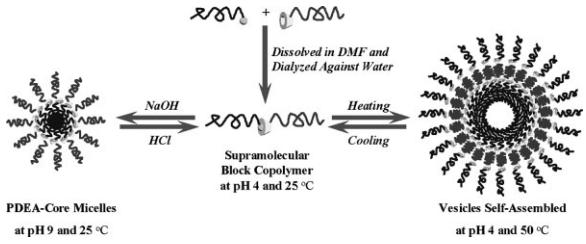
Multi-Responsive Supramolecular Double Hydrophilic Diblock Copolymer Driven by Host-Guest Inclusion Complexation between β-Cyclodextrin and Adamantyl Moieties

Hao Liu, Yanfeng Zhang, Jinming Hu, Changhua Li, Shiyong Liu*

Well-defined β-CD-terminated poly(*N*-isopropylacrylamide) (*β-CD*-PNIPAM) was synthesized via a combination of atom transfer radical polymerization (ATRP) and click chemistry. Moreover, adamantyl-terminated poly(2-(diethylamino)ethyl methacrylate) (*Ad*-PDEA) was synthesized by ATRP using an adamantane-containing initiator. Host-guest inclusion complexation between *β-CD* and adamantyl moieties drives the formation of supramolecular double hydrophilic block copolymers (DHBC) from β-CD-PNIPAM and *Ad*-PDEA. The obtained supramolecular PNIPAM-*b*-PDEA diblock copolymer exhibits intriguing multi-responsive and reversible micelle-to-vesicle transition behavior in aqueous solution by dually playing with solution pH and temperatures.



Introduction

Representing a special type of conventional amphiphilic block copolymers, the past decade has witnessed the fast development of stimuli-responsive double hydrophilic block copolymers (DHBCs).[1–3] They can self-assemble into one or more types of nanostructured aggregates, i.e., the so-called "schizophrenic" micellization, in aqueous solution upon selectively rendering one of the blocks water-insoluble by tuning external solution conditions.[4] Among them, pH- and thermo-responsive mechanisms have been frequently employed due to the fact that they can be conveniently applied in various circumstances.[5–11] Poly(*N*-isopropylacrylamide) (PNIPAM) is one of the most popular thermoresponsive polymers, which possesses dramatic and reversible phase transition behavior in aqueous solution and a lower critical solution temperature (LCST) of ≈32 °C.[12] On the other hand, poly(2-(diethylamino)ethyl methacrylate) (PDEA) is water-insoluble at neutral or alkaline pH, but becomes soluble due to protonation of tertiary amine residues at pH < 6–7.[13,14] The schizophrenic micellization behavior of linear PNIPAM-*b*-PDEA diblock copolymers has already been reported.[8,9,15]

Recently, various types of non-covalent interactions, such as hydrogen bonding interactions,[16–26] metal-ligand interactions[27–34] and host-guest recognition[35–37] have been employed to construct supramolecular block or graft copolymers.[38] In the context of supramolecular chemistry, the hierarchical self-assembly of this novel type of block copolymers possesses unique characteristics. The Jiang research group originated the concept of non-covalently-

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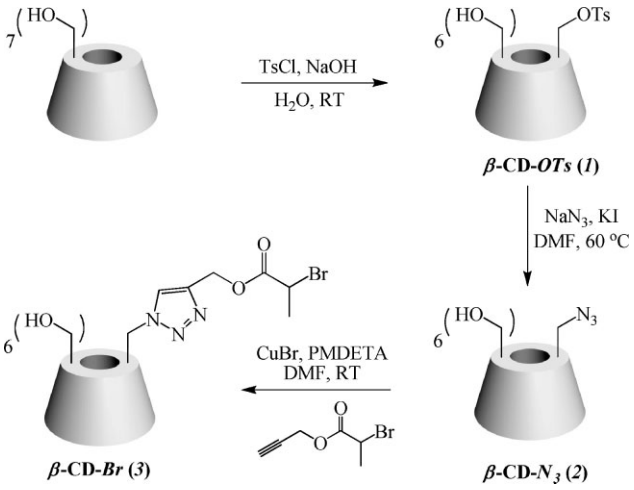
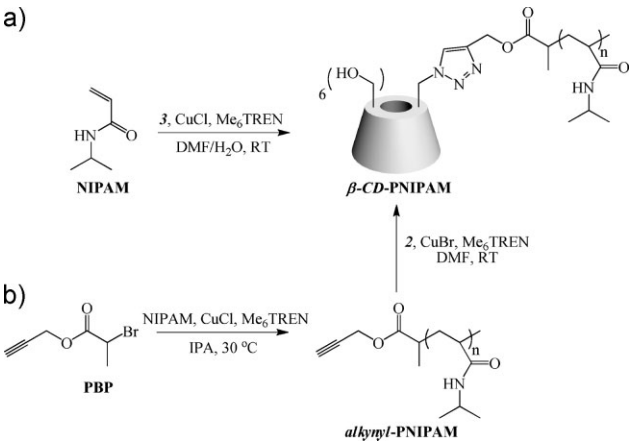
connected micelles (NCCM).[39–41] They reported a series of excellent works, focusing on the construction of supramolecular amphiphilic graft copolymers and their self-assembly behavior. Compared to conventional block copolymers, the non-covalent nature of supramolecular block copolymers endows them with enhanced structural versatility and adaptability to external stimuli.

Host-guest inclusion complexation has pioneered the development of the supramolecular chemistry field. Typical host molecules are crown ethers,[42,43] cyclodextrins (CDs)[44–48] and cucurbituril.[49–51] CDs are a series of natural cyclic oligosaccharides composed of 6, 7 or 8 D-(+)-glucose units linked by α-1,4-linkages, and named α-, β- or γ-CD, respectively.[47] They possess a hydrophilic exterior surface and hydrophobic interior cavity, which can accommodate a variety of molecules as guests.[44–46,52,53] The inclusion complexation between β-CD and the adamantly moiety (Ad) has been extensively investigated due to its high association constant.[48,54,55] In 2006, Jiang et al.[35] reported for the first time the construction of NCCM using β-CD/Ad inclusion complexation as the driving force. Ad-containing hydrophobic cores and CD-containing hydrophilic coronas were linked via host-guest molecular recognition. It should be noted that, in this study, a random copolymer of Ad-containing monomer and *t*-butyl acrylate was employed, thus molecular recognition moieties were arranged in a less-defined manner. Most recently, Shi et al.[56] reported the construction and self-assembly of a responsive water-soluble supramolecular diblock copolymer consisting of PNIPAM and poly(4-vinyl pyridine) (P4VP) sequences. They observed the formation of two types of non-covalently connected aggregates in response to solution pH and temperature. Li et al.[57] also reported the construction of supramolecular heteroarm star polymers between Ad-terminated poly(ethylene oxide), *Ad*-PEO, and star PNIPAM bearing a β-CD core. The incorporation of an PEO sequence into star PNIPAM can drastically modify the phase transition temperature. However, detailed thermoresponsive micellization of this novel type of supramolecular star polymer has not been given.

Our research group previously investigated the synthesis, supramolecular self-assembly and assembling kinetics of a variety of stimuli-responsive DHBCs with complex architectures.[8–11,58] Inspired by previous works relevant to supramolecular block and graft copolymers, herein we further extend the non-covalent concept to the field of stimuli-responsive DHBCs. A well-defined β-CD-terminated poly(*N*-isopropylacrylamide) (*β-CD*-PNIPAM) was synthesized via a combination of atom transfer radical polymerization (ATRP) and click chemistry, and two alternate strategies, direct ATRP of *N*-isopropylacrylamide (NIPAM) using β-cyclodextrin-based initiator (β-CD-Br, **3**) and click reaction of mono-6-deoxy-6-azido-β-cyclodextrin (β-CD-N_3, **2**) with alkynyl-terminated poly(*N*-isopropylacrylamide) (alkynyl-PNIPAM), were employed (Scheme 1 and 2). The latter strategy afforded well-defined *β-CD*-PNIPAM with narrow polydispersity. Moreover, adamantane-terminated poly(2-(diethylamino)ethyl methacrylate) (*Ad*-PDEA) was synthesized by ATRP using an adamantane-containing initiator (Scheme 3). In DMF, the supramolecular diblock copolymer consisting of PNIPAM and PDEA sequences forms due to inclusion complexation between β-CD and Ad moieties (Scheme 4). Taking advantage of the thermo-responsive and pH-responsive characters of PNIPAM and PDEA, respectively, the obtained supramolecular PNIPAM-*b*-PDEA can self-assemble into micelles and vesicles, depending on solution pH and temperatures. Most importantly, this novel type of thermo- and pH-responsive micelle-to-vesicle transition was fully reversible. Compared



Scheme 1. Synthetic routes employed for the preparation of β-CD derivatives: β-CD-OTs (**1**), β-CD-N_3 (**2**) and β-CD-Br (**3**).



Scheme 2. Two strategies employed for the preparation of β-CD-terminated PNIPAM (β-CD-PNIPAM): (a) ATRP of NIPAM monomer using β-CD-Br (**3**) as the initiator; (b) clicking reaction of β-CD-N_3 (**2**) with alkynyl-terminated PNIPAM.

Macromol. Chem. Phys. **2009**, *210*, 2125–2137

Macromolecular Journals

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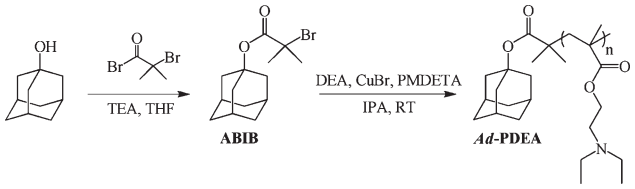


Scheme 3. Synthetic routes employed for the preparation of adamantane-based ATRP initiator ABIB and adamantyl-terminated PDEA (Ad-PDEA).

to conventional linear DHBCs,[8–11,58] the supramolecular PNIPAM-*b*-PDEA diblock copolymers reported in this work provide several advantages such as structural adaptability, additional responsiveness to guest molecules, and robust combination of different building blocks.

Experimental Part

Materials

β-Cyclodextrin (β-CD, Sinopharm Chemical Reagent Co.) was recrystallized twice from deionized water and dried under reduced pressure at 100 °C over P_2O_5 for 2 d. *N*-Isopropylacrylamide (NIPAM, 97%, Tokyo Kasei Kogyo) and tosyl chloride (TsCl, Sinopharm Chemical Reagent Co.) were purified by recrystallization from a mixture of *n*-hexane and benzene. Triethylamine (TEA) and isopropyl alcohol (IPA) were dried over CaH_2 and distilled prior to use. 2-Bromoisobutyryl bromide (98%, Aldrich), 2-bromopropionic bromide (97%, Aldrich), propargyl alcohol (99%, Aldrich), copper (I) bromide (CuBr, 98%, Aldrich), copper (I) chloride (CuCl, 99.995%, Aldrich), *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDETA, 99%, Aldrich), tris(2-aminoethyl)amine (TREN, 96%, Acros), sodium azide (NaN_3, 99%, Alfa Aesar), 1-adamantanol (99%, Aldrich) and 1-adamantanamine hydrochloride (99%, Aldrich) were used as received. Tris(2-(dimethylamino)ethyl)amine (Me_6TREN)[59] and mono-6-deoxy-6-(*p*-tolylsulfonyl)-β-cyclodextrin (β-CD-OTs, **1**)[60] were prepared from TREN and β-CD, respectively, according to literature procedures. Propargyl 2-bromopropionate (PBP) was prepared by the esterification reaction of propargyl alcohol with 2-bromopropionyl bromide.[61] All other reagents were purchased from Sinopharm Chemical Reagent Co. and used as received.

Synthesis of Mono-6-deoxy-6-azido-β-cyclodextrin (β-CD-N_3, 2)

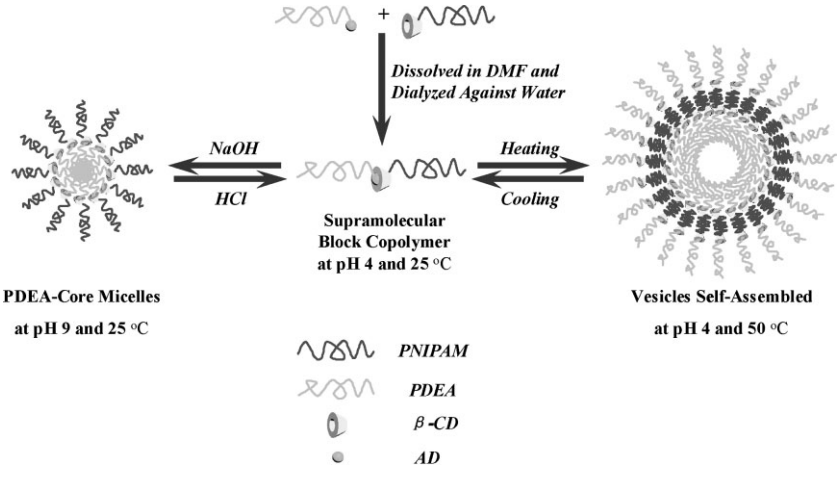
β-CD-N_3 (**2**) was prepared by the azidation of β-CD-OTs according to literature procedures[60] with a few modifications (Scheme 1). A mixture of β-CD-*OTs* (3.0 g, 2.33×10^{-3} mol), dry DMF (10 mL), KI (0.193 g, 1.16×10^{-3} mol), and NaN_3 (1.52 g, 23.4×10^{-3} mol) was stirred at 60 °C for 24 h. After cooling to room temperature, the mixture was precipitated into an excess of acetone/H_2O (2:1 v/v). Recovery by suction filtration and drying overnight in a vacuum oven yielded a white powder (2.38 g, yield: 88%).

^{1}H NMR (DMSO-d_6): δ = 5.85–5.55 (14H, OH-2,3), 4.93–4.73 (7H, H-1), 4.58–4.36 (6H, OH–6), 3.83–3.46 (28H, H-3,5,6), 3.44–3.18 (14H, OH-2,4).

Synthesis of β-CD-Based ATRP Initiator (β-CD-Br, 3)

β-CD-Br (**3**) was prepared via the click reaction of **2** with a slight excess of PBP (Scheme 1), and a typical procedure was as follows. To a Schlenk tube equipped with a magnetic stirring bar, β-CD-N_3 (1.16 g, 1.0×10^{-3} mol), PMDETA (210 μL, 1.0×10^{-3} mol), PBP (0.229 g, 1.2×10^{-3} mol), and DMF (5 mL) were added. After one brief freeze-thaw cycle, CuBr (0.143 g, 1.0×10^{-3} mol) was introduced under the protection of N_2 flow. The reaction tube was carefully degassed by three freeze-pump-thaw cycles, sealed under a vacuum, and the mixture was then stirred at room temperature for 24 h. The reaction mixture was then exposed to air and precipitated into an excess of acetone/H_2O (2:1 v/v). Recovery by suction filtration and drying overnight in a vacuum oven yielded a pure white solid (1.08 g, yield: 80%). The actual degree of functionality was determined to be 63% by ^{1}H NMR analysis in DMSO-d_6 (Figure 1).

^{1}H NMR (DMSO-d_6): δ = 8.13 (methine proton in 1,2,3-*triazole*), 5.93–5.59 (OH-2,3), 5.23 (−OCH_2-1,2,3-*triazole*), 4.98–4.72 (H-1), 4.66 (−OOCC*H*(CH_3)Br), 4.59–4.39 (OH-6), 3.84–3.47 (H-3,5,6), 3.46–3.12 (OH-2,4), 1.73 (−OOCCH(CH_3)Br).



Scheme 4. Schematic illustration of pH- and thermo-responsive micelle-to-vesicle transition of supramolecular double hydrophilic diblock copolymer, PNIPAM-*b*-PDEA.

Synthesis of β-CD-Terminated PNIPAM (β-CD-PNIPAM) via ATRP

β-CD-PNIPAM was synthesized by ATRP of NIPAM monomer using β-CD-Br as the initiator (Scheme 2(a)).[62] In a typical example, β-CD-Br initiator (0.643 g, 0.30×10^{-3} mol Br functionality), NIPAM monomer (2.26 g, 20.0×10^{-3} mol), and Me_6TREN (69 mg, 0.30×10^{-3} mol) were dissolved in 8 mL of DMF/H_2O (4:1 v/v), followed by degassing via

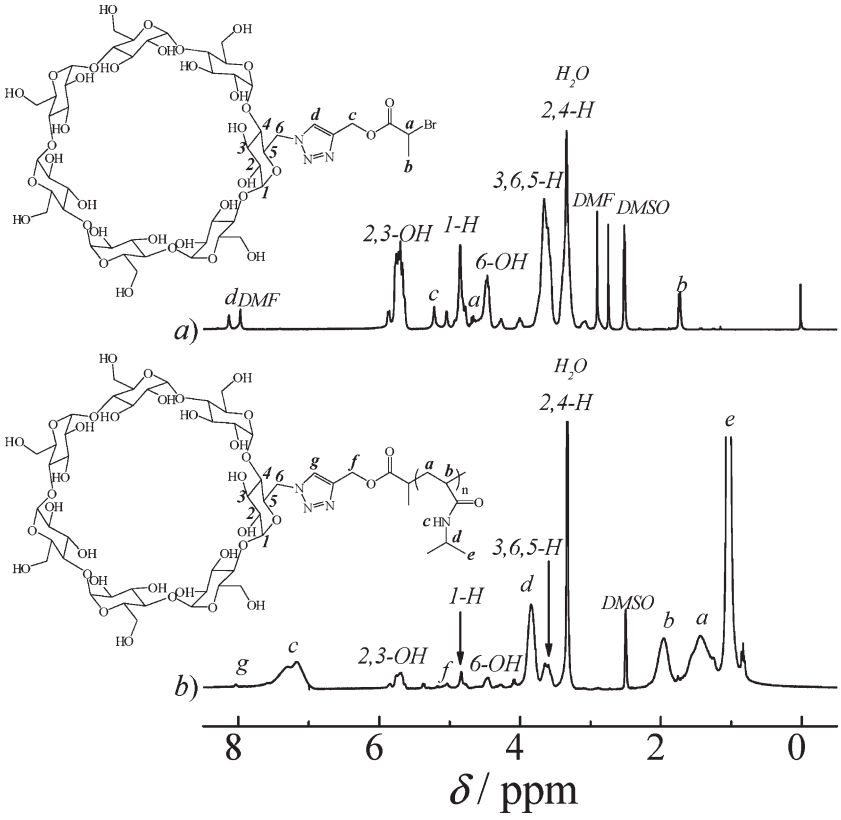


Figure 1. ^{1}H NMR spectra of (a) β-CD-Br (**3**) and (b) β-CD-PNIPAM synthesized from β-CD-Br in DMSO-d_6.

two freeze-pump-thaw cycles. CuCl (0.030 g, 0.30×10^{-3} mol) was then introduced into the reaction flask to start the polymerization at room temperature under a nitrogen atmosphere. The solution turned dark green and became more viscous as polymerization proceeded. After 5 h, the monomer conversion was determined to be 92%, as judged by ^{1}H NMR. The polymerization was terminated by exposing to air. The mixture was precipitated into an excess of diethyl ether. The crude product was dissolved in deionized water and dialyzed against deionized water for 2 d to remove the copper catalysts and small molecule β-CD derivatives. Finally, freeze-drying yielded a white powder (2.05 g, yield: 84%; $\overline{M}_{n,GPC} = 7.3$ kDa, $\overline{M}_w/\overline{M}_n = 1.16$, Figure 2). The number average $\overline{DP}$ of the PNIPAM block was determined to be 62 by ^{1}H NMR analysis in DMSO-d_6 (Figure 1). Thus, the polymer was denoted as β-*CD*-PNIPAM$_{62}$.

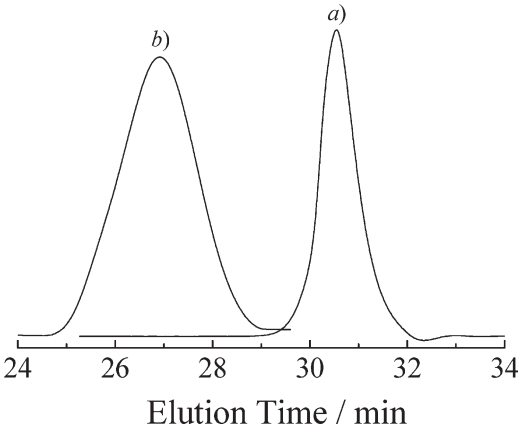


Figure 2. DMF GPC traces of (a) β-CD-Br (**3**) and (b) β-CD-PNIPAM synthesized from β-CD-Br.

Synthesis of Alkynyl-Terminated PNIPAM (alkynyl-PNIPAM)

A typical procedure employed for the preparation of alkynyl-PNIPAM was as follows.[63] Into a reaction flask equipped with a magnetic stirring bar, NIPAM (6.22 g, 55×10^{-3} mol), Me_6TREN (0.230 g, 1.0×10^{-3} mol), PBP (0.191 g, 1.0×10^{-3} mol) and IPA (12 mL) were added. The mixture was degassed by two freeze-pump-thaw cycles. After immersing in an oil bath thermostated at 30 °C, CuCl (99 mg, 1.0×10^{-3} mol) was introduced under the protection of N_2 flow to start the polymerization. The solution turned dark green and more viscous as polymerization proceeded. After 6 h, the monomer conversion was determined to be 93% as judged by ^{1}H NMR. The polymerization was quenched with $CuCl_2$, exposed to air, and diluted with 20 mL of THF. The reaction mixture was passed through a silica gel column to remove copper catalysts. After removing the solvents by a rotary evaporator, the residue was dissolved in THF and precipitated into an excess of diethyl ether. The above dissolution-precipitation cycle was repeated three times. The final product was dried in a vacuum oven, yielding a white solid (5.3 g, yield: 89%; $\overline{M}_{n,GPC} = 6.2$ kDa, $\overline{M}_w/\overline{M}_n = 1.14$, Figure 3). The number average $\overline{DP}$ of PNIPAM block was determined to be 51 by ^{1}H NMR analysis in $CDCl_3$ (Figure 4). Thus, the polymer was denoted as alkynyl-PNIPAM$_{51}$.

Synthesis of β-CD-Terminated PNIPAM (β-CD-PNIPAM) via Click Chemistry

β-CD-PNIPAM was synthesized via the click reaction of *alkynyl*-PNIPAM with an excess of β-CD-N_3 (Scheme 2(b)), and a typical procedure was as follows. Alkynyl-PNIPAM$_{51}$ (0.298 g, 0.05×10^{-3} mol) and β-CD-N_3 (0.270 g, 0.20×10^{-3} mol) were dissolved in DMF (5 mL) containing PMDETA (0.009 g, 0.05×10^{-3} mol). After one brief freeze-pump-thaw cycle, CuBr (7 mg, 0.05×10^{-3} mol) was introduced under the protection of N_2 flow. The reaction tube was carefully degassed by three freeze-pump-thaw cycles, and the mixture was then stirred at room temperature for 24 h. The reaction mixture was exposed to air and then precipitated into an excess of diethyl ether. The crude product was dissolved in deionized water and dialyzed against deionized water for 2 d to remove copper catalysts and excess β-CD-N_3. After freezing drying, β-*CD*-PNIPAM was obtained as a white powder

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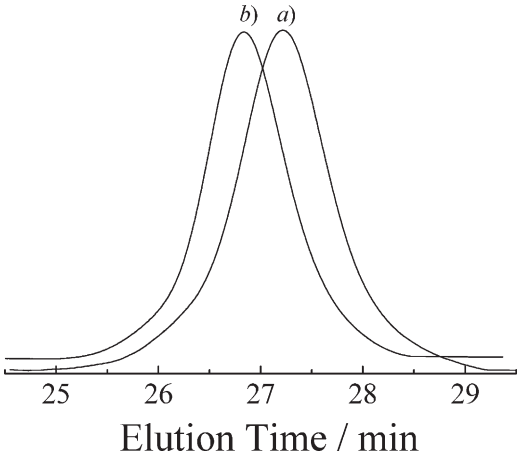

Figure 3. DMF GPC traces of (a) alkynyl-PNIPAM and (b) β-CD-PNIPAM synthesized via post-polymerization modification.

(0.31 g, yield: 85%; $\overline{M}_{n,GPC} = 7.7$ kDa, $\overline{M}_w/\overline{M}_n = 1.07$, Figure 3). The number average $\overline{DP}$ of PNIPAM block was determined to be 52 by ^{1}H NMR analysis in DMSO-d_6 (Figure 4). Thus, the polymer was denoted as β-CD-PNIPAM$_{52}$.

Preparation of 1-Adamantyl 2-Bromoisobutyrate (ABIB)

The ATRP initiator, ABIB, was prepared by the esterification reaction of 1-adamantanol with 2-bromoisobutyryl bromide (Scheme 3). A 250 mL round-bottom flask was charged with 1-adamantanol (7.61 g, 0.05 mol), TEA (6.07 g, 0.06 mol), and dry CH_2Cl_2 (100 mL). The mixture was cooled to 0 °C in an ice-water bath; 2-bromoisobutyryl bromide (7.42 mL, 0.06 mol) in CH_2Cl_2 (20 mL) was then added dropwise over 1 h. After the addition was completed, the reaction mixture was stirred at 0 °C for another 1 h and then at room temperature for 12 h. After removing the insoluble salts by suction filtration, the filtrate was concentrated and then purified by silica gel column chromatography using petroleum ether/ethyl acetate (1:1 v/v) as the eluent. After removing the solvents by a rotary evaporator, ABIB was obtained as a white solid (12.7 g, yield: 85%).

^{1}H NMR ($CDCl_3$): $\delta = 2.19$ (3H, C*H*), 2.14 (6H, CH_2), 1.88 (6H, $-$C(CH_3)$_2$Br), 1.67 (6H, CH_2) (Figure 6).

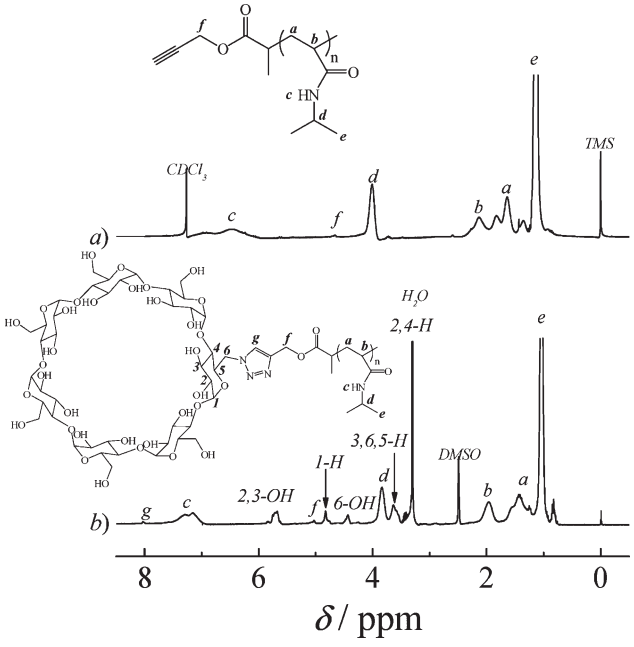

Figure 4. ^{1}H NMR spectra of (a) alkynyl-PNIPAM in $CDCl_3$ and (b) β-CD-PNIPAM synthesized via post-polymerization modification in DMSO-d_6.

Synthesis of Adamantyl-Terminated PDEA (*Ad*-PDEA)

Adamantyl-terminated PDEA, *Ad*-PDEA, was synthesized by the ATRP of DEA monomer using ABIB as the initiator. In a typical example, DEA monomer (9.26 g, 50.0×10^{-3} mol), PMDETA (0.173 g, 1.0×10^{-3} mol), ABIB (0.299 g, 1.0×10^{-3} mol), and IPA (10 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, 1.0×10^{-3} mol) was then introduced under protection of N_2 flow to start the polymerization at room temperature under a nitrogen atmosphere. After 6 h, the polymerization was terminated by exposing to air and diluting with THF. After passing though a column of neutral alumina to remove copper catalysts and removing all the solvent by a rotary evaporator, the residue was dissolved in THF and precipitated into cold *n*-hexane (−50 °C) to remove residual monomer. After drying in a vacuum oven overnight at room temperature, Ad-PDEA was obtained as a white solid (7.34 g, yield: 80%; $\overline{M}_{n,GPC} = 8.2$ kDa, $\overline{M}_w/\overline{M}_n = 1.12$). The number average $\overline{DP}$ of Ad-PDEA was calculated to be 48 by ^{1}H NMR analysis in $CDCl_3$ (Figure 6). Thus, the obtained product was denoted as Ad-PDEA$_{48}$. According to similar procedures, Ad-PDEA$_{30}$ was also prepared ($\overline{M}_{n,GPC} = 5.1$ kDa, $\overline{M}_w/\overline{M}_n = 1.15$).

Preparation of Micellar Solutions

In a typical example, 20 mg of β-CD-PNIPAM$_{52}$ with an equivalent molar Ad-PDEA$_{48}$ (26 mg) were dissolved in DMF (1.0 mL). Under vigorous stirring, 9 mL of deionized water was added via a syringe pump at a flow rate of 0.2 mL · min^{-1}. After the addition was completed, the dispersion was left stirring for another 5 h at room temperature. DMF was then removed by dialysis (MW cut-off, 3.5 kDa) against deionized water for 24 h. Fresh deionized water was replaced approximately every 6 h. Stock solutions with a characteristic bluish tinge were typically obtained. The micellar solution exhibited no macroscopic phase separation upon standing at room temperature for more than three weeks, suggesting the formation of stable aggregates. The solution pH of the stock solution was adjusted by the addition of 0.1 M NaOH or HCl.

Characterization

Nuclear Magnetic Resonance Spectroscopy (NMR)

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. $CDCl_3$ and DMSO-d_6 were used as the solvents. 2D NOESY spectrum was performed on a Varian UNITY plus-400 spectrometer (resonance frequency of 400 MHz for ^1H) using pulse sequences and standard procedures offered by Varian.

Fourier Transform Infrared Spectroscopy (FT-IR)

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}.

Gel Permeation Chromatography (GPC)

Molecular weights and molecular weight distributions were determined by gel permeation chromatography (GPC) equipped with Waters 1515 pump and 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 DMF at a flow rate of 1.0 $mL \cdot min^{-1}$. A series of low polydispersity polystyrene (PS) standards were employed for GPC calibration.

Temperature-Dependent Turbidimetry

The temperature-dependent optical transmittance of aqueous solutions at a wavelength of 700 nm was acquired on a Unico UV-vis 2802PCS spectrophotometer. A thermostatically controlled cuvette was employed and the heating rate was 0.2 $°C \cdot min^{-1}$. The lower critical solution temperature (LCST) value of the aqueous polymer solution at a specific concentration was determined as the temperature corresponding to 10% decrease in the optical transmittance.

Laser Light Scattering (LLS)

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 and static LLS measurements. Scattered light was collected at a fixed angle of 90° for duration of ≈10 min. Distribution averages and particle size distributions were computed using cumulants analysis and CONTIN routines. All data were averaged over three measurements.

Transmission Electron Microscopy (TEM)

TEM observations were conducted on a Hitachi H-800 electron microscope at an acceleration voltage of 100 kV. The samples for TEM observations were prepared by placing 10 μL of solution on copper grids coated with thin films of Formvar and carbon successively. No staining was required.

Results and Discussion

Synthesis of β-CD-Terminated PNIPAM (β-CD-PNIPAM)

End-functionalized polymers can be synthesized via direct polymerization using a functional initiator[64–69] or through the post-modification of polymers with reactive terminal moieties.[68–73] In this work, two strategies were employed for the preparation of β-CD-terminated PNIPAM (β-CD-PNIPAM) (Scheme 1 and 2). In the first one, β-CD-Br initiator was prepared and employed as initiator for the ATRP of NIPAM monomer. In the latter strategy, end group transformation of alkynyl-functionalized PNIPAM with β-CD-N_3 via click chemistry was employed.

Previously, β-CD terminally functionalized polymers were synthesized via free radical polymerization in the presence of thiolated β-CD as a chain-transfer agent[74] or RAFT polymerization using a β-CD-based RAFT agent.[56] In this work, we first attempted a three step approach by coupling click and ATRP techniques (Scheme 1 and 2). Monosubstituted β-CD derivative, β-CD-OTs (**1**), was prepared at first according to literature procedures,[60] and its azidation with NaN_3 afforded mono-6-deoxy-6-azido-β-cyclodextrin (β-CD-N_3, **2**). ^1H NMR analysis revealed that after azidation, characteristic signals of tosyl moieties completely disappeared, suggesting the quantitative end group transformation.[60,75,76] Moreover, the FT-IR spectrum of **2** clearly exhibited a sharp peak at 2 105 cm^{-1}, which is characteristic of the azide group (Figure 5). The click reaction of **2** with a slight excess of PBP afforded β-CD-functionalized ATRP initiator, β-CD-Br (**3**). From the FT-IR spectrum of β-CD-Br, we can clearly observe the complete disappearance of the absorbance peak characteristic of the azide group at 2 105 cm^{-1}. This suggested that the 1,3-dipolar cycloaddition reaction was essentially complete.

^1H NMR spectrum of **3** and the corresponding peak assignments are shown in Figure 1(a). All signals characteristic of the β-CD moiety can be clearly observed. Moreover, NMR signals associated with the terminal 2-bromopropionate residues in **3** are clearly discernible at $\delta = 4.7$ and 1.7 ppm (peaks *a* and *b*), which were accompanied by the appearance of a new resonance peak at ~8.1 ppm (methine proton of 1,2,3-triazole ring). The actual degree of bromine functionality of **3** was determined to be

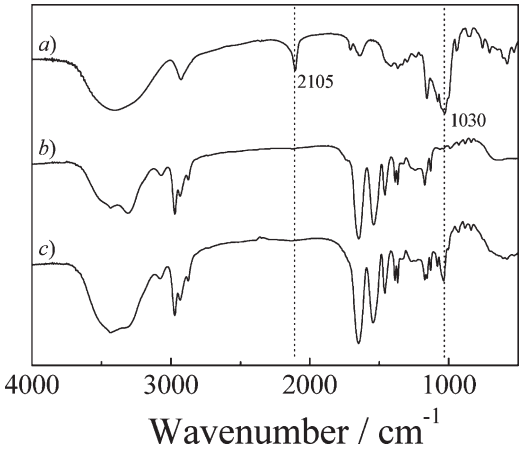

Figure 5. FT-IR spectra of (a) β-CD-N_3 (**2**), (b) alkynyl-PNIPAM and (c) β-CD-PNIPAM synthesized via post-polymerization modification.

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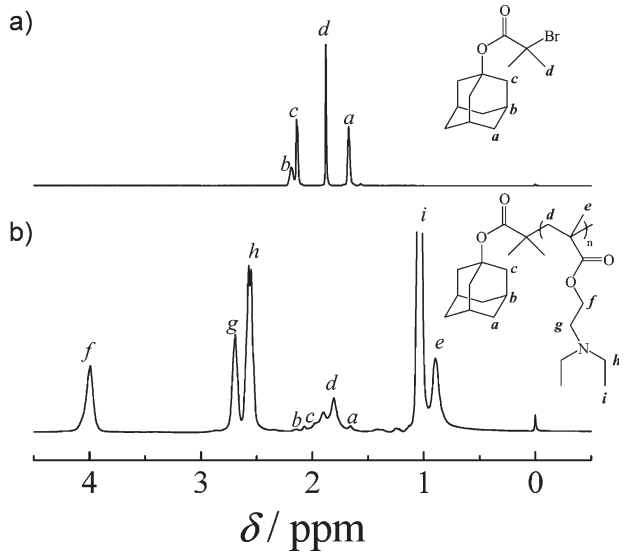

Figure 6. ^{1}H NMR spectra recorded in $CDCl_3$ for (a) ABIB and (b) adamantyl-terminated PDEA synthesized via the ATRP of DEA using ABIB as the initiator.

63% by ^{1}H NMR analysis, based on the integral ratio of peak *b* (1.7 ppm, $-OOCCH(CH_3)Br$) to the peak in the range of 4.98–4.72 ppm (H-1 protons in β-CD moiety). Though all azide moieties in β-CD-N_3 are consumed in the presence of excess PBP, the relatively low end bromine functionality suggested the loss of Br under click conditions, which is reasonable considering under monomer-starved conditions; generated radicals from PBP in the presence of CuBr/PMDETA catalysts will tend to be terminated to some extent.[77–79] However, the obtained β-CD-Br initiator can still be employed in the ATRP of NIPAM as unreacted β-CD derivatives can be removed via dialysis.

The ATRP of NIPAM has been typically conducted in branched alcohols such as IPA and *tert*-butyl alcohol, yielding PNIPAM with controlled MW and narrow polydispersity.[63,80] Unfortunately, β-CD-Br is insoluble in various alcohols and highly soluble in DMF. Recently, Masci et al.[62] reported that the ATRP of NIPAM can be carried in a controlled manner in DMF/water mixture using CuCl/Me_6TREN catalysts. Thus, the ATRP of NIPAM in this study was conducted in DMF/water mixture (4:1 v/v) using β-CD-Br as the initiator and CuCl/Me_6TREN as catalysts (Scheme 2(a)).

After purification by dialysis, β-*CD*-PNIPAM was obtained as a white powder. GPC traces in Figure 2 clearly showed that the elution peak of β-*CD*-PNIPAM shifted to the higher MW side, compared to that of **3**. The elution peak was relatively symmetric and shows no tailing at the lower molecular weight side, suggesting the absence of any residual small molecule β-CD derivatives in the final product. GPC analysis revealed an $\overline{M}_n$ of 7.3 kDa and an $\overline{M}_w/\overline{M}_n$ of 1.16 (Table 1). The ^{1}H NMR spectrum of β-CD-PNIPAM is shown in Figure 1(b), and all signals characteristic of β-CD and PNIPAM moieties can be clearly observed. The number average $\overline{DP}$ of PNIPAM was determined to be 62 by ^{1}H NMR analysis from the integral ratio of peak *d* (3.85 ppm, methine protons in NIPAM units, $-CH(CH_3)_2$) to that of peak at $\delta = 4.83$ ppm (H-1 protons in β-CD). Thus, the obtained polymer was denoted as β-CD-$PNIPAM_{62}$.

In the alternative approach (Scheme 2(b)), β-CD-PNIPAM was also prepared via the click reaction of alkynyl-terminated PNIPAM (alkynyl-PNIPAM) with β-CD-N_3. Alkynyl-PNIPAM was prepared via ATRP using PBP as the initiator and CuCl/Me_6TREN as catalysts at 30 °C in IPA. Previous reports indicated that well-defined end-functionalized PNIPAM can be prepared under selected conditions.[80,81] GPC analysis in DMF revealed a mono-modal peak with an $\overline{M}_{n,GPC}$ of 6.2 kDa and an $\overline{M}_w/\overline{M}_n$ of 1.14 (Figure 3(a)). The ^{1}H NMR spectrum of alkynyl-PNIPAM is shown in Figure 4(a), the number average $\overline{DP}$ of PNIPAM was calculated to be 51 by ^{1}H NMR based on integral ratios of resonance peaks from terminal methylene protons

Table 1. Summary of structural parameters of precursor polymers synthesized in this work.

Samples	Initiator	$\overline{M}_{n,NMR}$	$\overline{DP}_{NMR}$	$\overline{M}_{n,GPC}$ [c)]	$\overline{M}_w/\overline{M}_n$ [c)]
		kDa		kDa	
β-CD-$PNIPAM_{62}$ [a)]	β-CD-Br	8.4	62	7.3	1.16
alkynyl-$PNIPAM_{51}$	PBP	6.0	51	6.2	1.14
β-CD-$PNIPAM_{52}$ [b)]	/	7.2	52	7.7	1.07
Ad-$PDEA_{30}$	ABIB	5.9	30	5.1 [d)]	1.15 [d)]
Ad-$PDEA_{48}$	ABIB	9.2	48	8.2 [d)]	1.12 [d)]

[a)]Synthesized via the ATRP of NIPAM using β-CD-Br as initiator; [b)]Synthesized by the click reaction of alkynyl-PNIPAM with β-CD-N_3; [c)]Molecular weights ($\overline{M}_n$) and molecular distributions ($\overline{M}_w/\overline{M}_n$) were determined by GPC using DMF as eluent relative to polystyrene standards; [d)]Determined by GPC using THF as eluent relative to polystyrene standards.

(−CH_2C≡CH, peak *f*, 4.76 ppm) and those characteristic of PNIPAM. Thus, the obtained polymer was denoted as alkynyl-$PNIPAM_{51}$.

The subsequent click reaction of alkynyl-$PNIPAM_{51}$ with *β*-CD-N_3 led to the formation of well-defined *β*-CD-PNIPAM. An excess of *β*-CD-N_3 was used to ensure the complete consumption of alkynyl moieties in alkynyl-$PNIPAM_{51}$. The removal of excess *β*-CD-N_3 and copper catalysts were facilely achieved by dialysis in water (MW cut-off, 3.5 kDa). Compared to those of *β*-CD-N_3 and alkynyl-$PNIPAM_{51}$, the FT-IR spectrum of *β*-CD-PNIPAM clearly showed the complete disappearance of the absorbance peak characteristic of the azide group at ≈2 105 cm^{-1} (Figure 5). Moreover, absorption peaks characteristic of CD and PNIPAM can be clearly observed, as evidenced by the presence of a strong C−O−C stretching vibration at ≈1 030 cm^{-1} and a carbonyl stretching vibration at ≈1 650 cm^{-1}.[82]

GPC analysis further supported the successful preparation of *β*-CD-PNIPAM. The GPC trace of *β*-CD-PNIPAM is shown in Figure 3(b). Compared to that of alkynyl-$PNIPAM_{51}$, the elution peak of *β*-CD-PNIPAM is shifted slightly to the higher MW side, and both traces are monomodal and quite symmetric. GPC analysis revealed an $\overline{M}_n$ of 7.7 kDa and an $\overline{M}_w/\overline{M}_n$ of 1.07 for *β-CD*-PNIPAM (Table 1). The narrower polydispersity of *β*-CD-PNIPAM compared to that of the alkynyl-$PNIPAM_{51}$ precursor can be reasonably attributed to the removal of low MW PNIPAM during dialysis. Figure 4(b) shows the ^{1}H NMR spectrum of the obtained *β-CD*-PNIPAM, together with the corresponding peak assignments. The number average $\overline{DP}$ of PNIPAM was calculated to be 52 by ^{1}H NMR analysis, based on the integral ratio of peak *d* (3.85 ppm, methine protons in PNIPAM, −C*H*$(CH_3)_2$) to that of the peak at ≈4.83 ppm (H-1 protons in *β*-CD moiety). Table 1 summarizes the structural parameters of *β-CD*-PNIPAM prepared via the two alternate approaches. In terms of structural integrity and applicability, the second strategy is preferred due to the fact that the alkynyl-PNIPAM precursor can be prepared in a quite controlled manner under well-established conditions.

Synthesis of Adamantyl-Terminated PDEA (Ad-PDEA) via ATRP

Ad-PDEA was prepared via ATRP of DEA monomer using ABIB as the initiator and CuBr/PMDETA as catalysts (Scheme 3). The adamantane-based ATRP initiator, ABIB, was prepared by the esterification reaction of 1-adamantanol with 2-bromoisobutyryl bromide. The ^{1}H NMR spectrum of ABIB (Figure 6(a)) revealed the presence of the characteristic signal of the 2-bromoisobutyryl group at ≈1.88 ppm. Peak integral ratios were consistent with the chemical structure of the target compound. The subsequent ATRP of DEA using ABIB initiator facilely afforded two *Ad*-PDEA homopolymers with different molecular weights. GPC analysis in THF revealed mono-modal peaks for both Ad-PDEA homopolymers and the structural parameters are summarized in Table 1. The number average $\overline{DP}$ of PDEA were calculated to be 48 and 30 by ^{1}H NMR analysis on the basis of integral ratios of resonance peaks characteristic of terminal adamantyl protons to those of PDEA (Figure 6(b)). Thus, the obtained polymers were denoted as AD-$PDEA_{48}$ and AD-$PDEA_{30}$, respectively.

"Schizophrenic" Aggregation Behavior of Multi-Responsive Supramolecular Double Hydrophilic Diblock Copolymer

The hydrophobic interior cavity of *β*-CD can accommodate a variety of guest molecules.[44–46,52,53] Among them, the *β*-CD/Ad pair is well-known due to its high association constant (≈10^4–10^5 M^{-1}).[48,55,56] Previously, Shi et al.[56] and Li et al.[57] constructed linear and non-linear DHBCs based on *β*-CD/Ad host-guest inclusion complexation. In the current work, supramolecular DHBC will form in a mixture of *β*-CD-NIPAM and Ad-PDEA due to the inclusion complexation between terminal CD and Ad moieties. Possessing thermoresponsive PNIPAM and pH-responsive PDEA blocks, the obtained supramolecular PNIPAM-*b*-PDEA diblock copolymer is expected to exhibit intriguing aggregation properties in aqueous solution.

During initial attempts, supramolecular PNIPAM-*b*-PDEA was prepared by directly mixing aqueous solutions of *β*-CD-$PNIPAM_{52}$ and Ad-$PDEA_{48}$ at pH 4. Though both component polymers were soluble at pH 4 and room temperature, we found stable aggregates cannot be obtained upon adjusting to pH 9 or heating to above the phase transition temperature of PNIPAM at pH 4. This might be due to the hydrophobic association of terminal adamantyl groups in Ad-$PDEA_{48}$,[56] which will prevent the effective formation of supramolecular block copolymers. Inspired by the work of Jiang et al.,[35,55] we attempted to prepare the supramolecular diblock copolymer in DMF first, followed by the addition of water to induce self-assembly and the subsequent dialysis to remove DMF. It is interesting to note that after ultrasonication, the mixture of Ad-$PDEA_{48}$ and DMF-d_7 forms a slightly turbid dispersion due to the presence of the adamantyl group, which is insoluble in DMF-d_7. However, upon addition of equimolar *β*-CD-$PNIPAM_{52}$ (1:1 CD/Ad molar ratio), a clear and stable mixture was formed. This strongly suggested the inclusion of terminal adamantyl groups into the hydrophobic cavities of CD moieties and the formation of supramolecular PNIPAM-*b*-PDEA diblock copolymer. Water was slowly added to the *β*-CD-$PNIPAM_{52}$/Ad-$PDEA_{48}$ mixture to induce self-assembly. After dialysis, a stable dispersion (≈pH 7–8) with a bluish tinge formed. After adjusting to pH 4, a clear solution was obtained.

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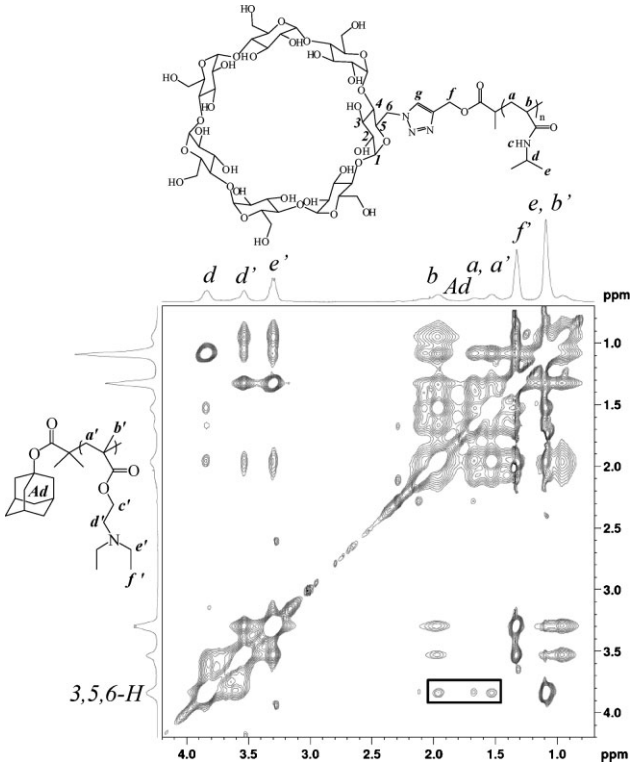

Figure 7. 2D NOESY spectra showing the NOESY cross-peaks enclosed in rectangles arising from host-guest inclusion in a mixed solution of equimolar β-CD-PNIPAM$_{52}$ and Ad-PDEA$_{48}$ in D_2O at pH 4 and 25 °C. The concentration of PNIPAM was 10 g · L^{-1}.

A 2D ^{1}H NOESY NMR experiment was performed in D_2O at pH 4 and 25 °C to provide direct evidence for the construction of the supramolecular DHBC via inclusion complexation. Cross-peaks observed in 2D NOESY spectra identify protons undergoing "through space" dipolar interactions which are significant at interaction distances of <4 Å. In 2D NOESY spectra of the mixed solution containing equimolar amounts of β-CD-PNIPAM$_{52}$ and Ad-PDEA$_{48}$, the signals at $\delta = 1.5$–2.0 ppm due to the adamantyl moieties of Ad-PDEA$_{48}$, which were partially overlapped by protons in the main chain, show strong cross-peaks arising from dipolar interactions with the signals at $\delta \approx 3.8$ ppm ascribed to the H-3, H-5 and H-6 protons located within the cavity of β-CD moieties of β-CD-PNIPAM$_{52}$. This strongly indicates that Ad moieties are deeply embedded within the cavities of β-CD (Figure 7).

To determine the thermosensitive properties of the obtained supramolecular PNIPAM-*b*-PDEA diblock polymer and the corresponding precursor PNIPAM polymers, the temperature-dependent optical transmittance of alkynyl-PNIPAM, *β-CD*-PNIPAM and supramolecular PNIPAM-*b*-PDEA in aqueous solutions (1.0 g · L^{-1}) were recorded

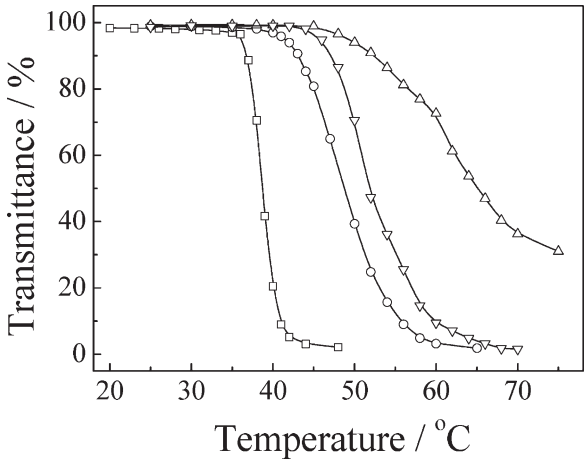

Figure 8. Temperature dependence of optical transmittance at a wavelength of 700 nm obtained for aqueous solutions (pH 4) of alkynyl-PNIPAM$_{51}$ (-□-), *β-CD*-PNIPAM$_{52}$ (-○-), supramolecular PNIPAM-*b*-PDEA formed from an equimolar mixture of *β-CD*-PNIPAM$_{52}$ and Ad-PDEA$_{48}$ in the absence (-△-) and presence (-▽-) of 1-admantanamine hydrochloride (100 equiv. to that of CD moieties). The concentration of PNIPAM was fixed at 1.0 g · L^{-1}.

(Figure 8). In the current study, the LCST was arbitrarily defined as the temperature corresponding to a 10% decrease of transmittance (1.0 g · L^{-1}). Compared to that of alkynyl-PNIPAM$_{51}$ (36.8 °C), the LCST of β-CD-PNIPAM$_{52}$ was determined to be 43.2 °C. The higher LCST value and relatively broader phase transition for β-CD-PNIPAM$_{52}$ should be ascribed to the presence of the hydrophilic β-CD terminal moiety.[57,80]

Figure 8 also shows the temperature-dependent optical transmittance of supramolecular PNIPAM-*b*-PDEA in aqueous solution (pH 4). It was found that optical transmittance exhibited more gradual decrease at temperatures above 45 °C, accompanied by the appearance of a bluish tinge, which is characteristic of colloidal dispersions. This suggested the formation of PNIPAM-core aggregates stabilized by protonated PDEA blocks due to the insolubility of PNIPAM sequences at elevated temperatures. In marked contrast to those of alkynyl-PNIPAM and β-CD-PNIPAM, which exhibited macroscopic phase transition at elevated temperatures, supramolecular PNIPAM-*b*-PDEA forms a stable dispersion at pH 4 even when heated to ≈75 °C. We further found that in the presence of excess 1-admantanamine hydrochloride, which can competitively form an inclusion complex with *β-CD*-PNIPAM, the equimolar mixture of β-CD-PNIPAM$_{52}$ and Ad-PDEA$_{48}$ behaves similarly to that of β-CD-PNIPAM$_{52}$ in terms of temperature-dependent optical transmittance, and macroscopic phase separation occurs in both cases.

The "schizophrenic" aggregation behavior of supramolecular PNIPAM-*b*-PDEA formed from an equimolar mixture of β-CD-PNIPAM$_{52}$ and Ad-PDEA$_{48}$ was further investigated

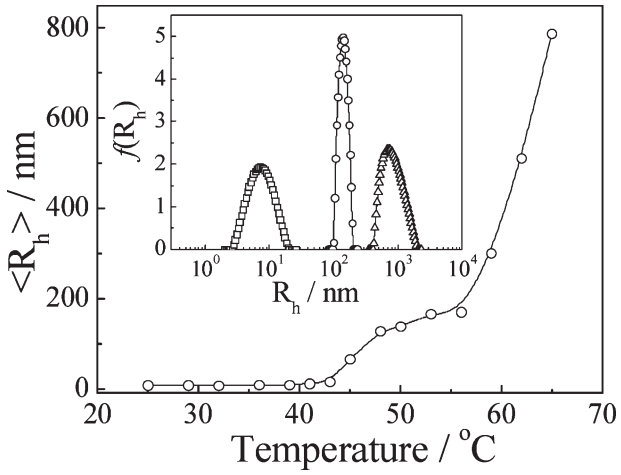

Figure 9. Temperature-dependence of intensity-average hydrodynamic radius, $\langle R_h \rangle$, obtained for supramolecular PNIPAM-*b*-PDEA formed from an equimolar mixture of β-CD-PNIPAM$_{52}$ and Ad-PDEA$_{48}$ in aqueous solution at pH 4. The inset shows typical hydrodynamic radius distributions, $f(R_h)$, obtained at 25 °C (-□-), 50 °C (-○-) and 65 °C (-△-). The concentration of PNIPAM was 0.2 g · L^{-1}.

by dynamic LLS. Figure 9 shows the intensity-average hydrodynamic radius $\langle R_h \rangle$ of supramolecular PNIPAM$_{52}$-*b*-PDEA$_{48}$ in aqueous solution (pH 4) at varying temperatures. Below 43 °C, supramolecular PNIPAM-*b*-PDEA molecularly dissolves in aqueous solution with quite a low scattering intensity, and the intensity-average hydrodynamic radius, $\langle R_h \rangle$, is ≈8 nm. Over the temperature range 43–48 °C, Contin analysis revealed the presence of two types of diffusing species, which indicated the coexistence of unimers and PNIPAM-core aggregates. Upon heating to 50 °C, $\langle R_h \rangle$ increases to 138 nm, accompanied with the large increase of scattering intensity, the polydispersity of the micelles, as evaluated by the ratio μ_2/I^2 from cumulants analysis, were relatively narrow (<0.10). Moreover, Contin analysis revealed the presence of only one type of diffusing species. This suggested the formation of PNIPAM-core aggregates (Scheme 4). Upon further heating to 65 °C, even larger aggregates form with a $\langle R_h \rangle$ of 788 nm. Previous studies by Jiang et al.[35] revealed that CD/Ad host-guest interactions tend to be partially disrupted at elevated temperatures. The decreased stabilization of hydrophobic PNIPAM cores by well-solvated PDEA coronas can well explain the dramatic increase of $\langle R_h \rangle$ with increasing temperatures. For supramolecular PNIPAM$_{52}$-*b*-PDEA$_{30}$ diblock copolymer with shorter PDEA chains, it was found that its aggregation behavior is quite similar compared to that of supramolecular PNIPAM$_{52}$-*b*-PDEA$_{48}$ diblock copolymer. Dynamic LLS revealed one population with $\langle R_h \rangle$ of ≈71 nm corresponding to PNIPAM-core aggregates at pH 4 and 50 °C (Table 2).

Figure 10 shows dynamic LLS results for supramolecular PNIPAM$_{52}$-*b*-PDEA$_{48}$ diblock copolymer at 25 °C and varying pH. Below pH 6, the diblock copolymer molecularly dissolves with $\langle R_h \rangle$ of ≈8 nm and very low scattering intensity. Upon addition of NaOH, micellization occurred above pH 7, as indicated by the appearance of a bluish tinge characteristic of micellar solutions. Dynamic LLS revealed one population with $\langle R_h \rangle$ of ≈47 nm corresponding to micelles above ≈pH 7–8. These formed aggregates are expected to consist of hydrophobic PDEA cores stabilized by well-solvated PNIPAM coronas (Scheme 4). In the case of supramolecular PNIPAM$_{52}$-*b*-PDEA$_{30}$ diblock copolymer, dynamic LLS revealed considerably smaller PDEA-core micelles with a $\langle R_h \rangle$ of ≈28 nm (Table 2). This is due to the presence of a shorter PDEA block.

Transmission electron microscopy (TEM) was then performed on solids obtained by evaporation of solutions of supramolecular PNIPAM-*b*-PDEA to examine the morphologies of the formed aggregates. Typical TEM images are shown in Figure 11, revealing the presence of quite uniform spherical nanoparticles with diameters in the range 50–80 nm at pH 9 and 25 °C. On the other hand, at pH 4 and 50 °C, TEM observation revealed the presence of robust vesicles with diameters in the range of 150–200 nm.

Table 2. Characterization of aggregates formed from supramolecular PNIPAM-*b*-PDEA diblock copolymer at different conditions in aqueous media.

Samples	Conditions	$\langle R_h \rangle$ [a]	μ_2/I^2 [a]	$\langle R_g \rangle$ [b]	$\overline{M}_{w,app}$ [b]
		nm		nm	
PNIPAM$_{52}$-*b*-PDEA$_{48}$	pH 9 and 25 °C	47	0.062	38	1.85×10^7
	pH 4 and 50 °C	138	0.015	134	5.60×10^7
PNIPAM$_{52}$-*b*-PDEA$_{30}$	pH 9 and 25 °C	28	0.036	22	5.91×10^6
	pH 4 and 50 °C	71	0.076	70	7.83×10^6

[a]Determined by dynamic LLS; [b]Determined by static LLS.

Macromol. Chem. Phys. **2009**, *210*, 2125–2137

Macromolecular Journals

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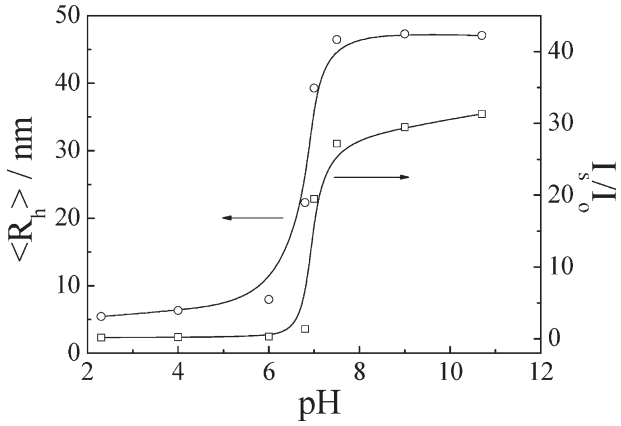

Figure 10. Variations of intensity-average hydrodynamic radius, $\langle R_h \rangle$, and relative scattering intensity, I_s/I_o, as a function of solution pH obtained for supramolecular PNIPAM-*b*-PDEA formed from an equimolar mixture of *β-CD*-PNIPAM$_{52}$ and *Ad*-PDEA$_{48}$ in aqueous solution at 25 °C. The concentration of PNIPAM was 0.2 g · L^{-1}.

Thus, supramolecular PNIPAM-*b*-PDEA formed from an equimolar mixture of β-CD-PNIPAM$_{52}$ and Ad-PDEA$_{48}$ exhibited an intriguing micelle-to-vesicle transition in aqueous solution depending on solution pH and temperatures, and a schematic illustration is shown in Scheme 4. Further investigation by LLS revealed that the switching of nanostructured aggregates between micelles, unimers, and vesicles are fully reversible.

Static LLS was further employed to investigate structural properties of aggregates formed from supramolecular PNIPAM-*b*-PDEA diblock copolymer at different conditions (Table 2). For PDEA-core micelles formed from supramolecular PNIPAM$_{52}$-*b*-PDEA$_{48}$ diblock copolymer at pH 9 and 25 °C, static LLS revealed an average radius of gyration, $\langle R_g \rangle$, of 38 nm and an apparent weight-average molar mass, $\overline{M}_{w,app}$, of 1.85×10^7 g · mol^{-1}. Possessing shorter PDEA chains, aggregates of supramolecular PNIPAM$_{52}$-*b*-PDEA$_{30}$ diblock copolymer exhibit an $\langle R_g \rangle$ of 22 nm and an $\overline{M}_{w,app}$ of 5.91×10^6 g · mol^{-1}. On the other hand, vesicles formed at pH 4 and 50 °C possess a $\langle R_g \rangle$ of 134 nm and an $\overline{M}_{w,app}$ of 5.60×10^7 g · mol^{-1} for supramolecular PNIPAM$_{52}$-*b*-PDEA$_{48}$ diblock copolymer, and a $\langle R_g \rangle$ of 70 nm and an $\overline{M}_{w,app}$ of 7.83×10^6 g · mol^{-1} for supramolecular PNIPAM$_{52}$-*b*-PDEA$_{30}$ diblock copolymer, respectively. It should be noted aggregates formed at pH 4 and 50 °C possess a $\langle R_g \rangle / \langle R_h \rangle$ ratio of 0.97–0.99, which is close to the theoretical value of 1.0 for hollow nanospheres.[83,84] This further supports the presence of vesicular nanostructures (Scheme 4).

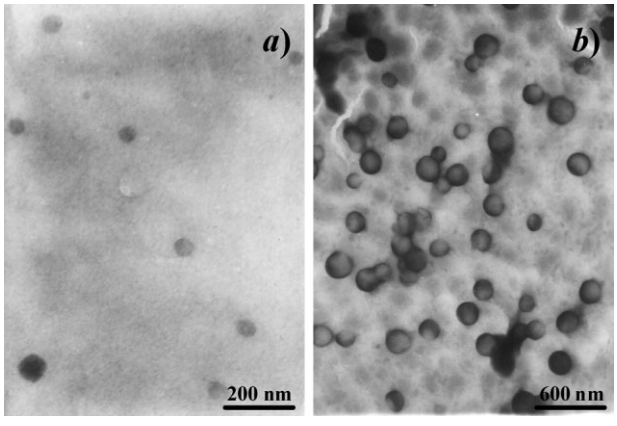

Figure 11. Typical TEM images obtained by drying the aqueous solutions of supramolecular PNIPAM-*b*-PDEA formed from an equimolar mixture of β-CD-PNIPAM$_{52}$ and Ad-PDEA$_{48}$ at (a) pH 9 and 25 °C and (b) pH 4 and 50 °C.

Conclusion

In summary, well-defined β-CD-terminated PNIPAM (β-CD-PNIPAM) was synthesized via a combination of atom transfer radical polymerization (ATRP) and click chemistry through two alternate strategies: direct ATRP of NIPAM monomer using β-CD-Br as the initiator (**3**) and click reaction of β-CD-N$_3$ (**2**) with alkynyl-terminated PNIPAM (Scheme 1 and 2). Moreover, adamantane-terminated PDEA (Ad-PDEA) was synthesized by ATRP using an adamantane-containing initiator (Scheme 3). In the driving of host-guest inclusion complexation between β-CD and Ad moieties, β-CD-PNIPAM was used as a thermoresponsive building block with Ad-PDEA as a pH-responsive building block to fabricate a supramolecular double hydrophilic diblock copolymer. The obtained supramolecular PNIPAM-*b*-PDEA diblock copolymer exhibits intriguing "schizophrenic" self-assembling behavior in aqueous solution by dually playing with solution pH and temperatures (Scheme 4). At room temperature, it molecularly dissolves at pH < 6 and forms PDEA-core micelles at pH > 8. In acidic media, vesicular nanostructures form at temperatures above the lower critical solution temperature (LCST) of PNIPAM sequences. Most importantly, this novel type of thermo- and pH-responsive micelle-to-vesicle transition was fully reversible.

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