/mol, Aldrich) was passed through a silica column prior to polymerization. MEO₂MA (95%, Aldrich), DMA (99%, Aldrich), and DEA (99%, Aldrich) were dried over calcium hydride, vacuum-distilled, and then stored at -20 °C prior to use. THF was distilled from a purple sodium ketyl solution. Propargyl bromide, tetra(ethylene glycol) dimesylate, ethyl 2-bromoisobutyrate (EBIB), sodium azide (NaN₃), copper(I) chloride (CuCl), and 2,2'-bipyridine (bpy) were purchased from Aldrich and used without further purification. Tetra(ethylene glycol) diazide was synthesized from tetra(ethylene glycol) dimesylate and sodium azide according to literature procedures.⁵³ Isopropyl alcohol (IPA),

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Scheme 1. Synthetic Route for the Preparation of $\text{PMEO}_2\text{MA}-b\text{-P}(\text{DMA}-co\text{-QDMA})-b\text{-PDEA}$ Triblock CopolymerScheme 2. Schematic Illustration of the Schizophrenic Micellization Behavior of $\text{PMEO}_2\text{MA}_{45}\text{-}b\text{-P}(\text{DMA}_{0.65}\text{-}co\text{-QDMA}_{0.35})_{47}\text{-}b\text{-PDEA}_{36}$ and the Preparation of Two Types of SCL Micelles with Inverted Structures in Aqueous Solution

n-hexane, sodium ascorbate, copper sulfate (CuSO_4), and all other chemicals were purchased from Shanghai Chemical Reagent Co. and used as received.

Preparation of $\text{PMEO}_2\text{MA}-b\text{-PDMA}-b\text{-PDEA}$ Triblock Copolymer. The triblock copolymer was fabricated in a one-pot synthesis via ATRP using EBIB as the initiator. A typical procedure was as follows: A reaction flask with a magnetic stirrer was charged with EBIB (74 μL , 0.5 mmol), MEO_2MA (4.70 g, 25 mmol), bpy (156 mg, 1.0 mmol), and IPA (5.5 mL). The reaction mixture was degassed by three freeze-pump-thaw cycles, backfilled with N_2 , and then placed in an oil bath thermostated at 60 °C. After ~ 3 min, CuCl (49 mg, 0.5 mmol) was added to the reaction flask to start the polymerization under a nitrogen atmosphere. After 4 h, the MEO_2MA conversion reached $\geq 90\%$, as judged by ^1H NMR sampled at regular time intervals. An aliquot of the reaction mixture was withdrawn for subsequent gel permeation chromatography (GPC) analysis before the introduction of a degassed mixture of DMA monomer (3.93 g, 25 mmol) and IPA (4.0 mL) via a double-tipped needle.

After 3 h, a 0.5 mL aliquot of the reaction mixture was extracted from the polymerizing $\text{PMEO}_2\text{MA}-b\text{-PDMA}$ precursor for the characterization by ^1H NMR spectroscopy and GPC analysis. The

conversion of DMA had reached 94% calculated from the ^1H NMR spectrum. Then degassed DEA monomer (4.63 g, 25 mmol) diluted with IPA (5.0 mL) was added to the reaction flask under a nitrogen atmosphere. After another 14 h, the reaction flask was quenched into liquid nitrogen, exposed to air, and diluted with 15 mL of IPA. After passage through a neutral alumina column to remove the copper catalysts and removal of all the solvent, the obtained solids were thoroughly washed with an excess of hexane to remove the possible presence of residual DEA monomer. The resulting colorless product was dried in a vacuum oven overnight at room temperature. The overall yield was $\sim 80\%$. THF GPC analyses of the $\text{PMEO}_2\text{MA}-b\text{-PDMA}-b\text{-PDEA}$ triblock copolymer precursor revealed a symmetric monomodal trace. The M_n of the triblock copolymer was 25 600 g/mol, and the M_w/M_n was 1.27. The actual degrees of polymerization (DP) of PMEO_2MA , PDMA, and PDEA blocks were calculated to be 45, 47, and 36, respectively, from the ^1H NMR spectrum in D_2O at pH 3 and 25 °C. The triblock copolymer was then denoted $\text{PMEO}_2\text{MA}_{45}\text{-}b\text{-PDMA}_{47}\text{-}b\text{-PDEA}_{36}$. According to similar procedures, the $\text{P}(\text{MEO}_2\text{MA}-co\text{-OEGMA})\text{-}b\text{-PDMA}-b\text{-PDEA}$ triblock copolymers were also synthesized from an initial monomer feed possessing different amounts of OEGMA in the MEO_2MA polymerization, and their structural parameters are summarized in Table 1.

Preparation of $\text{PMEO}_2\text{MA}-b\text{-P}(\text{QDMA}-co\text{-DMA})-b\text{-PDEA}$ Triblock Copolymer. Selective quaternization of the DMA residues in the $\text{PMEO}_2\text{MA}_{45}\text{-}b\text{-PDMA}_{47}\text{-}b\text{-PDEA}_{36}$ triblock copolymer was carried out using propargyl bromide relative to the 50 mol % DMA content of triblock copolymer in THF at room temperature for 6 h. The purification of selectively quaternized copolymer was achieved simply by precipitation in excess *n*-hexane three times. Then the resulting copolymer was dried in a vacuum oven overnight at room temperature. The extent of quaternization was assessed to be 35% by ^1H NMR spectroscopy. The product was then denoted as $\text{PMEO}_2\text{MA}_{45}\text{-}b\text{-P}(\text{DMA}_{0.65}\text{-}co\text{-QDMA}_{0.35})_{47}\text{-}b\text{-PDEA}_{36}$ triblock copolymer.

Preparation of Micelles and SCL Micelles. The $\text{PMEO}_2\text{MA}_{45}\text{-}b\text{-P}(\text{DMA}_{0.65}\text{-}co\text{-QDMA}_{0.35})_{47}\text{-}b\text{-PDEA}_{36}$ triblock copolymer was molecularly dissolved at a 2.0 g/L concentration in water at pH 3 and room temperature. When the solution pH was adjusted to 9, PDEA-core micelles were formed at room temperature. Inverted micelles with PMEO_2MA cores could be induced only by heating the solution to 50 °C and adjusting the pH to 3. The SCL micelles with PDEA cores or PMEO_2MA cores were achieved by adding tetra(ethylene glycol) diazide into the respective micelle solution in

Table 1. Molecular Parameters and CMT of the Triblock Copolymer Used in This Study

sample ^a	M_n^b (g/mol)	M_w/M_n^b	CMT ^c (°C)
P(MEO ₂ MA) ₄₅ - <i>b</i> -PDMA ₄₇ - <i>b</i> -PDEA ₃₆	25 600	1.27	38
P(MEO ₂ MA) _{0.95} - <i>co</i> -OEGMA _{0.05}) ₄₅ - <i>b</i> -PDMA ₄₈ - <i>b</i> -PDEA ₄₅	28 210	1.31	40
P(MEO ₂ MA) _{0.9} - <i>co</i> -OEGMA _{0.1}) ₄₅ - <i>b</i> -PDMA ₄₇ - <i>b</i> -PDEA ₄₆	27 900	1.21	43
P(MEO ₂ MA) ₄₅ - <i>b</i> -P(DMA) _{0.65} - <i>co</i> -QDMA _{0.35}) ₄₇ - <i>b</i> -PDEA ₃₆ ^d			41

^a Determined by ¹H NMR in CDCl₃ or D₂O. ^b Determined by GPC using THF as the eluent at a flow rate of 1.0 mL/min. ^c Determined at a copolymer concentration of 5.0 g/L at pH 4. ^d Quaternized with propargyl bromide, and the degree of quaternization was 35 mol %.

the presence of copper catalysts and stirring the solution for at least 3 days to ensure effective covalent stabilization of self-assembled micelles.

In a typical procedure, A 250 mL round-bottom flask with a magnetic stir bar was charged with tetra(ethylene glycol) diazide (12 mg, 0.05 mmol), CuSO₄ (16 mg, 0.1 mmol), H₂O (74 mL), and sodium ascorbate (40 mg, 0.2 mmol). The mixture was allowed to stir at room temperature for 30 min. Subsequently, the 2.0 g/L aqueous self-assembled PDEA-core micelle solution (74 mL, 0.1 mmol of alkynyl group) was added to the flask. The reaction mixture was allowed to stir for 3 days at room temperature and then dialyzed (MW cutoff 12000–14000) against deionized water for 3 days to remove copper catalysts. SCL micelles with PDEA cores was obtained as a white solid after lyophilization. The concentration of the solution used in this study was 1.0 g/L unless otherwise specified. Using the above method, the inverted SCL micelles were also obtained from the PMEO₂MA-core micelles at 50 °C and pH 3.

Characterization. Molecular weights and molecular weight distributions were determined by GPC on an instrument equipped with a Waters 1515 pump and a Waters 2414 differential refractive index detector (set at 30 °C). A series of three linear Styragel columns, HT2, HT4, and HT5, were used at an oven temperature of 45 °C. The eluent used was THF at a flow rate of 1.0 mL/min. A series of low-polydispersity polystyrene standards were employed for the GPC calibration.

All ¹H NMR spectra were recorded in D₂O or CDCl₃ using a Bruker 300 MHz spectrometer. Fourier transform infrared (FT-IR) spectra were recorded on a Bruker VECTOR-22 IR spectrometer. The spectra were collected at 64 scans with a spectral resolution of 4 cm⁻¹.

A commercial spectrometer (ALV/DLS/SLS-5022F) equipped with a multi- τ digital time correlator (ALV5000) and a cylindrical 22 mW UNIPHASE He–Ne laser ($\lambda_0 = 632$ nm) as the light source was employed for dynamic LLS measurements. Scattered light was collected at a fixed angle of 90° for a duration of 10 min. Distribution averages and particle size distributions were computed using cumulant analysis and CONTIN routines. All data were averaged over three measurements.

TEM images were recorded using a Philips CM120 electron microscope at an accelerating voltage of 200 KV. TEM samples were prepared by placing 10 μ L aqueous solutions of SCL micelles (0.2 g/L) on copper grids coated with thin films of Formvar and carbon. No staining was required.

Results and Discussion

Synthesis of PMEO₂MA-*b*-PDMA-*b*-PDEA Triblock Copolymer. ATRP is a versatile technique for the controlled polymerization of many functional hydrophilic and amphiphilic monomers and can be conveniently employed for the preparation of block copolymers containing DMA and DEA segments in alcohol media under mild conditions.^{5,29,30} However, the controlled polymerization of PMEO₂MA monomer via ATRP still needs to be addressed due to problems of broad polydispersity of the obtained PMEO₂MA homopolymer and slow polymerization in ethanol.²⁴ Therefore, to control the living polymerization of MEO₂MA, the polymerization was performed in isopropyl alcohol at 60 °C using CuCl/bpy catalyst.

As expected, relatively good control was achieved and well-defined PMEO₂MA homopolymer could be obtained. Further-

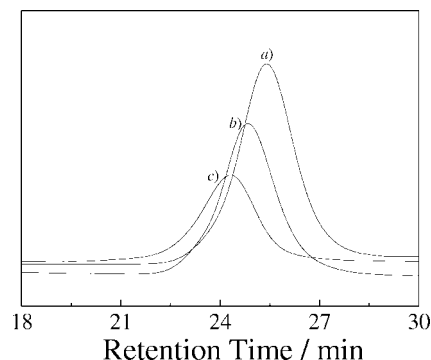


Figure 1. THF GPC traces of (a) (PMEO₂MA)Cl macroinitiator ($M_n = 9800$ g/mol, $M_w/M_n = 1.26$), (b) PMEO₂MA-*b*-PDMA diblock copolymer ($M_n = 18 800$ g/mol, $M_w/M_n = 1.28$), and (c) PMEO₂MA-*b*-PDMA-*b*-PDEA triblock copolymer ($M_n = 25 600$ g/mol, $M_w/M_n = 1.27$).

more, the conversion had reached more than 90% as judged by ¹H NMR after 4 h. THF GPC analysis revealed a narrow and symmetric peak with an $M_n \approx 9800$ g/mol, and an M_w/M_n of 1.26 (Figure 1a). It clearly shows the polydispersity of PMEO₂MA was typically less than 1.3, and M_n was quite close to the theoretical data. The PMEO₂MA homopolymer with good conversion, controlled molecular weight, and narrow molecular weight distribution could easily be obtained in IPA as the solvent with CuCl/bpy catalyst at 60 °C.

Therefore, the one-pot polymerization method was employed for the preparation of PMEO₂MA-*b*-PDMA-*b*-PDEA triblock copolymer shown in Scheme 1. The MEO₂MA monomer was polymerized first, and after a conversion of 90% or above, a degassed IPA solution of DMA monomer was then transferred to the reaction flask to start the chain extension of the first block. After 3 h of DMA polymerization, samples were withdrawn for GPC analysis, which showed a symmetric peak with an $M_n \approx 18 800$ g/mol and an M_w/M_n of 1.28 (Figure 1b). A clear shift to higher molecular weight after the chain extension with PDMA block was noted, and there is no tailing at the lower molecular weight region, indicating the high initiating efficiency of PMEO₂MA macroinitiator for DMA polymerization. The ¹H NMR spectrum indicated that the conversion of DMA had reached 94%.

Subsequently, DEA monomer was added, and the polymerization was allowed to proceed for 14 h. After passage through a neutral alumina column and removal of all the solvent, the residues were further purified to remove residual monomers and the possible presence of terminated PMEO₂MA-*b*-PDMA chains. The GPC trace of the purified product is shown in Figure 1c, revealing a monomodal and symmetric peak, with an M_n of 25 600 g/mol and a polydispersity M_w/M_n of 1.27. The shift to higher molecular weight compared to that of the diblock copolymer precursor is clearly evident from the GPC data. Moreover, there is no tailing at the lower molecular weight region, indicating a successful chain extension of PMEO₂MA-*b*-PDMA.

The ¹H NMR spectrum of the final PMEO₂MA-*b*-PDMA-*b*-PDEA triblock copolymer in D₂O at pH 3 and 25 °C is shown

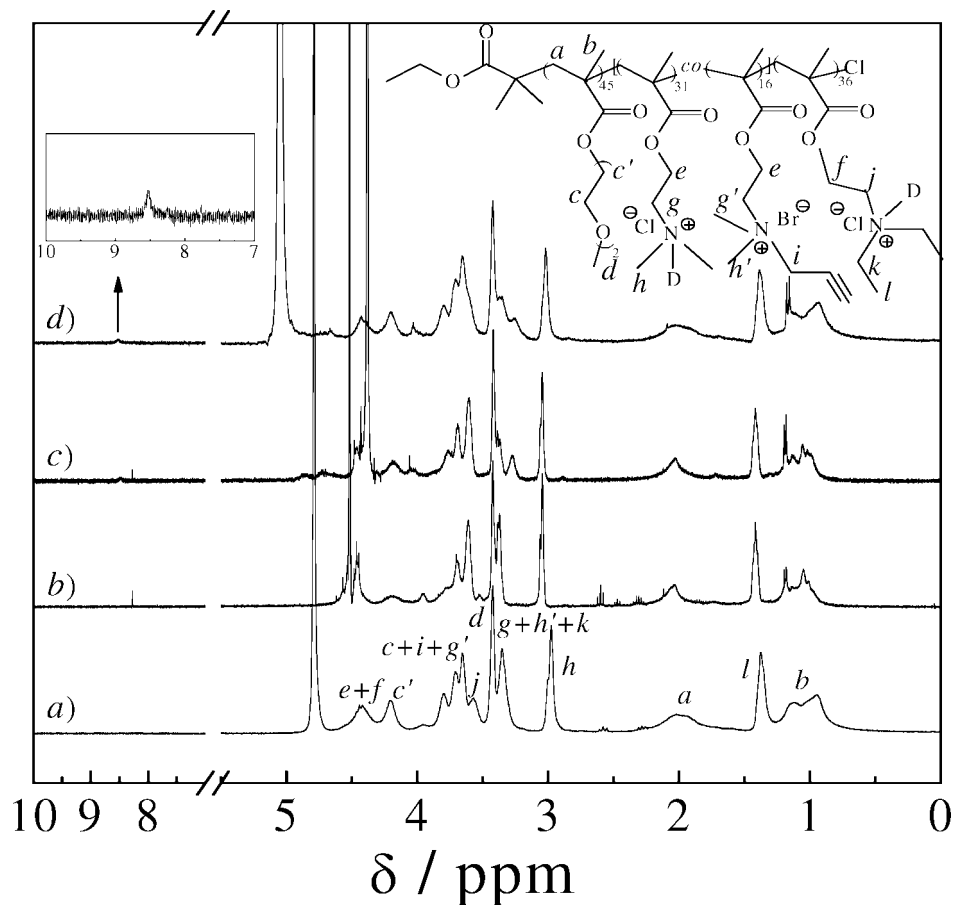


Figure 2. ^1H NMR spectra of $\text{PMEO}_2\text{MA}_{45}\text{-b-P(DMA}_{0.65}\text{-co-QDMA}_{0.35})_{47}\text{-b-PDEA}_{36}$ triblock copolymers at (a) pH 3 and 25 °C and (b) pH 3 and 50 °C, (c) SCL micelles prepared from $\text{PMEO}_2\text{MA}_{45}\text{-b-P(DMA}_{0.65}\text{-co-QDMA}_{0.35})_{47}\text{-b-PDEA}_{36}$ triblock copolymers at pH 3 and 50 °C, and (d) the obtained SCL micelles at pH 3 and 25 °C. The inset shows the magnified area of the methine peak on the 1,2,3-triazole ring.

in Figure 2a. The spectrum reveals the presence of characteristic signals of PMEO_2MA , PDMA, and PDEA blocks. The actual DP values of the PMEO_2MA , PDMA, and PDEA blocks were calculated to be 45, 47, and 36, respectively, on the basis of the integral ratios of those characteristic peaks of each segment and conversion of the PMEO_2MA block as determined by the ^1H NMR spectrum. Thus, the triblock copolymer was denoted $\text{PMEO}_2\text{MA}_{45}\text{-b-PDMA}_{47}\text{-b-PDEA}_{36}$.

Synthesis of $\text{PMEO}_2\text{MA-b-P(DMA-co-QDMA)-b-PDEA}$ Triblock Copolymer. The quaternization of amines by alkyl halides is known as the Menshutkin reaction, and quaternization of copolymers containing two types of amine groups such as the DMA and DEA residues has been widely investigated by Armes et al. It has been shown previously that DMA residues are significantly more reactive toward quaternization than DEA residues.^{30,54,55} Therefore, this difference in reactivity allowed the selective quaternization of DMA-based diblock or triblock copolymer. Selective quaternization of the DMA residues in $\text{PMEO}_2\text{MA}_{45}\text{-b-PDMA}_{47}\text{-b-PDEA}_{36}$ was carried out using propargyl bromide relative to the 50 mol % DMA content of triblock copolymer in THF at room temperature for 6 h. The extent of quaternization was assessed by ^1H NMR analysis in D_2O to be 35% (pH 3) by comparing the peak integrals of the unquaternized methylene proton signal (*h*) at δ 2.8–3.0 ppm to that of the two methyl groups (*l*) of DEA at δ 1.4 ppm (shown in Figure S1,

Supporting Information). Thus, the targeted product was denoted as $\text{PMEO}_2\text{MA}_{45}\text{-b-P(DMA}_{0.65}\text{-co-QDMA}_{0.35})_{47}\text{-b-PDEA}_{36}$.

Schizophrenic Micellization of $\text{PMEO}_2\text{MA-b-P(DMA-co-QDMA)-b-PDEA}$ PDMA and PDEA homopolymers are both weak polybases, and their conjugated acids have pK_a values of 7.0 and 7.3, respectively.^{54–59} At room temperature, PDMA homopolymer is water-soluble over the whole pH range with slightly lower water solubility at $\text{pH} > 9$ –10. In contrast, PDEA homopolymer is water-insoluble at neutral or alkaline pH. Below pH 6–7, it is soluble as a weak cationic polyelectrolyte due to the protonation of tertiary amine groups. On the other hand, PMEO_2MA homopolymer dissolves in cold and dilute aqueous solution but becomes insoluble above ~ 28 °C due to the LCST phase behavior.^{22,23} Thus, it was quite expected that $\text{PMEO}_2\text{MA-b-P(DMA-co-QDMA)-b-PDEA}$ triblock copolymer will exhibit temperature- and pH-responsive schizophrenic micellization behavior in aqueous solution (Scheme 2).

The aqueous solution of $\text{PMEO}_2\text{MA-b-P(DMA-co-QDMA)-b-PDEA}$ at a concentration of 1.0 g/L was clear at pH 3.0 and room temperature. Upon heating to 50 °C at pH 3.0, or adjustment to pH 9.0 at 25 °C, a large increase of light scattering and the appearance of a blue tinge characteristic of a colloidal dispersion

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can clearly be observed. This apparently indicates the triblock copolymer can exhibit temperature- and pH-responsive micellization. It should be noted that the thermoresponsive nature of the PMEO₂MA-*b*-P(DMA-*co*-QDMA)-*b*-PDEA triblock copolymer can be conveniently adjusted by inserting different amounts of OEGMA into the PMEO₂MA block. P(MEO₂MA-*co*-OEGMA)-*b*-PDMA-*b*-PDEA triblock copolymers with different amounts of OEGMA were synthesized via ATRP using the same method (Table 1).

The CMTs of these copolymers were measured using optical transmittance at 500 nm and 5.0 g/L aqueous solution (Table 1). The CMT of P(MEO₂MA-*co*-OEGMA)-*b*-PDMA-*b*-PDEA triblock copolymers possessing 5 or 10 mol % OEGMA increased to 40 or 43 °C at acidic conditions, respectively, which is reasonable and in accordance with the previous observations. Well-defined P(MEO₂MA-*co*-OEGMA) copolymers with 5 or 10 mol % OEGMA reported by Lutz et al. possess CMTs of 32 or 39 °C, respectively.²³ It has also been identified that the CMT of copolymer containing P(MEO₂MA-*co*-OEGMA) would shift to higher temperature by the addition of a hydrophilic block. Therefore, the protonation of both tertiary amine residues of PDMA and PDEA at pH 3 clearly increases the whole copolymer hydrophilicity and then obviously leads the CMT to shift to high temperature.

Above all, the P(MEO₂MA-*co*-OEGMA)-*b*-PDMA-*b*-PDEA triblock copolymers synthesized from an initial monomer feed with different amounts of OEGMA possess a tunable CMT in the range of 30–45 °C (Table 1). This adjustable thermoresponsive nature of these triblock copolymers will become more interesting and greatly broaden their potential application.

Thermoinduced Formation of Three-Layer Onion-like Micelles and SCL Micelles with PMEO₂MA Cores. The PMEO₂MA₄₅-*b*-P(DMA_{0.65}-*co*-QDMA_{0.35})₄₇-*b*-PDEA₃₆ triblock copolymer dissolves molecularly in aqueous solution at acidic pH and 25 °C. Micellization occurred at 50 °C to form three-layer onion-like micelles comprising PMEO₂MA cores, P(DMA-*co*-QDMA) inner shells, and fully protonated PDEA outer coronas, which was confirmed by ¹H NMR spectra and dynamic LLS.

Figure 2 shows the ¹H NMR spectra recorded for PMEO₂MA-*b*-P(DMA-*co*-QDMA)-*b*-PDEA in D₂O at different conditions. All the blocks are fully solvated in D₂O at acidic pH and 25 °C, and all the signals characteristic of PMEO₂MA, PDMA-*co*-QDMA, and PDEA blocks are visible (note the prominent signals at 3.7–3.8 ppm characteristic of the PMEO₂MA block and at 1.4 ppm for the PDEA residues) (Figure 2a). When the temperature is above 40 °C, a blue tinge of the solution can be observed, which indicates the formation of colloidal aggregates. Characteristic signals of the PMEO₂MA block ($\delta = 3.7\text{--}3.8$ ppm) broaden and diminish in intensity, which shows the PMEO₂MA block becomes insoluble above its LCST, while the characteristic signal of the PDEA block at $\delta = 1.4$ ppm is clearly visible (Figure 2b). This indicates the formation of PMEO₂MA-core micelles with P(DMA-*co*-QDMA) inner shells and stabilized by the well-solvated and protonated PDEA corona at acidic pH. It should be noted that the PMEO₂MA core still retains solvent molecules even at 40 °C such that the characteristic signal of the PMEO₂MA block does not completely disappear, which is consistent with the previous results.²⁴

Dynamic LLS was then employed to characterize the temperature-induced formation of PMEO₂MA-core micelles at acidic pH. Figure 3 shows the temperature dependence of dynamic LLS results for the PMEO₂MA-*b*-P(DMA-*co*-QDMA)-*b*-PDEA triblock copolymer at pH 3.0 and a concentration of 1.0 g/L.

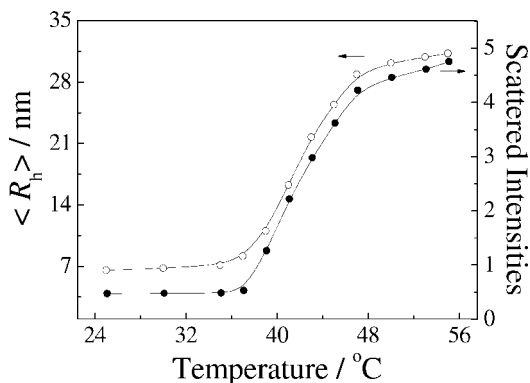


Figure 3. Variation of the intensity-average hydrodynamic radius, $\langle R_h \rangle$, and scattered light intensities with temperature obtained for a 1.0 g/L aqueous solution of PMEO₂MA₄₅-*b*-P(DMA_{0.65}-*co*-QDMA_{0.35})₄₇-*b*-PDEA₃₆ at pH 3.

Below 35 °C, the intensity-average hydrodynamic radius, $\langle R_h \rangle$, is ~7–8 nm. The scattered light intensity is quite low, confirming that the triblock copolymer dissolves molecularly. Above 35 °C, both the $\langle R_h \rangle$ and light scattering intensity start to increase with temperature, suggesting the thermoresponsive micellization above the critical micellization temperature due to the thermal phase transition of the PMEO₂MA block. Above 37 °C, only one population is revealed by dynamic LLS, $\langle R_h \rangle$ remains almost constant at ~30 nm, and the polydispersities (μ_2/Γ^2) of the formed micelles is typically less than 0.10. This indicates that the temperature-induced micellization is complete and the formed micelles with PMEO₂MA cores are quite monodisperse.

Wooley and co-workers have prepared amphiphilic PS-*b*-PAA diblock copolymer with the shell-forming PAA block derivatized with alkynyl groups and further successfully fixed the micellar structures by “click” cross-linking of the PAA shell in the presence of dendrimer surfaces functionalized with azide groups.⁶⁰ However, the core of the SCL micelles is hydrophobic and does not exhibit any stimulus-responsive behavior. In this study, the layer of the micelles with the PMEO₂MA block formed at elevated temperature contains reactive alkynyl groups. Thus, click reaction in the presence of difunctional azide compounds, such as tetra(ethylene glycol) diazide, should lead to the facile fixation of the temperature-induced micelles. Stimulus-responsive SCL micelles could easily be fabricated via click chemistry. It should be noted that click chemistry could be carried out at room or high temperature and even at a wide range of pH from acidic to basic conditions.^{61,62}

The tetra(ethylene glycol) diazide was added to the self-assembled micellar solution at 50 °C and pH 3. The molar ratio of tetra(ethylene glycol) diazide to that of alkynyl residues was kept constant at 1:2, targeting a theoretical degree of cross-linking of 100%. The reaction was quantitative, and the absorbance peak characteristic of the alkynyl group at ~2120 cm⁻¹ completely disappeared via click reaction as revealed by the FT-IR spectra of triblock copolymer and SCL micelles after freeze-drying (Figure 4a,c), which clearly showed quantitative conversion.

After freeze-drying of the SCL micellar solution, the obtained powder was redispersed in D₂O, and its ¹H NMR spectrum (pH 3) was recorded (Figure 2). After shell cross-linking, we can see

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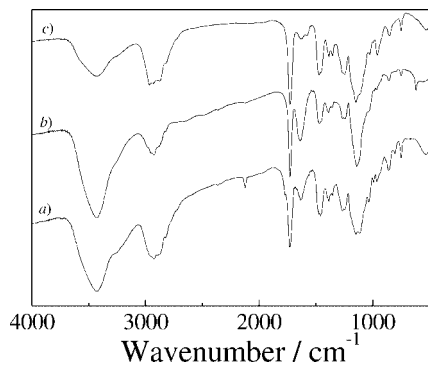


Figure 4. FT-IR spectra of (a) PMEO₂MA₄₅-*b*-P(DMA_{0.65}-*co*-QDMA_{0.35})₄₇-*b*-PDEA₃₆ triblock copolymer, (b) SCL micelles with PDEA cores, and (c) SCL micelles with PMEO₂MA cores.

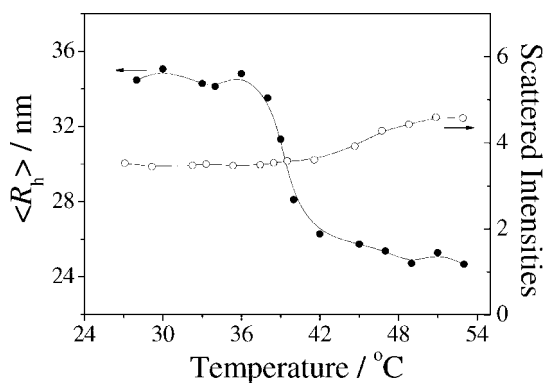


Figure 5. Variation of the intensity-average hydrodynamic radius, $\langle R_h \rangle$, and scattered light intensities with temperature obtained for a 1.0 g/L aqueous solution of SCL micelles prepared from PMEO₂MA₄₅-*b*-P(DMA_{0.65}-*co*-QDMA_{0.35})₄₇-*b*-PDEA₃₆ triblock copolymer at pH 3 and 50 °C.

the appearance of a new characteristic signal at δ 8.5 ppm, which should be the characteristic peak of the 1,2,3-triazole ring (Figure 2c,d). This clearly shows the successful click reaction. The signals characteristic of the PMEO₂MA segment of the SCL micelles at 25 °C is enhanced compared with that at elevated temperature as the PMEO₂MA cores of SCL micelles were solvated and turned hydrophilic at this condition (Figure 2d).

After copper catalyst removal and redispersion in aqueous solution, the SCL micelles still exhibit a blue tinge at room temperature which shows a successful shell-cross-linking reaction. Otherwise, the micelles will dissociate into unimers under this condition, and the obtained solution should be clear. After shell cross-linking, the size of the micelles, $\langle R_h \rangle$, of 25 nm is slightly smaller than that of non-cross-linked micelles at 50 °C and pH 3.0. Polydispersity indices of these micelles with PMEO₂MA cores before and after cross-linking were found to be constant at around ~ 0.10 . This suggests that the cross-linking reaction takes place exclusively inside the P(DMA-*co*-QDMA) inner layer and intermicellar cross-linking does not occur due to the steric repulsion imparted by the coronal PDEA chains.

To further identify the covalent stabilization, the PMEO₂MA-core SCL micelle solution was allowed to cool to room temperature. If the shell cross-linking were unsuccessful, dissociation into individual triblock copolymer chains would be expected to occur with $\langle R_h \rangle$ of several nanometers and furthermore no spherical nanoparticles would be observed since the PMEO₂MA block would become soluble under this condition. Figure 9b shows the TEM image of SCL micelles with PMEO₂MA cores via click chemistry, which reveals the presence of spherical

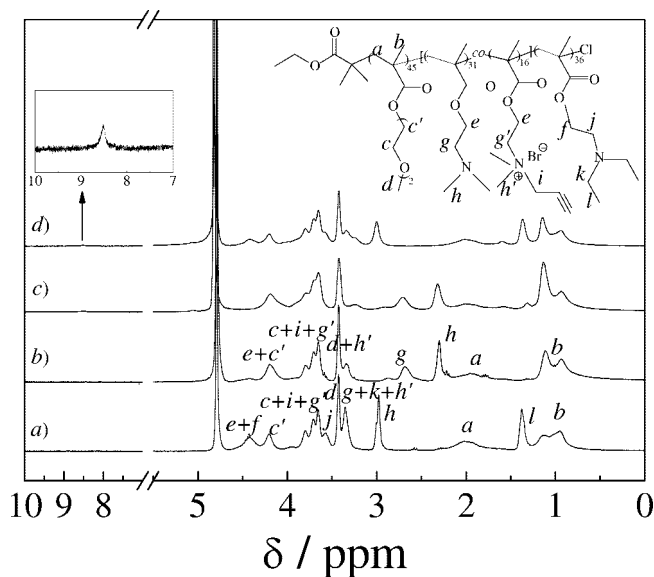


Figure 6. ¹H NMR spectra of PMEO₂MA₄₅-*b*-P(DMA_{0.65}-*co*-QDMA_{0.35})₄₇-*b*-PDEA₃₆ triblock copolymers at (a) pH 3 and 25 °C and (b) pH 9 and 25 °C, (c) SCL micelles prepared from PMEO₂MA₄₅-*b*-P(DMA_{0.65}-*co*-QDMA_{0.35})₄₇-*b*-PDEA₃₆ triblock copolymers at pH 9 and 25 °C, and (d) the obtained SCL micelles at pH 3 and 25 °C. The inset shows the magnified area of the methine peak on the 1,2,3-triazole ring.

nanoparticles with an average diameter of ~ 60 – 80 nm. Dynamic LLS was also used to examine the temperature dependence of $\langle R_h \rangle$ of SCL micelles with PMEO₂MA cores (Figure 5). The micelle size, $\langle R_h \rangle$, increased when the solution temperature was lowered below the CMT of the PMEO₂MA block and exhibited the most dramatic increase in the temperature range of 36–42 °C. This is in agreement with the CMT value of the triblock copolymer (~ 41 °C). The size increase at low temperature should be due to the swelling of the PMEO₂MA cores. Furthermore, LLS studies revealed the thermoinduced swelling/deswelling of PMEO₂MA cores is fully reversible. These results clearly substantiated the successful covalent stabilization of SCL micelles after shell cross-linking via click chemistry. As most of the size changes take place around physiological temperature, potential applications of such structurally stable SCL micelles is highly viable in the field of drug delivery for the “triggered release” of encapsulated hydrophobic drugs.

pH-Induced Formation of Inverted Micelles and SCL Micelles with PDEA Cores. The PDEA homopolymer and block copolymer containing PDEA chains have been widely studied for their pH-responsive property. PDEA homopolymer is water-insoluble at neutral or alkaline pH; below pH 7.0, it is soluble as a weak cationic polyelectrolyte due to the protonation of tertiary amine groups. Figure 6 shows the ¹H NMR spectra recorded for PMEO₂MA-*b*-P(DMA-*co*-QDMA)-*b*-PDEA in D₂O at different conditions. As described above, all the blocks are fully solvated in D₂O at acidic pH and 25 °C and all the signals characteristic of PMEO₂MA, P(DMA-*co*-QDMA), and PDEA blocks are visible (Figure 6a). Upon increasing the solution pH to 9, the intensities of the characteristic PDEA signals at $\delta = 1.4$ and 3.5 ppm completely disappear, while signals characteristic of PMEO₂MA at $\delta = 3.7$ – 3.8 ppm and PDMA at $\delta = 2.4$ – 2.8 ppm are still clearly visible (Figure 7b). This indicates the formation of structurally inverted onion-like PDEA-core micelles with the inner shell comprising P(DMA-*co*-QDMA) and a corona consisting of the solvated PMEO₂MA block (Scheme 2).

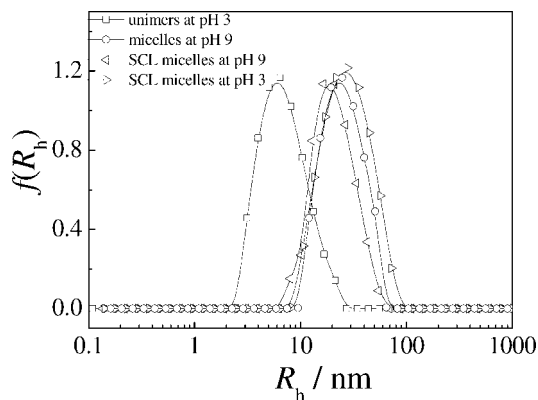


Figure 7. Typical hydrodynamic radius distributions, $f(R_h)$, obtained for 1.0 g/L aqueous solutions of unimers, micelles, and SCL micelles of $\text{PMEO}_2\text{MA}_{45}\text{-}b\text{-P}(\text{DMA}_{0.65}\text{-}co\text{-QDMA}_{0.35})_{47}\text{-}b\text{-PDEA}_{36}$ triblock copolymer at different pH values and 25 °C. The shell cross-linking was conducted at pH 9 and 25 °C.

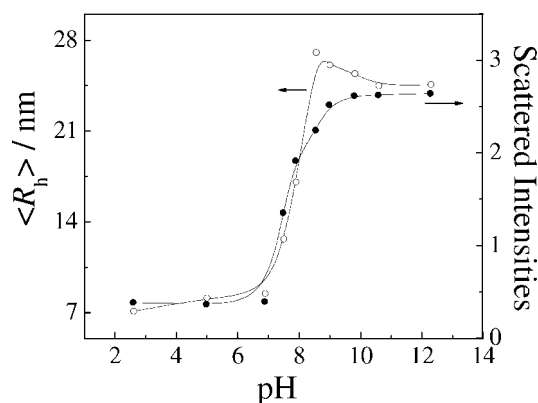


Figure 8. Variation of the intensity-average hydrodynamic radius, $\langle R_h \rangle$, and scattered light intensities as a function of pH obtained for 1.0 g/L aqueous solutions of $\text{PMEO}_2\text{MA}_{45}\text{-}b\text{-P}(\text{DMA}_{0.65}\text{-}co\text{-QDMA}_{0.35})_{47}\text{-}b\text{-PDEA}_{36}$ triblock copolymer at 25 °C.

The hydrodynamic radius distributions, $f(R_h)$, of unimers and micelles prepared from the $\text{PMEO}_2\text{MA}_{45}\text{-}b\text{-P}(\text{DMA}_{0.65}\text{-}co\text{-QDMA}_{0.35})_{47}\text{-}b\text{-PDEA}_{36}$ triblock copolymer at different pH values are shown in Figure 7. The $\text{PMEO}_2\text{MA}_{45}\text{-}b\text{-P}(\text{DMA}_{0.65}\text{-}co\text{-QDMA}_{0.35})_{47}\text{-}b\text{-PDEA}_{36}$ triblock copolymer dissolves molecularly with several nanometers in aqueous solution at room temperature and pH 3. Micellar self-assembly occurred at pH > 7 with R_h in the range of 9–51 nm with the peak located at 26 nm. Figure 8 represents the variation of the intensity-average hydrodynamic radius, $\langle R_h \rangle$, and the light scattering intensities as a function of pH obtained for a 1.0 g/L aqueous solution of $\text{PMEO}_2\text{MA}_{45}\text{-}b\text{-P}(\text{DMA}_{0.65}\text{-}co\text{-QDMA}_{0.35})_{47}\text{-}b\text{-PDEA}_{36}$ triblock copolymer at 25 °C. Below pH 7, the $\langle R_h \rangle$ is ~7–8 nm and the scattered light intensity is very low, which further confirms that the triblock copolymer dissolves molecularly. Above pH 7, $\langle R_h \rangle$ starts to increase with solution pH, followed by an increase of the light scattering intensity and the appearance of a blue tinge that is characteristic of micellar solutions, suggesting micellization occurred. Above pH 9, the micelle size remains almost constant, with $\langle R_h \rangle \approx 26$ nm. The size distribution is relatively monodisperse with a polydispersity (μ_2/Γ^2) of 0.09. This agrees quite well with the previous ^1H NMR results, which further identified the formation of PDEA-core micelles with the clickable P(DMA-*co*-QDMA) shell and PMEO_2MA corona at pH 9 and 25 °C.

Owing to the presence of click-cross-linkable alkyne groups in the P(DMA-*co*-QDMA) shell, the self-assembled micelles could be fixed to preserve the structural integration and avoid the structural disintegration or inversion upon the addition of tetra(ethylene glycol) diazide in the presence of copper catalysts. After shell cross-linking via click chemistry, the PDEA-core SCL micelles with an $\langle R_h \rangle$ of 20 nm and a polydispersity (μ_2/Γ^2) of 0.09 were obtained. The almost constant polydispersity values of the PDEA-core micelles before and after cross-linking suggest that the cross-linking reaction takes place exclusively inside the P(DMA-*co*-QDMA) inner layer and mainly intramicellar cross-linking occurs due to the protection of coronal PMEO_2MA chains.

After shell cross-linking via click chemistry, a new characteristic signal at $\delta = 8.5$ ppm of the 1,2,3-triazole ring was

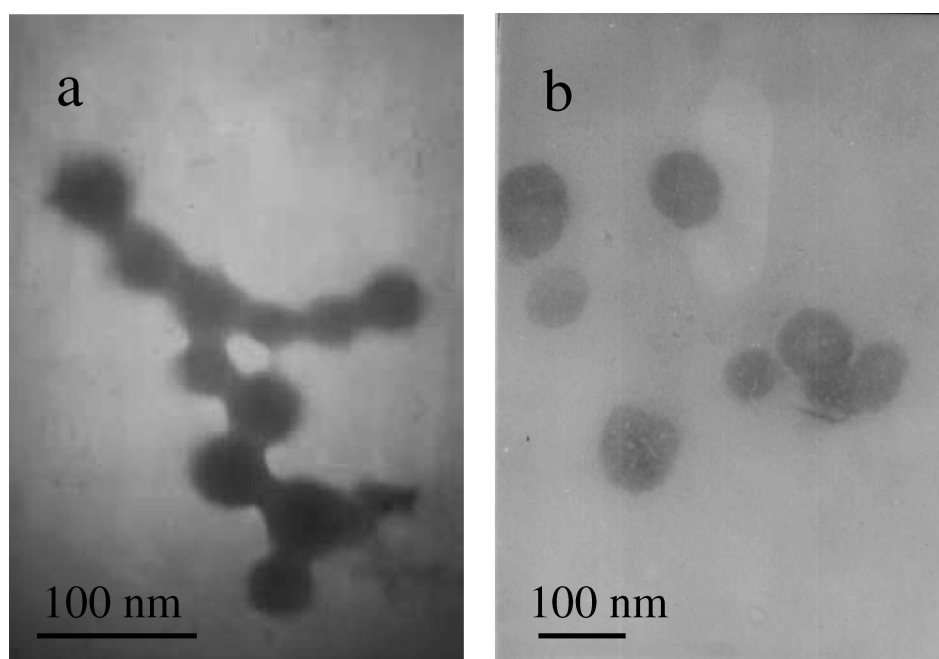


Figure 9. Typical TEM images of SCL micelles of $\text{PMEO}_2\text{MA}_{45}\text{-}b\text{-P}(\text{QDMA}_{0.35}\text{-}co\text{-DMA}_{0.65})_{47}\text{-}b\text{-PDEA}_{36}$ triblock copolymer. The shell cross-linking was conducted at (a) pH 9 and 25 °C and (b) pH 3 and 50 °C.

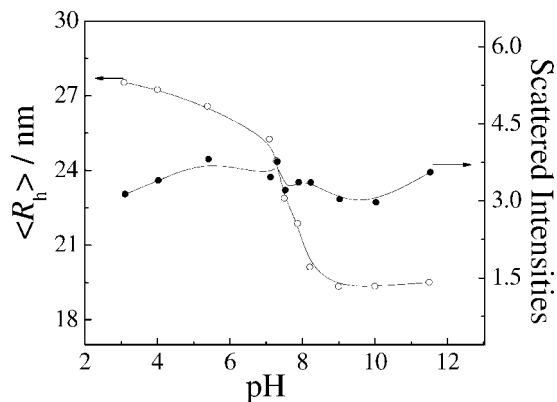


Figure 10. Variation of the intensity-average hydrodynamic radius, $\langle R_h \rangle$, and scattered light intensities as a function of pH obtained for a 1.0 g/L aqueous solution of SCL micelles of $\text{PMEO}_2\text{MA}_{45}\text{-}b\text{-P(DMA}_{0.65}\text{-}co\text{-QDMA}_{0.35})_{47}\text{-}b\text{-PDEA}_{36}$ triblock copolymer at 25 °C. The shell cross-linking was conducted at pH 9 and 25 °C.

detected by ^1H NMR analysis (Figure 6c,d), and we can see the absorbance peak characteristic of the alkynyl group at $\sim 2120\text{ cm}^{-1}$ completely disappeared from the FT-IR spectra of SCL micelles with PDEA cores after freeze-drying (Figure 4b), suggesting the click groups were fully reactive for the quantitative click reaction.

To identify the covalent stabilization of SCL micelles with PDEA cores, the solution pH of SCL micelles was adjusted to 3 using concentrated HCl solution. If no shell cross-linking had occurred or the cross-linking was not successful, the micelles would be expected to dissociation into individual triblock copolymer chains with an $\langle R_h \rangle$ of several nanometers, since the PDEA blocks become soluble under these conditions. Figure 5a shows the TEM image of SCL micelles with PDEA cores, which clearly reveals the presence of spherical nanoparticles with a mean diameter of $\sim 20\text{--}30\text{ nm}$ at pH 3 and 25 °C. Figure 7 shows the swelling of the SCL micelles with PDEA cores at acidic pH in terms of the shift of the hydrodynamic radius R_h distribution. At pH 9, the R_h of the PDEA-core SCL micelles ranged from 8 to 54 nm with the peak located at 20 nm. At pH 3, R_h was in the range of 8–72 nm with the peak located at 28 nm, which apparently revealed an increase of the SCL micelle size with a decrease of pH due to the PDEA swelling at acidic pH. This clearly indicated the successful fixation of the micelles with PDEA cores via click chemistry. The signals characteristic of PDEA in SCL micelles at pH 3 are shown in Figure 6d, also suggesting the PDEA cores of SCL micelles were solvated and turned hydrophilic at this condition (Figure 2d).

The pH dependence of $\langle R_h \rangle$ for the obtained SCL micelles with PDEA cores is illustrated in Figure 10. We can see that the most dramatic increase of micelle sizes occurs within the pH

range of 7–8, while scattered light intensity remains almost constant in this pH range. This again confirms the successful shell cross-linking and the size increase upon a pH decrease is due to the solvation and swelling of PDEA cores. Potential applications of such structurally stable SCL micelles are highly viable in the field of drug delivery for the triggered release of encapsulated hydrophobic drugs.

Conclusion

In summary, well-defined novel schizophrenic water-soluble $\text{PMEO}_2\text{MA}\text{-}b\text{-PDMA}\text{-}b\text{-PDEA}$ triblock copolymer was prepared via ATRP by using the one-pot method. Subsequently, the PDMA segment in the copolymer was partially quarternized to generate “clickable” $\text{PMEO}_2\text{MA}\text{-}b\text{-P(DMA}\text{-}co\text{-QDMA})\text{-}b\text{-PDEA}$ triblock copolymer. The resulting triblock copolymer dissolves molecularly in aqueous solution at 25 °C and acidic pH. Two micellar aggregates with PDEA or PMEO_2MA cores with inverse structures were obtained at 50 °C and pH 3 or 25 °C and pH 9, respectively. Both micellizations are reversible, and the micelles were decorated with “click-reactive” groups in the middle shell. Finally, click cross-linking of the inner $\text{P(DMA}\text{-}co\text{-QDMA})$ shell of micelles resulted in the formation of two types of shell-cross-linked micelles with inverted structures in aqueous solution. Those SCL micelles have different transitions on their swelling and deswelling of the SCL structures for the change of solution pH or temperature. It should be noted that the SCL micelles with thermoresponsive cores have a “slow transition” for the temperature range from 36 to 42 °C for the swelling/deswelling of PMEO_2MA cores, whereas a “sharp transition” occurs in another kind of SCL micelles for the sizes of the PDEA cores with an abrupt change around 1 pH unit. This should be very interesting for its application in drug delivery. To the best of our knowledge, the formation of two types of SCL micelles with inverted structures by the same schizophrenic triblock copolymers in pure aqueous solution is unprecedented.

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Supporting Information Available: ^1H NMR spectra of the triblock copolymers. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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