Synthesis and Aggregation Behavior of Multi-Responsive Double Hydrophilic ABC Miktoarm Star Terpolymer[a]

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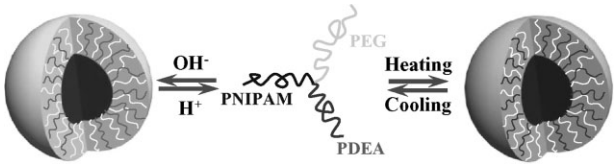
We report the first example of the synthesis and the "schizophrenic" micellization behavior of a multi-responsive double hydrophilic ABC miktoarm star terpolymer. A well-defined miktoarm star terpolymer consisting of poly(ethylene glycol), poly(2-(diethylamino)ethyl methacrylate), and poly(*N*-isopropylacrylamide) arms, PEG(-*b*-PDEA)-*b*-PNIPAM, was synthesized via the combination of atom transfer radical polymerization (ATRP) and click reaction. Containing pH-responsive PDEA and thermo-responsive PNIPAM arms, this novel type of miktoarm star terpolymer molecularly dissolves in aqueous solution at acidic pH and room temperature, but supramolecularly self-assembles into PDEA-core micelles at alkaline pH and room temperature, and PNIPAM-core micelles at acidic pH and elevated temperatures. Most importantly, both types of micellar aggregates possess well-solvated hybrid coronas.



Introduction

In the past decade, ever-increasing attention has been paid to the field of stimuli-responsive double hydrophilic block copolymers (DHBCs), which exhibit the so-called "schizophrenic" aggregation behavior in aqueous solution upon tuning external solution conditions such as pH, ionic strength, and temperature.[1–12] Previous reports concerning DHBCs mainly focused on the synthesis and supramolecular self-assembly of linear ones.[2–13] It has been established that chain architectures of block copolymers can exert dramatic effects on their self-assembling properties. In the context of nonlinear-shaped DHBCs, Armes et al.[14] reported the first example of stimuli-responsive Y-shaped (AB_2) miktoarm star copolymers, which can self-assemble into micelles with drastically different dimensions compared to their linear counterparts. Previously, we report the synthesis and self-assembly of double hydrophilic AB_4 miktoarm star copolymers consisting of one poly(*N*-isopropylacrylamide) (PNIPAM) arm and four poly(2-(diethylamino)ethyl methacrylate) (PDEA) arms.[15] DHBCs with more complex chain architectures including H-shaped A_2BA_2, super H-shaped A_4BA_4, and purely polypeptide-based AB_2 Y-shaped miktoarm star terpolymers were also synthesized.[16,17]

The above examples of nonlinear DHBCs consist of only two types of polymer sequences. It can be expected that when more than two types of polymer sequences are arranged in a nonlinear fashion in DHBCs, their responsive supramolecular assembling behavior should be more complex and fascinating. The simplest form would be

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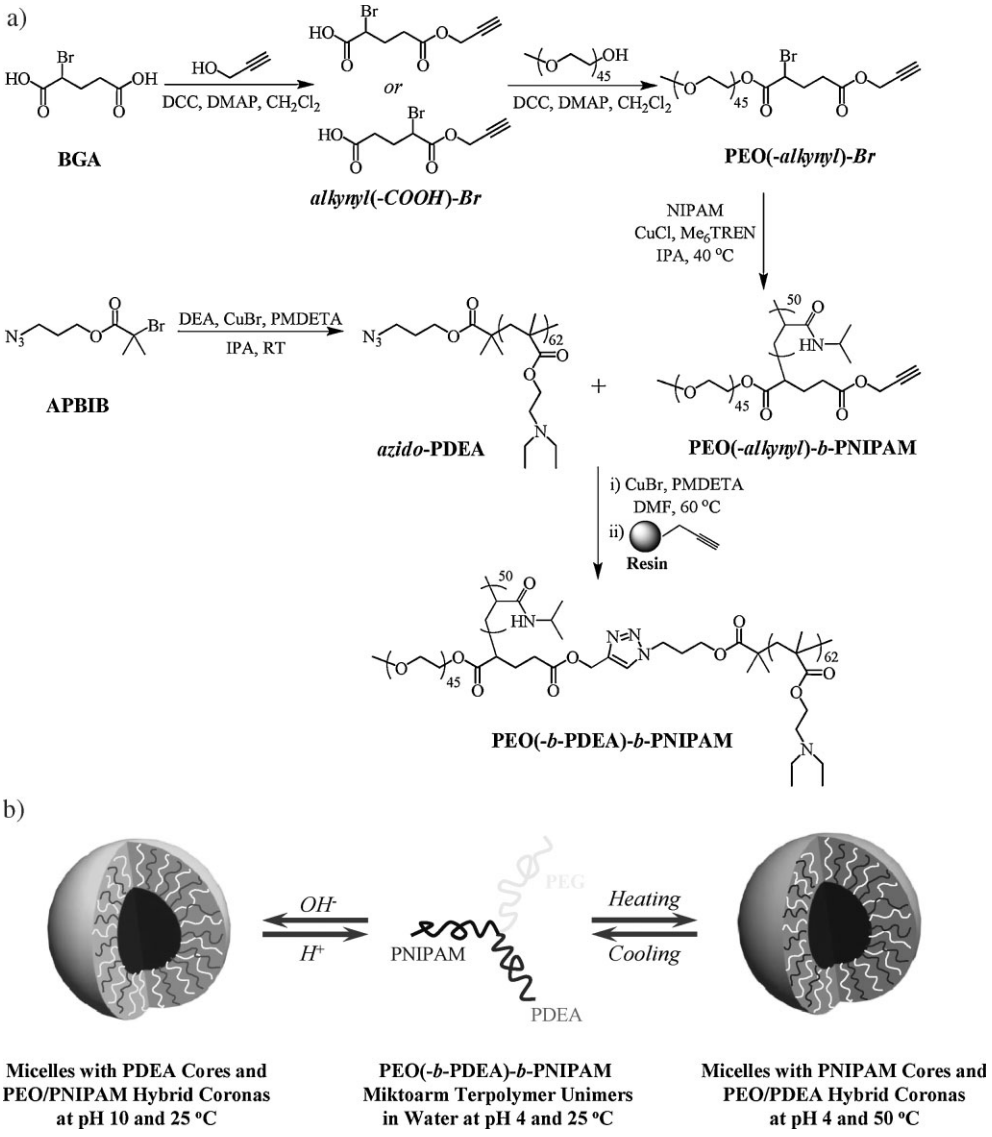
ABC miktoarm star terpolymers consisting of three different water-soluble and responsive arms. To the best of our knowledge, the synthesis and "schizophrenic" micellization behavior of double hydrophilic ABC miktoarm star terpolymers have not been reported yet.

In terms of the synthesis of miktoarm star terpolymers, the combination of relatively mature techniques such as controlled radical polymerizations (CRP), ring-opening polymerization (ROP), and click chemistry have rendered their preparation much easier in the past few years.[18–21] In this communication, novel double hydrophilic ABC miktoarm star terpolymer consisting of poly(ethylene glycol) (PEG), PDEA, and PNIPAM arms, PEG(-*b*-PDEA)-*b*-PNIPAM, was synthesized via the combination of atom transfer radical polymerization (ATRP) and click reaction (Scheme 1a). Containing pH-responsive PDEA and thermo-responsive PNIPAM arms, the obtained PEG(-*b*-PDEA)-*b*-PNIPAM double hydrophilic miktoarm star terpolymer molecularly dissolves in aqueous solution at acidic pH and room temperature, but self-assembles into PDEA-core micelles at alkaline pH and room temperature, and PNIPAM-core micelles at acidic pH and elevated temperatures. Most importantly, both types of micellar aggregates possess well-solvated hybrid coronas (Scheme 1b). This work represents the first example of synthesis and "schizophrenic" micellization behavior of multi-responsive double hydrophilic ABC miktoarm star terpolymer.



Scheme 1. Schematic illustrations for (a) the preparation of PEG(-*b*-PDEA)-*b*-PNIPAM double hydrophilic ABC miktoarm star terpolymer, and (b) pH- and thermo-induced supramolecular self-assembly of PEG(-*b*-PDEA)-*b*-PNIPAM ABC miktoarm star terpolymer into two types of micellar aggregates possessing hybrid coronas in aqueous solution.

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Experimental Part

Materials

Poly(ethylene glycol) monomethyl ether (PEG_{45}-OH, $\overline{M}_n = 2.0$ kDa) was purchased from Aldrich and used as received. 2-(Diethylamino)ethyl methacrylate (DEA, 99%, Aldrich) was dried over calcium hydride, vacuum-distilled, and stored at −20 °C prior to use. *N*-Isopropylacrylamide (NIPAM) (97%, Tokyo Kasei Kagyo Co.) was recrystallized from a mixture of benzene and *n*-hexane (1/3, v/v). Copper(I) bromide (CuBr, 98%), copper(I) chloride (CuCl, 99.995%), *N,N,N′,N″,N″*-Pentamethyldiethylenetriamine (PMDETA, 99%), Wang resin (1.47 mmol · g^{-1}), and tris(aminoethyl)amine (TREN) were purchased from Aldrich and used as received. Dichloromethane (CH_2Cl_2) was dried by refluxing over CaH_2 and distilled prior to use. *N,N*-Dicyclohexylcarbodimide (DCC), 4-dimethylaminopyridine (DMAP), L-glutamic acid, propargyl alcohol, and all other chemicals were purchased from Sinopharm Chemical Reagent Co. Ltd. and used as received. Tris(2-(dimethylamino)ethyl)amine (Me_6TREN) was prepared from TREN according to literature procedures.[22] 2-Bromoglutaric acid (BGA),[23] 3-azidopropyl 2-bromoisobutyrate (APBIB),[24] and alkynyl-functionalized Wang resin[17] were available from previous studies.

Synthesis of Monopropargyl 2-Bromoglutarate (Alkynyl(-COOH)-Br)

Into a dry 250 mL round-bottom flask, BGA (10.0 g, 47.4 mmol), DCC (14.6 g, 70.8 mmol), and dry CH_2Cl_2 (100 mL) were added. After cooling to 0 °C in an ice-water bath, propargyl alcohol (1.77 g, 32.7 mmol) and DMAP (0.855 g, 7.0 mmol) in 50 mL dry CH_2Cl_2 was added dropwise over 0.5 h under magnetic stirring. After the addition was completed, the reaction mixture was stirred at 0 °C for 1 h and then at room temperature for 12 h. After removing insoluble *N,N′*-dicyclohexylurea via suction filtration, the solvents were removed under reduced pressure. The crude product was dissolved in saturated aqueous $NaHCO_3$ solution (40 mL). After filtration, the filtrate was extracted with CH_2Cl_2 (3 × 20 mL). After discarding the organic phase, the aqueous phase was adjusted to pH = 1 and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phase was dried over anhydrous $MgSO_4$ and then evaporated to dryness, affording a slightly yellow liquid (1.42 g, yield: 17%).

^{1}H NMR ($CDCl_3$, TMS): $\delta = 4.72$ (2H, $-COOCH_2C{\equiv}CH$), 4.40 (1H, $-CHBrCH_2CH_2$ COO−), 2.71–2.56 (2H, $-CHBrCH_2CH_2COO-$), 2.56–2.47 (1H, $-COOCH_2C{\equiv}CH$), and 2.47–2.16 (2H, $-CHBrCH_2$ CH_2COO-) (Figure S1 in Supporting Information).

Synthesis of PEG-Based Macroinitiator (PEG_{45}(-alkynyl)-Br)

Into a dry 250 mL round-bottom flask, PEG_{45}-OH (5.60 g, 2.8 mmol), *alkynyl*(*-COOH*)*-Br* (1.39 g, 5.6 mmol), and 20 mL dry toluene were added. After azeotropic distillation of ≈10 mL toluene out of the mixture, 100 mL dry CH_2Cl_2 was added. The mixture was cooled to 0 °C in an ice-water bath, DCC (1.73 g, 8.4 mmol) and DMAP (0.208 g, 1.7 mmol) in 20 mL dry CH_2Cl_2 were added dropwise over 0.5 h under magnetic stirring. The mixture was stirred at 0 °C for 1 h and then at room temperature for 12 h. After filtration, the filtrate was concentrated and precipitated into an excess of diethyl ether. The above dissolution and precipitation cycle was repeated for three times. After drying in a vacuum oven overnight at room temperature, PEG_{45}(*-alkynyl*)*-Br* was obtained as a white powder (5.06 g, yield: 81%; $\overline{M}_{n,GPC} = 1.8$ kDa, $\overline{M}_w/\overline{M}_n = 1.08$).

^{1}H NMR ($CDCl_3$, TMS): $\delta = 4.71$ (2H, $-COOCH_2C{\equiv}CH$), 4.42 (1H, $-CHBrCH_2CH_2COO-$), 4.35 (2H, $-OCH_2CH_2COO-$), 3.67 (176H, $-OCH_2CH_2O-$), 3.40 (3H, $-OCH_3$), 2.61 (2H, $-CHBrCH_2CH_2COO-$), 2.53 (1H, $-COOCH_2C{\equiv}CH$), and 2.48–2.21 (2H, $-CHBrCH_2$ CH_2COO-) (Figure S1).

Synthesis of PEG(-alkynyl)-*b*-PNIPAM Diblock Copolymer

To a Schlenk tube equipped with a magnetic stirring bar, PEG_{45} (*-alkynyl*)*-Br* macroinitiator (1.0 g, 0.45 mmol), NIPAM (3.06 g, 27.0 mmol), Me_6TREN (0.115 g, 0.50 mmol), and IPA (8 mL) were added. After one brief freeze-pump-thaw cycle, CuCl (49 mg, 0.50 mmol) was introduced under the protection of N_2 flow. The reaction tube was carefully degassed by three freeze-pump-thaw cycles and then placed in an oil bath thermostated at 40 °C. After 7 h, the polymerization was terminated by quenching into liquid nitrogen, diluted with 20 mL THF, and then exposed to air. The reaction mixture was passed through a silica gel column to remove copper catalysts. After removing the solvents, the residues were dissolved in THF and precipitated into an excess of ethyl ether. The above dissolution-precipitation cycle was repeated twice. The final product was dried in a vacuum oven, yielding a white solid (2.84 g, yield: 80%; $\overline{M}_{n,GPC} = 6.8$ kDa, $\overline{M}_w/\overline{M}_n = 1.13$). The actual DP of PNIPAM block was determined to be 50 by ^{1}H NMR analysis in $CDCl_3$. Thus, the obtained diblock copolymer was denoted as PEG_{45}(*-alkynyl*)*-b*-$PNIPAM_{50}$.

Synthesis of Azido-Terminated PDEA (PDEA-N_3).

In a typical example, DEA monomer (12.97 g, 70.0 mmol), PMDETA (0.173 g, 1.0 mmol), APBIB (0.250 g, 1.0 mmol), and IPA (12 mL) were charged into a reaction flask. The flask was degassed via three freeze-thaw-pump cycles and back-filled with N_2. CuBr (0.143 g, 1.0 mmol) was introduced into the reaction mixture under protection of N_2 flow to start the polymerization at room temperature under N_2 atmosphere. After 5 h, the polymerization was terminated by exposing to air and diluting with THF. After passing through a column of neutral alumina to remove copper catalysts and removing all the solvents, the residues were dissolved in THF and precipitated into cold *n*-hexane (−50 °C) to remove residual monomers. After drying in a vacuum oven overnight at room temperature, PDEA-N_3 was obtained as a white viscous solid (11.0 g, yield: 83%; $\overline{M}_{n,GPC} = 11.0$ kDa, $\overline{M}_w/\overline{M}_n = 1.10$). The actual DP of PDEA-N_3 was calculated to be 62 by ^{1}H NMR analysis in $CDCl_3$. Thus, the obtained product was denoted as $PDEA_{62}$-N_3.

Preparation of PEG(-*b*-PDEA)-*b*-PNIPAM ABC Miktoarm Star Terpolymer via Click Chemistry

$PDEA_{62}$-N_3 (1.76 g, 0.15 mmol), PEG_{45}(*-alkynyl*)*-b*-$PNIPAM_{50}$ (0.789 g, 0.10 mmol), and PMDETA (17 mg, 0.10 mmol) were dissolved in

10 mL DMF. After one brief freeze-thaw cycle, CuBr (14 mg, 0.10 mmol) was introduced under the protection of N_2 flow. The reaction tube was then carefully degassed by three freeze-pump-thaw cycles, and placed in an oil bath thermostated at 60 °C. After stirring for 24 h, alkynyl- functionalized Wang resin (0.2 g, 0.294 mmol alkynyl moieties) was then added. The suspension was kept stirring for another 8 h at 60 °C. After suction filtration, the filtrate was diluted with THF, and passed through a neutral alumina column to remove the copper catalysts. After removing all the solvents, the residues were dissolved in THF and precipitated into an excess of *n*-hexane. After drying in a vacuum oven overnight at room temperature, PEG_{45}(-*b*-$PDEA_{62}$)-*b*-$PNIPAM_{50}$ was obtained as a white solid (1.47 g, yield: 75%; $\overline{M}_{n,GPC} = 15.4$ kDa, $\overline{M}_w/\overline{M}_n = 1.09$).

Characterization

All ^{1}H NMR spectra were recorded on a Bruker AV300 NMR spectrometer (resonance frequency of 300 MHz for ^{1}H) operated in the Fourier transform mode. $CDCl_3$ or D_2O was used as the solvent. Molecular weights and molecular weight distributions were determined by gel permeation chromatography (GPC) equipped with a Waters 1515 pump and a Waters 2414 differential refractive index detector (set at 30 °C). It used a series of three linear Styragel columns HT2, HT4, and HT5 at an oven temperature of 45 °C. The eluent was THF at a flow rate of 1.0 mL·min^{-1}. A series of low polydispersity polystyrene standards were employed for the calibration. Fourier transform infrared (FT-IR) spectra were recorded on a Bruker VECTOR-22 IR spectrometer. A commercial spectrometer (ALV/DLS/SLS-5022F) equipped with a multi-tau 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 laser light scattering (LLS) measurements. Scattered light was collected at a fixed angle of 90° for duration of ≈10 min.

Results and Discussion

Synthesis of PEG(-*b*-PDEA)-*b*-PNIPAM ABC Miktoarm Star Terpolymer

The synthetic routes employed for the preparation of well-defined double hydrophilic ABC miktoarm star terpolymer, PEG(-*b*-PDEA)-*b*-PNIPAM, is shown in Scheme 1a. The trifunctional core molecule propargyl monoester 2-bromoglutarate, *alkynyl*(-*COOH*)-*Br*, was synthesized via the esterification of propargyl alcohol with an excess of BGA. Figure S1 shows the ^{1}H NMR spectrum of *alkynyl*(-*COOH*)-*Br*. It should be noted that due to the presence of two carboxyl residues in BGA, the esterification reaction afforded a mixture of 1-propargyl monoester 2-bromoglutarate and 5-propargyl monoester 2-bromoglutarate. For simplicity, in Scheme 1 and the text below, 5-propargyl monoester 2-bromoglutarate was used to represent the esterification product. It should be noted that both propargyl monoester 2-bromoglutarate behave similarly in subsequent reactions.

The esterification reaction of PEG_{45}-OH with *alkynyl*(-*COOH*)-*Br* afforded difunctional PEG-based macroinitiator, PEG_{45}(-*alkynyl*)-*Br*, in the presence of DCC and DMAP (Scheme 1a). ^{1}H NMR spectroscopy studies indicated that the esterification reaction was essentially complete (Figure S1b). The signal at 3.7 ppm (peak *g*) can be ascribed to the methylene protons of PEG main chain, whereas signals at 4.7 ppm (peak *b*) and 2.5 ppm (peak *a*) were ascribed to methylene and alkynyl protons of terminal propargyl group, respectively. By comparing integral ratios of peaks *b* to that of *g*, the degree of end group functionalization was calculated to be nearly 100%, i.e., a quantitative end group transformation was achieved.

The ATRP of NIPAM led to the preparation of PEG(-*alkynyl*)-*b*-PNIPAM bearing a reactive alkynyl group at the diblock junction point (Scheme 1a). Compared to that of PEG_{45}(-*alkynyl*)-*Br*, GPC analysis clearly revealed that the elution peak of PEG_{45}(-*alkynyl*)-*b*-$PNIPAM_{50}$ shifts to the higher MW side (Figure 1b). Moreover, the diblock copolymer elution peak was relatively symmetric and shows no tailing at the lower molecular weight side. GPC analysis revealed an $\overline{M}_n$ of 6.8 kDa and an $\overline{M}_w/\overline{M}_n$ of 1.13. ^{1}H NMR spectrum of PEG_{45}(-*alkynyl*)-*b*-$PNIPAM_{50}$ is shown in Figure S2 (in Supporting Information), and all signals characteristic of PEG and PNIPAM segments can be clearly observed.

PDEA-N_3 was prepared via ATRP using APBIB as the initiator and CuBr/PMDETA as the catalysts at room temperature. GPC analysis in THF revealed a mono-modal peak with an $\overline{M}_{n,GPC}$ of 11.0 kDa and an $\overline{M}_w/\overline{M}_n$ of 1.10 (Figure 1c). The actual DP of PDEA was calculated to be 62 by ^{1}H NMR based on integral ratio of resonance peak of terminal methylene protons neighboring to azido group and that characteristic of PDEA main chain (Figure S2b). Thus, the obtained polymer was denoted as $PDEA_{62}$-N_3.

In the final step, the synthesis of ABC miktoarm star terpolymer was accomplished by the click reaction of

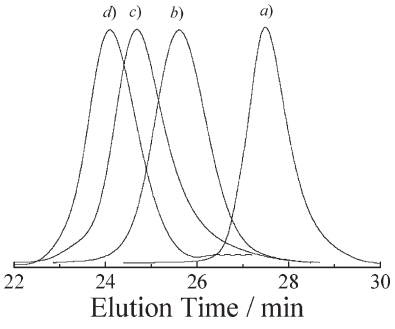

Figure 1. GPC traces of (a) difunctional PEG macroinitiator, PEG_{45}(-*alkynyl*)-*Br*, (b) PEG_{45}(-*alkynyl*)-*b*-$PNIPAM_{50}$ diblock copolymer, (c) PDEA-N_3, and (d) PEG_{45}(-*b*-$PDEA_{62}$)-*b*-$PNIPAM_{50}$ double hydrophilic miktoarm star terpolymer.

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PEG_{45}(-*alkynyl*)-*b*-$PNIPAM_{50}$ with $PDEA_{62}$-N_3 (Scheme 1a). An excess of $PDEA_{62}$-N_3 was used to ensure the complete consumption of alkynyl moieties in PEG_{45}(-*alkynyl*)-*b*-$PNIPAM_{50}$. The removal of excess $PDEA_{62}$-N_3 was achieved by "clicking" onto alkynyl-functionalized Wang resin, followed by the subsequent filtration and precipitation steps. FT-IR spectrum of the purified product clearly revealed the presence of absorption peaks of all three arms (Figure S3*c* in Supporting Information). Most importantly, compared to that of $PDEA_{62}$-N_3, we can clearly observe the complete disappearance of the absorbance peak characteristic of the azido group at 2 115 cm^{-1}. This suggested the successful covalent attachment of PDEA arm to the diblock junction of PEG_{45}(-*alkynyl*)-*b*-$PNIPAM_{50}$.

From the ^{1}H NMR spectrum of PEG_{45}(-*b*-$PDEA_{62}$)-*b*-$PNIPAM_{50}$ (Figure S2c), we can discern all characteristic signals of PEG, PDEA, and PNIPAM segments, and integral ratios between these peaks agreed quite well with relative segment lengths. The GPC trace of PEG_{45}(-*b*-$PDEA_{62}$)-*b*-$PNIPAM_{50}$ was again mono-modal and symmetric. Compared to those of PEG_{45}(-*alkynyl*)-*b*-$PNIPAM_{50}$ and $PDEA_{62}$-N_3, the elution peak of PEG_{45}(-*b*-$PDEA_{62}$)-*b*-$PNIPAM_{50}$ clearly shifted to the higher MW side (Figure 1d). GPC analysis revealed an $\overline{M}_n$ of 15.4 kDa and an $\overline{M}_w/\overline{M}_n$ of 1.09. Based on the above results, we can conclude that well-defined miktoarm star terpolymer, PEG_{45}(-*b*-$PDEA_{62}$)-*b*-$PNIPAM_{50}$, has been reliably obtained via a combination of ATRP and click reaction.

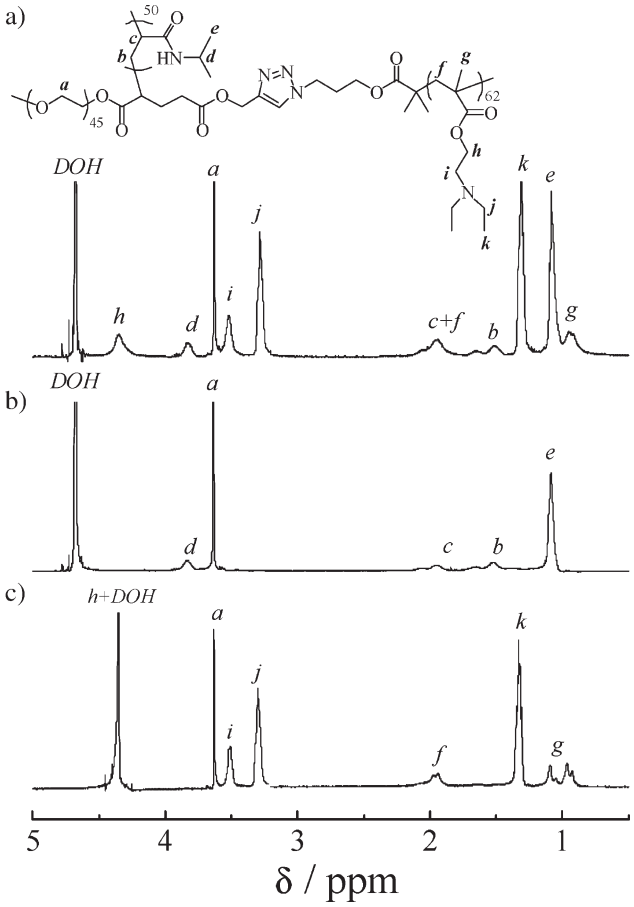

Figure 2. ^{1}H NMR spectra PEG_{45}(-*b*-$PDEA_{62}$)-*b*-$PNIPAM_{50}$ double hydrophilic ABC miktoarm star terpolymer recorded in D_2O at different conditions: (a) pH 4 and 25 °C, (b) pH 10 and 25 °C, and (c) pH 4 and 50 °C.

"Schizophrenic" Micellization of PEG_{45}(-*b*-$PDEA_{62}$)-*b*-$PNIPAM_{50}$ Miktoarm Star Terpolymer

The obtained miktoarm star terpolymer contains a permanently hydrophilic PEG block, a pH-responsive PDEA block, and a thermoresponsive PNIPAM block. Thus, for the PEG_{45}(-*b*-$PDEA_{62}$)-*b*-$PNIPAM_{50}$ miktoarm star terpolymer, we can expect that they will exhibit pH- and thermo-responsive "schizophrenic" micellization behavior via finely tuning solution pH and temperatures (Scheme 1b).

Figure 2 shows ^{1}H NMR spectra of PEG_{45}(-*b*-$PDEA_{62}$)-*b*-$PNIPAM_{50}$ miktoarm star terpolymer in D_2O at varying solution conditions, together with the peak assignments. At pH = 4 and 25 °C, all the three arms are hydrophilic, thus the miktoarm star terpolymer molecularly dissolves in aqueous solution and ^{1}H NMR signals characteristic of PEG, PDEA, and PNIPAM arms (Figure 2a). Upon adjusting the solution pH to 10, signals characteristic of the PDEA arm at δ = 1.3, 3.3, 3.5, and 4.4 ppm completely disappeared, while the signals from PEG and PNIPAM blocks are clearly visible (Figure 2b), indicating the formation of micelles consisting of hydrophobic cores and well-solvated hybrid PEG/PNIPAM coronas. At pH = 4 and 50 °C, ^{1}H NMR resonance signals characteristic of PNIPAM block at δ = 1.1 and 3.8 ppm completely disappear, indicating the formation of PNIPAM-core micelles possessing well-solvated PEG and protonated PDEA coronas. This conclusion was further confirmed by the fact that signals characteristic of PEG and PDEA segments can be clearly discerned (Figure 2c). Scheme 1b summarized the pH- and thermo-responsive "schizophrenic" micellization behavior for PEG_{45}(-*b*-$PDEA_{62}$)-*b*- $PNIPAM_{50}$ miktoarm star terpolymer in aqueous solution.

Dynamic LLS was further employed to characterize the multi-responsive formation of two types of aggregates from PEG_{45}(-*b*-$PDEA_{62}$)-*b*-$PNIPAM_{50}$. Figure 3a shows the pH-dependency of PEG_{45}(-*b*-$PDEA_{62}$)-*b*-$PNIPAM_{50}$ in aqueous solution at a concentration of 1.0 $g \cdot L^{-1}$ and 25 °C measured by dynamic LLS. Below pH 6–7, the miktoarm star terpolymer molecularly dissolves, yielding an intensity-average hydrodynamic radius, $\langle R_h \rangle$, of ~8 nm and very low scattering intensity. Upon addition of NaOH, micellization occurred above pH 7–8, as indicated by the appearance of bluish tinge characteristic of micellar

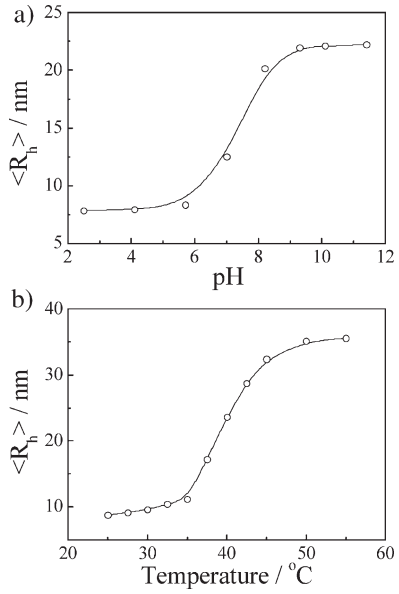

Figure 3. (a) Variation of intensity-average hydrodynamic radius, $\langle R_h \rangle$, as a function of solution pH at 25 °C for PEG_{45}(-*b*-$PDEA_{62}$)-*b*-$PNIPAM_{50}$. (b) Temperature-dependent $\langle R_h \rangle$ changes in aqueous solution at pH 4 obtained for PEG_{45}(-*b*-$PDEA_{62}$)-*b*-$PNIPAM_{50}$ double hydrophilic ABC miktoarm star terpolymer.

solutions. On the basis of chemical intuition and previous ^{1}H NMR results, the formed micellar aggregates are expected to possess core-corona nanostructures, with the PDEA sequences occupying micelle cores (Scheme 1b). Above pH 8, the micelle size remains almost constant, at a $\langle R_h \rangle$ of ≈22 nm. Moreover, the formed PDEA-core micelles are quite monodisperse, with polydispersities (μ_2/Γ^2) typically less than 0.10.

Starting from the unimer state of PEG_{45}(-*b*-$PDEA_{62}$)-*b*-$PNIPAM_{50}$ in aqueous solution at pH 4 and 25 °C, micelles consisting of PNIPAM cores and PEO/PDEA hybrid coronas can also be fabricated upon heating (Scheme 1b). At 50 °C and pH 4, bluish tinge characteristic of colloidal dispersions also appeared. Figure 3b shows the temperature dependence of $\langle R_h \rangle$ for the aqueous solution of PEG_{45}(-*b*-$PDEA_{62}$)-*b*-$PNIPAM_{50}$ at pH 4. Below ≈35 °C, the miktoarm star terpolymer molecularly dissolves with $\langle R_h \rangle$ of ca. 10 nm. Above that, micellization starts to occur, accompanied with a dramatic increase of $\langle R_h \rangle$. Dynamic LLS only revealed one population corresponding to micelles above 50 °C. The size of the micelle remain almost constant with $\langle R_h \rangle$ of ≈35 nm.

Compared to those of linear AB diblock and ABC triblock copolymers,[13,25] PEG_{45}(-*b*-$PDEA_{62}$)-*b*-$PNIPAM_{50}$ miktoarm star terpolymer tends to form considerably smaller pH- and thermo-induced aggregates, which should be ascribed to its miktoarm star topology. This was also in agreement with the results reported by Pispas and coworkers.[26] The presence of two soluble polymer sequences at the triarm junction point favors the bending of core-corona interface toward the core and the formation of smaller micelles.

Conclusion

Multi-responsive double hydrophilic ABC miktoarm star terpolymer, PEG(-*b*-PDEA)-*b*-PNIPAM, was synthesized for the first time via a combination of ATRP and click chemistry. Due to the fact that hydrophilic PEG, pH-responsive PDEA, and thermo-responsive PNIPAM arms are covalently attached to a common junction point in the miktoarm star terpolymer, PEG(-*b*-PDEA)-*b*-PNIPAM exhibits intriguing "schizophrenic" micellization behavior in aqueous solution, forming two distinct types of micellar aggregates stabilized by well-solvated hybrid coronas. This work represents the first example of synthesis and "schizophrenic" micellization behavior of multi-responsive double hydrophilic ABC miktoarm star terpolymers.

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