

## Synthesis and Self-Assembly of CO<sub>2</sub>-Temperature Dual Stimuli-Responsive Triblock Copolymers

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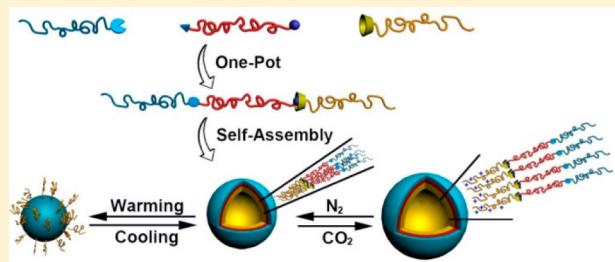
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### Supporting Information

**ABSTRACT:** Poly(*N,N*-dimethylaminoethyl methacrylate) (PDMAEMA) with a  $\beta$ -cyclodextrin ( $\beta$ -CD) at the chain end was synthesized via atom transfer radical polymerization (ATRP); poly( $\epsilon$ -caprolactone) (PCL) with a  $-C=C-$  segment and an adamantine (Ada) group at two ends, respectively, was prepared through ring-opening polymerization (ROP), and poly(*N*-isopropylacrylamide) (PNIPAM) with a  $-S-C(S)-S-$  segment, which can be converted into a thiol group, was yielded by reversible addition–fragmentation chain transfer polymerization (RAFT). A supramolecular triblock stimuli-responsive copolymer PNIPAM-*b*-PCL-*b*-PDMAEMA having good biocompatibility with PNIPAM and PDMAEMA hydrophilic segments and PCL hydrophobic segment was constructed by thiol–ene Michael addition and host–guest interaction. The triblock copolymer could self-assemble into vesicles and respond to carbon dioxide (CO<sub>2</sub>) gas and temperature reversibly. Under the stimulation of CO<sub>2</sub>, the vesicular assemblies swelled obviously; while raising the temperature from 25 to 40 °C, the assemblies displayed a conversion between vesicles and spherical micelles.



## INTRODUCTION

Stimuli-responsive polymers have attracted considerable interest due to their extensive applications in various fields.<sup>1–12</sup> For example, in biology, the “smart” polymer used in controlled drug-release and gene-delivery can improve the efficacy and reduce the side effects.<sup>13</sup> To date, pH,<sup>14–21</sup> temperature,<sup>22–33</sup> light,<sup>34–38</sup> ultrasound,<sup>39</sup> redox agents,<sup>40–43</sup> and voltage,<sup>44,45</sup> as well as carbon dioxide (CO<sub>2</sub>),<sup>46–49</sup> have been used as external stimuli for stimuli-responsive systems.

As one of the most important metabolic substances of body, CO<sub>2</sub> features some unique characteristics like nontoxicity, renewability and high abundance, making it an environmentally friendly trigger for stimuli-responsive systems. Additionally, thermo-responsive polymers have made a profound influence in biological field due to their biocompatibility and controllability.<sup>22–33</sup> Recently, stimuli-responsive systems which can be response to two or more stimuli have been extensively studied owing to their complex controllability. Among them, the CO<sub>2</sub>–temperature dual stimuli-responsive intelligent polymers can be conveniently applied in various circumstances and have great potential in targeting transport and controlled release of drugs.

On the other hand, following crown ether, cyclodextrin (CD), as the second generation host molecule, has very excellent properties in terms of molecular recognition, molecular interaction, and molecular aggregation.<sup>50</sup> It has been found

that CDs have remarkable abilities to form highly stable inclusion complexes with a variety of guest molecules in their hydrophobic cavities. Thereinto, with good biocompatibility and availability,  $\beta$ -CD is extensively explored in pharmaceutical field. Benefiting from a high association constant, the host–guest inclusion complexation between  $\beta$ -CD and adamantine (Ada)<sup>51</sup> has been frequently investigated as a building block in various polymeric architectures.<sup>52–59</sup>

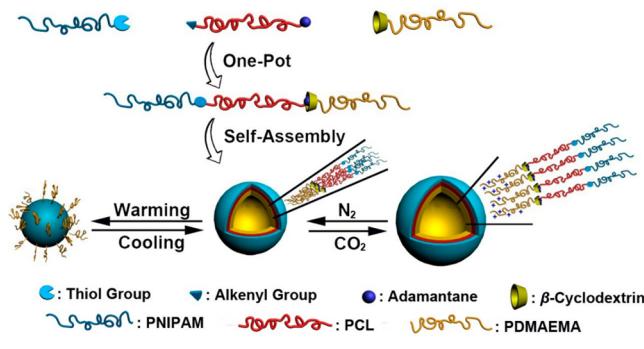
Herein, we reported a stimuli-responsive ABC supramolecular triblock copolymer<sup>60–62</sup> poly(*N*-isopropylacrylamide)-block-poly( $\epsilon$ -caprolactone)-block-poly(*N,N*-dimethylaminoethyl methacrylate) (PNIPAM-*b*-PCL-*b*-PDMAEMA). As shown in Scheme 1, Ada end-capped PNIPAM-*b*-PCL,<sup>63,64</sup> prepared via thiol–ene Michael addition, was assembled with  $\beta$ -CD terminated PDMAEMA<sup>65,66</sup> through host–guest inclusion complexation between  $\beta$ -CD and Ada. The amphiphilic triblock copolymer could self-assemble to form vesicular micelles in water. By tuning the level of CO<sub>2</sub> and temperature, reversible variation on the morphology and size of the assembly was achieved as shown in Scheme 1.

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**Scheme 1. Illustration for Synthesis and Self-Assembly of the Supramolecular Triblock Copolymer PNIPAM-*b*-PCL-*b*-PDMAEMA, as Well as Their CO<sub>2</sub>-Temperature Dual Stimuli-Responsive Process**



We developed this supramolecular triblock copolymer combining thiol–ene Michael addition and host–guest inclusion complexation between  $\beta$ -CD and Ada for several reasons: (1) thiol–ene Michael addition click reaction and host–guest inclusion complexation are independent and have no interference with each other; (2) both of the two reactions have extremely high efficiency and pretty wonderful selectivity; (3) the forming structures of the two reactions are incredibly stable; (4) this synthesis strategy can be used to efficiently avoid the wide PDI obtained through the general copolymerization; (5) comparing with common single bond, the link of host–guest inclusion complexation between  $\beta$ -CD and Ada has a greater degree of freedom due to the near-spherical structure of Ada.

To the best of our knowledge, this is the first report of a CO<sub>2</sub>–temperature dual responsive polymer vesicle with good biocompatibility and controllability. Because of the perfect characteristics under stimuli of CO<sub>2</sub> and temperature, we expect

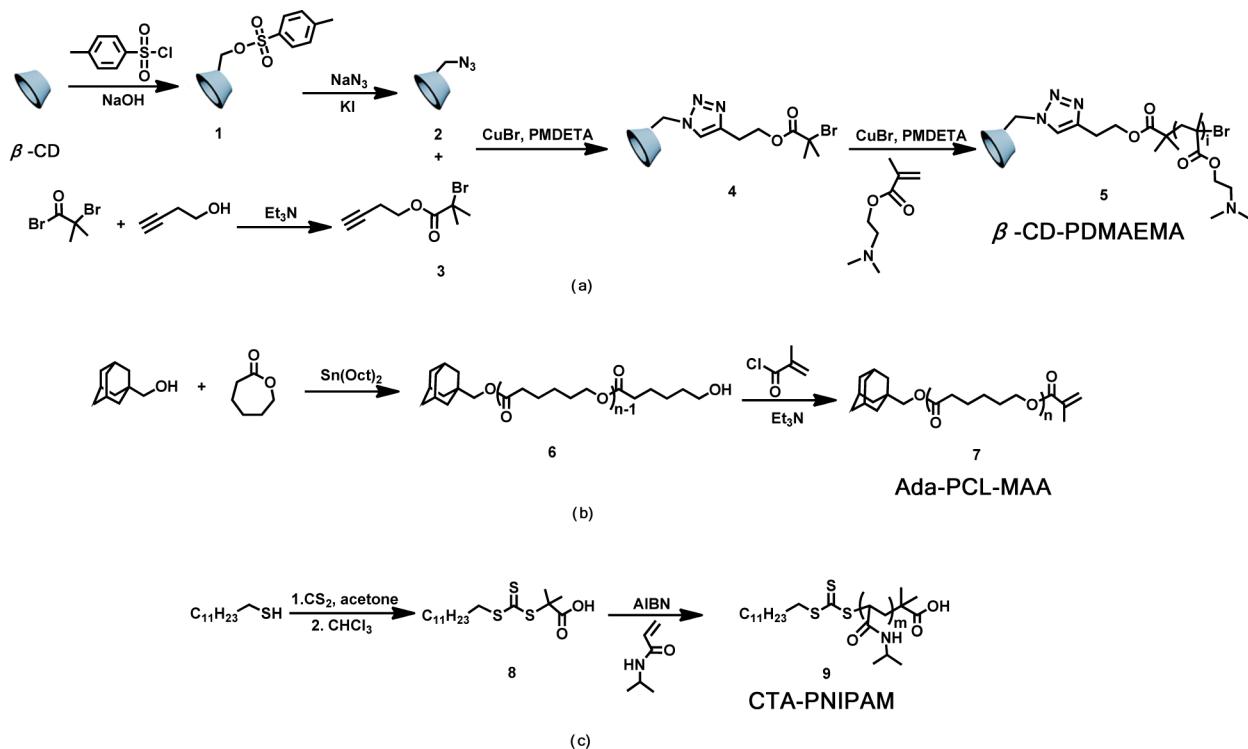
that this kind of vesicle can be widely used in targeting transport and controlled release.

## EXPERIMENTAL SECTION

**Materials.**  $\beta$ -Cyclodextrin ( $\beta$ -CD, Kermel, China) was purified by recrystallization from water before use. Copper bromide (CuBr, Alfa Aesar, 99%) was purified by stirring in acetic acid and washed with ethanol for three times.  $\epsilon$ -Caprolactone ( $\epsilon$ -CL, Acros, 98%) was stirred overnight with CaH<sub>2</sub> and distilled under reduced pressure prior to use. N,N-Dimethylaminoethyl methacrylate (DMAEMA, Acros, 98%) was passed through a column of basic aluminum oxide prior to use. N-Isopropylacrylamide (NIPAM, Acros, 98.5%) was recrystallized twice from toluene and hexane (1: 3). Azodiisobutyronitrile (AIBN, Beijing Chemical Technology Co., 98%) was recrystallized in *n*-hexane twice. Tosyl chloride (TsCl, Acros, 99%), sodium azide (NaN<sub>3</sub>, Acros, 99%), 1-adamantanemethanol (Ada-OH, Acros, 99%), stannous octoate (Sn(Oct)<sub>2</sub>, Acros, 99%), triethylamine (TEA, Acros, 98%), methacryloyl chloride (TCI, 80%), 2-bromo-2-methylpropanoyl bromide (Alfa Aesar, 99%), 3-Butyn-1-ol (J&K, 98%), N,N,N',N'',N'''-Pentamethyldiethylenetriamine (PMDETA, Acros, 98%), rhodamine B (Acros, 99%) and dodecylthiol (Acros, 99%) were used as received. Dimethylformamide (DMF), xylene, and tetrahydrofuran (THF) were refluxed with CaH<sub>2</sub> and then distilled; 1,2-dichloroethane was dried with P<sub>2</sub>O<sub>5</sub> and distilled prior to use. NaOH, KI, CS<sub>2</sub>, and ethylenediamine as well as solvents such as acetone, petroleum ether, methanol, chloroform, and dichloromethane and so on were used as received.

**Characterizations.** Nuclear Magnetic Resonance Spectroscopy (NMR). <sup>1</sup>H NMR spectra for the structural analysis were obtained from a JEOL JNM-ECA300 (300 MHz) or JEOL JNM-ECA400 (400 MHz), and 2D <sup>1</sup>H NOESY spectrum and <sup>1</sup>H NMR spectra of PNIPAM-*b*-PCL-*b*-PDMAEMA self-assembling

**Scheme 2. Synthetic Route (a) for  $\beta$ -CD-PDMAEMA (5), (b) for Ada-PCL-MAA (7), and (c) for CTA-PNIPAM (9)**



aggregates were recorded on a JEOL JNM-ECA600 (600 MHz) spectrometer.

**Gel Permeation Chromatography (GPC).** GPC analyses of polymers were performed using *N,N*-dimethylformamide (DMF) as the eluent. The GPC system was a Shimadzu LC-20AD pump system, a MZ-Gel SDplus 10.0  $\mu\text{m}$  guard column ( $50 \times 8.0 \text{ mm}$ ,  $10^2 \text{ \AA}$ ) followed by a MZ-Gel SDplus 5.0  $\mu\text{m}$  bead-size column ( $50\text{--}10^6 \text{ \AA}$ , linear) and a Shimadzu RID-10A refractive index detector. The system was calibrated with narrow molecular weight distribution polystyrene standards ranging from 200 to  $10^6 \text{ g/mol}$ .

**Fourier Transform Infrared Spectroscopy (FT-IR).** The absorption spectra were recorded on an AVATAR 360 ESP FT-IR spectrometer and the results were collected at 30 scans with a spectral resolution of  $1 \text{ cm}^{-1}$ .

**UV-Vis Spectroscopy.** The UV-visible spectra of copolymer solutions were acquired on a HITACHI U-3010 spectrophotometer.

**Fluorescence Spectroscopy (FS).** Fluorescence was measured with a Hitachi F-7000 spectrofluorometer.

**Transmission Electron Microscopy (TEM).** The visualized images of the assemblies were obtained from a JEM-2010 microscope with an accelerating voltage of 120 kV and H-7650B microscope with an accelerating voltage of 80 kV, and the samples were prepared by drop-coating the aqueous solution on a carbon-coated copper grid and staining with 0.1% phosphotungstic acid hydrate and then drying under vacuum overnight.

**Dynamic Light Scattering (DLS).** The average diameter and size distribution of the aggregates was analyzed by a Malvern 3000HS Zetasizer using a monochromatic coherent He-Ne laser (633 nm) as the light source and a detector that detected the scattered light at an angle of  $90^\circ$ .

**Synthesis of  $\beta$ -CD-based ATRP Initiator ( $\beta$ -CD-Br) (4).** From  $\beta$ -CD, Mono-6-deoxy-6-(*p*-tolylsulfonyl)- $\beta$ -CD ( $\beta$ -CD-OTs) (1) and mono-6-deoxy-6-azido- $\beta$ -CD ( $\beta$ -CD-N<sub>3</sub>) (2) were prepared according to literature.<sup>67</sup> But-3-ynyl-2-bromo-2-methylpropanoate (Alkynyl-Br) (3) was prepared by the esterification reaction of 3-butyn-1-ol with 2-bromo-2-methylpropanoyl bromide.<sup>55,67</sup>  $\beta$ -CD-Br was prepared via the click reaction of 2 and 3 (Scheme 2a). In a typical example, 2 (1.0 g, 0.862 mmol), 3 (0.283 g, 1.293 mmol), and PMDETA (0.149 g, 0.862 mmol) were dissolved in 30 mL dry DMF. After one freeze-pump-thaw cycle, CuBr (0.124 g, 0.862 mmol) was introduced under the protection of argon (Ar) flow. The reaction flask was degassed by three freeze-pump-thaw cycles and then placed in an oil bath stirring at 35 °C for 35 h. The reaction mixture was then exposed to air, and precipitated in 300 mL acetone. The precipitation was obtained by suction filtration and washed three times with diethyl ether, yielding a light blue solid dried overnight in a vacuum oven (1.047 g, yield: 88.0%). 400 MHz <sup>1</sup>H NMR ( $\delta$ , ppm, DMSO-*d*<sub>6</sub>): 7.93–7.86 (m, 1H, the methine proton in 1,2,3-triazole ring), 5.71 (s, 14H, 2,3-OH in  $\beta$ -CD), 4.84 (s, 7H, 1-H in  $\beta$ -CD), 4.45 (s, 6H, 6-OH in  $\beta$ -CD), 3.85–3.46 (m, 28H, 3,5,6-H in  $\beta$ -CD), 3.34 (s, 14H, 2,4-H in  $\beta$ -CD), 1.84 (d,  $J = 13.7 \text{ Hz}$ , 6H, CH<sub>3</sub>- in  $\beta$ -CD-Br).

**Synthesis of  $\beta$ -CD-PDMAEMA (5).** The polymer 5 with a  $\beta$ -CD at the chain end was synthesized via the atom transfer radical polymerization (ATRP) of DMAEMA monomer with 4 as the initiator (Scheme 2a) and a typical procedure was as follows. The initiator 4 (0.276 g, 0.2 mmol), DMAEMA monomer (4.72 g, 30 mmol), and PMDETA (35 mg, 0.2 mmol) were dissolved in 6 mL of dry DMF followed by one freeze-pump-thaw cycle. CuBr (28 mg, 0.2 mmol) was introduced to initiate the

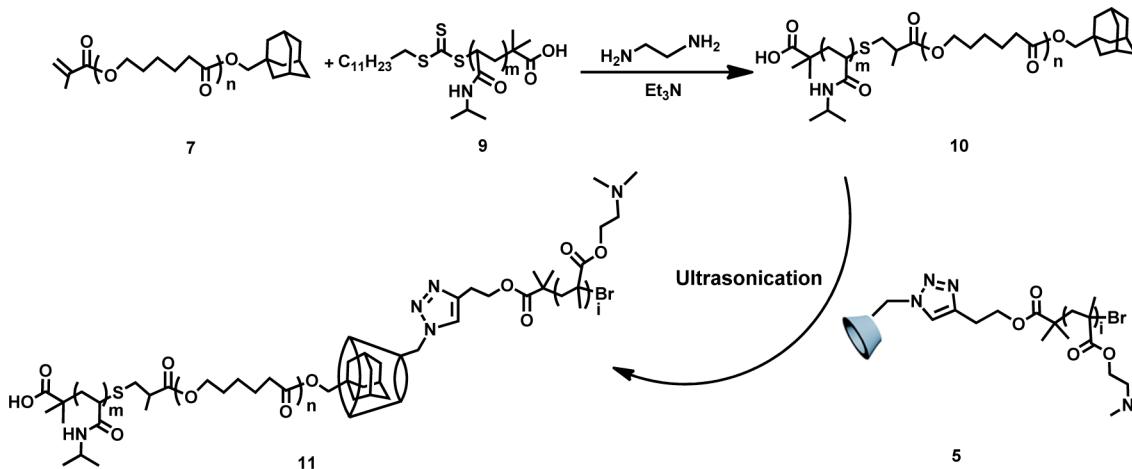
polymerization under the protection of Ar flow. The reaction flask was degassed by three freeze-pump-thaw cycles and then placed in an oil bath stirring at 90 °C for 10 h under Ar atmosphere. The reaction mixture was then exposed to air to terminate the polymerization. The solution was dialyzed ( $M_w$  cutoff, 3.5 kDa) against deionized water for 5 days to remove DMF, unreacted DMAEMA monomer, and initiator, as well as the copper catalysts. Finally, a pale powder was attained by freeze-drying with yield of 49.7% (0.92 g) and monomer conversion of 16.7%.  $M_n$ , <sup>13</sup>C NMR = 9.2 kDa,  $M_n$ , GPC = 9.8 kDa,  $M_w/M_n$  = 1.19. 400 MHz <sup>1</sup>H NMR ( $\delta$ , ppm, D<sub>2</sub>O): 4.24 (d,  $J = 61.9 \text{ Hz}$ , 100H, –COOCH<sub>2</sub>CH<sub>2</sub>– in PDMAEMA), 3.90–3.35 (m, 42H, the 2,3,4,5,6-H protons on the glucose units of  $\beta$ -CD), 2.75 (dd,  $J = 31.1, 22.1 \text{ Hz}$ , 100H, –COOCH<sub>2</sub>CH<sub>2</sub>– in PDMAEMA), 2.33 (s, 300H, –CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>3</sub>)<sub>2</sub> in PDMAEMA), 1.95 (dd,  $J = 48.7, 33.9 \text{ Hz}$ , 100H, –CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>– in PDMAEMA), 1.01 (d,  $J = 69.4 \text{ Hz}$ , 150H, –CH<sub>2</sub>C(CH<sub>3</sub>)<sub>2</sub>– in PDMAEMA).

**Synthesis of Ada-PCL (6).** The polymer 6 was prepared through ring-opening polymerization (ROP) (Scheme 2b). A typical polymerization procedure was shown as follows: Ada-OH (0.25 g, 1.5 mmol),  $\epsilon$ -CL (10.27 g, 90 mmol) and a catalytic amount of Sn(Oct)<sub>2</sub> (364 mg, 0.9 mmol) were dissolved in 6 mL of freshly dried xylene in an anhydrous flask. The reaction flask was degassed by three freeze-pump-thaw cycles and then immersed into an oil bath thermostated at 120 °C under Ar atmosphere with vigorous stirring for 24 h. The reaction mixture was then exposed to air to terminate the polymerization and cooled to room temperature. The resultant was dissolved in 15 mL of dichloromethane and precipitated in 200 mL of petroleum ether three times to afford the purified product. The product was dried in vacuum until constant weight (6.33 g, yield: 89.2% and monomer conversion: 59.9%).  $M_n$ , <sup>13</sup>C NMR = 4.7 kDa,  $M_n$ , GPC = 5.5 kDa,  $M_w/M_n$  = 1.17. 400 MHz <sup>1</sup>H NMR ( $\delta$ , ppm, CDCl<sub>3</sub>): 4.06 (t,  $J = 6.7 \text{ Hz}$ , 80H, –OCHH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CO– in PCL), 3.68–3.63 (m, 2H, terminal –CH<sub>2</sub>OH), 2.31 (t,  $J = 7.5 \text{ Hz}$ , 80H, –OCHH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CO– in PCL), 1.78–1.56 (m, 160H, –OCHH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CO– in PCL), 1.49–1.30 (m, 80H, –OCHH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CO– in PCL).

**Synthesis of Ada-PCL-MAA (7).** The terminal esterification reaction of 6 to synthesize 7 was performed as follows: 6 (0.94 g, 0.2 mmol) and TEA (202 mg, 2 mmol) were dissolved in 5 mL of 1,2-dichloroethane in an ice-water bath. After stirring for 10 min, methacryloyl chloride (80%, 262 mg, 2 mmol) in 5 mL of 1,2-dichloroethane was added dropwise. Subsequently, the reaction mixture was stirred at room temperature for 1 h and then refluxed for 3 days. The resultant was precipitated in 100 mL of cold methanol three times to afford the purified product (684 mg, yield: 71.7%). 300 MHz <sup>1</sup>H NMR ( $\delta$ , ppm, CDCl<sub>3</sub>): 6.10 (s, 1H, C=C(H)H in MAA), 5.56 (s, 1H, C=C(H)H in MAA), 4.28–3.97 (m, 81H, –OCHH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CO– in PCL), 3.68 (s, 0.67H, terminal –CH<sub>2</sub>OH), 2.52–2.20 (m, 80H, –OCHH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CO– in PCL), 1.82–1.58 (m, 164H, –OCHH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CO– in PCL), 1.50–1.27 (m, 81H, –OCHH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CO– in PCL).

**Synthesis of CTA-PNIPAM (9).** As illustrated in Scheme 2c, PNIPAM with a –S–C(S)–S– segment which can be converted to thiol group was yielded by reversible addition–fragmentation chain transfer polymerization (RAFT). The initiator 2-(((dodecylthio)carbonothioyl)thio)-2-methylpropanoic acid (8) was synthesized according to previous literature.<sup>68</sup>

In a typical example, 8 (0.146 g, 0.4 mmol), NIPAM monomer (2.8 g, 25 mmol) and AIBN (7 mg, 0.04 mmol) were dissolved in 8 mL of dry DMF followed by three freeze-pump-thaw cycles.

Scheme 3. Synthetic Route of the Supramolecular Triblock Polymer PNIPAM-*b*-PCL-*b*-PDMAEMA (11)

Subsequently, the reaction flask was placed in an oil bath thermostated at 70 °C for 12 h with magnetic stirring under Ar atmosphere. The reaction mixture was then exposed to air to terminate the polymerization and cooled to room temperature. The reaction solution was dialyzed ( $M_w$  cutoff, 3.5 kDa) against deionized water for 3 days to remove DMF and the unreacted NIPAM monomer. Finally, a light yellow solid was produced by freeze-drying with yield of 95.4% (2.06 g) and monomer conversion of 68.6%.  $M_n, \text{NMR} = 5.4 \text{ kDa}$ ,  $M_n, \text{GPC} = 6.1 \text{ kDa}$ ,  $M_w/M_n = 1.08$ . 300 MHz  $^1\text{H}$  NMR ( $\delta$ , ppm,  $\text{CDCl}_3$ , Figure S1 in Supporting Information): 6.92–5.85 (m, 45H,  $-\text{NHCH}(\text{CH}_3)_2$  in PNIPAM), 4.31–3.65 (m, 45H,  $-\text{NHCH}(\text{CH}_3)_2$  in PNIPAM), 3.35 (d,  $J = 4.1 \text{ Hz}$ , 2H,  $\text{C}_{11}\text{H}_{23}\text{CH}_2\text{SCSS}-$ ), 2.77–1.48 (m, 135H,  $-\text{CH}-\text{CH}_2-$  in PNIPAM), 1.22–0.86 (m, 270H,  $-\text{NHCH}(\text{CH}_3)_2$  in PNIPAM).

**Synthesis of PNIPAM-*b*-PCL-*b*-PDMAEMA (11).** The synthetic route of the supramolecular triblock polymer PNIPAM-*b*-PCL-*b*-PDMAEMA (11) is described in Scheme 3.

Typically, **7** (0.096 g, 0.02 mmol), in which the mole of the carbon–carbon double bond at the terminal of the chain is 0.015 mmol, and **9** (0.162 g, 0.03 mmol) were dissolved in 4 mL of THF. The flask was covered with tinfoil to avoid daylight. The reaction flask was degassed by three freeze–pump–thaw cycles and then immersed into an ice–water bath. After the reaction was stirred for 10 min under Ar atmosphere, ethylenediamine (0.04 mmol, 2.67  $\mu\text{L}$ ) and TEA (0.04 mmol, 5.56  $\mu\text{L}$ ) in 1 mL of THF were added using a 1 mL syringe. The mixture was then stirred in an ice–water bath for 4 h in dark. Afterward, the reaction mixture was exposed to air and dialyzed ( $M_w$  cutoff, 3.5 kDa) against deionized water for 2 days to remove THF and the small molecules. Then the product PNIPAM-*b*-PCL (**10**) was yielded by freeze-drying and the  $^1\text{H}$  NMR spectra of **10** is shown in Figure 5. (Here, **10** was a mixture of the diblock polymer PNIPAM-*b*-PCL and the polymer with a -SH group produced via the aminolysis of **9**, and the latter can be removed through the dialysis ( $M_w$  cutoff, 8.0–14.0 kDa) of the next step when preparing PNIPAM-*b*-PCL-*b*-PDMAEMA.) Detailed explanations were given in Supporting Information, referring to the section “Some details for synthesis of PNIPAM-*b*-PCL-*b*-PDMAEMA (11)”.

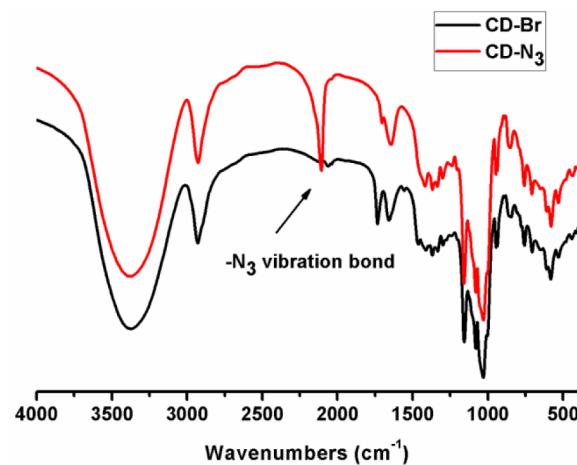
Afterward, **5** (0.039 mmol, 369 mg, the molar ratio between  $\beta$ -CD and Ada was kept at 3: 1) in 1 mL of THF was gradually added into two-third of **10** obtained above in 4 mL of THF under a vigorous stirring, and then the mixture was treated with

ultrasound for 30 min to form the inclusion complex. Subsequently, the reaction solution was dialyzed ( $M_w$  cutoff, 8.0–14.0 kDa) against deionized water for 3 days to remove THF, the small molecules, unreacted **5** and the polymer with a -SH group produced via the aminolysis of **9**. The supramolecular triblock copolymer PNIPAM-*b*-PCL-*b*-PDMAEMA (11) was obtained by freeze-drying for further characterization.  $M_n, \text{GPC} = 23.1 \text{ kDa}$ ,  $M_w/M_n = 1.42$ .

**Preparation of Supramolecular Nanoparticles Solution.** The typical procedure to prepare the supramolecular nanoparticles solution was as follows. First, 43.6 mg of **11** was dissolved in DMF (1.0 mL). With vigorous stirring, 9 mL of deionized water was dropped via a syringe pump at a flow rate of 1 mL/h. After the addition, the solution was dialyzed ( $M_w$  cutoff, 3.5 kDa) against deionized water for 1 day to remove DMF. After dialysis, the volume of the solution was increased to 13.5 mL, and an aggregate solution with a concentration of 3.2 mg/mL was obtained for further experiments.

## RESULTS AND DISCUSSION

**Synthesis of  $\beta$ -CD-Based ATRP Initiator ( $\beta$ -CD-Br) (4).** In this work, the end-functionalized polymer **5** was synthesized via direct polymerization using the functional initiator **4** which was prepared through the click reaction of **2** and **3** (Scheme 2a). As shown in Figure 1, the FT-IR spectrum (red line) of  $\beta$ -CD- $\text{N}_3$

Figure 1. FT-IR spectra of  $\beta$ -CD- $\text{N}_3$  (red) and  $\beta$ -CD-Br (black)

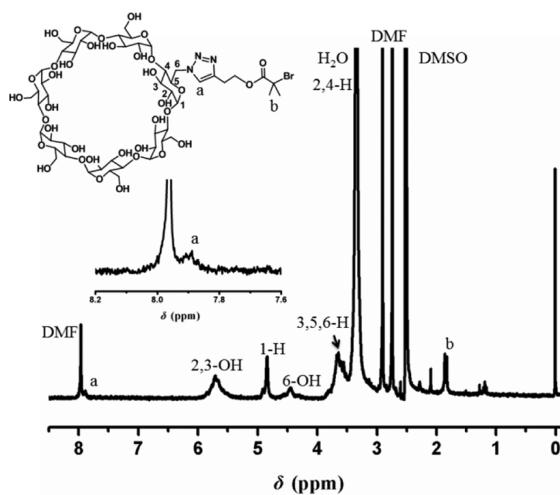
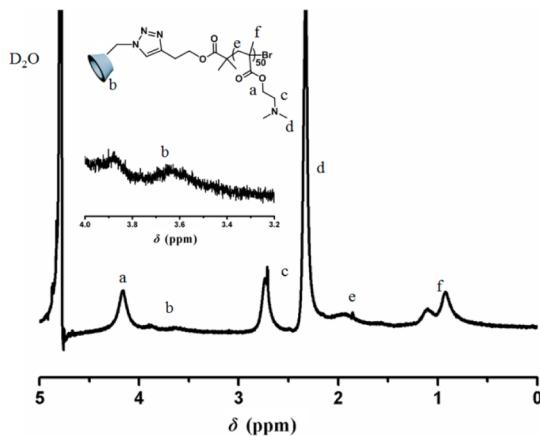
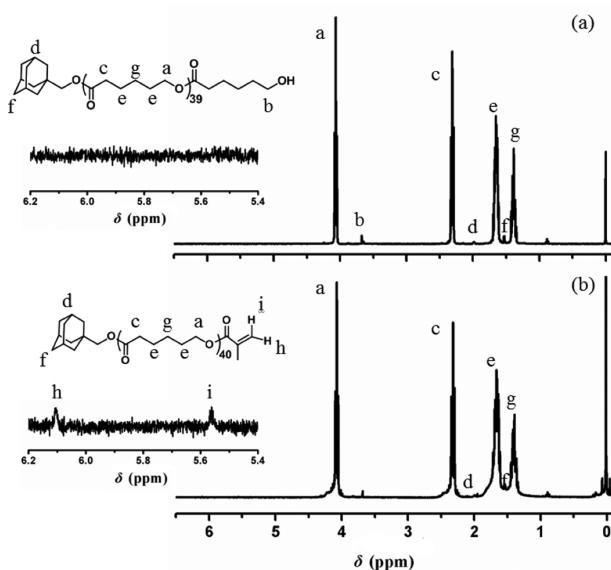
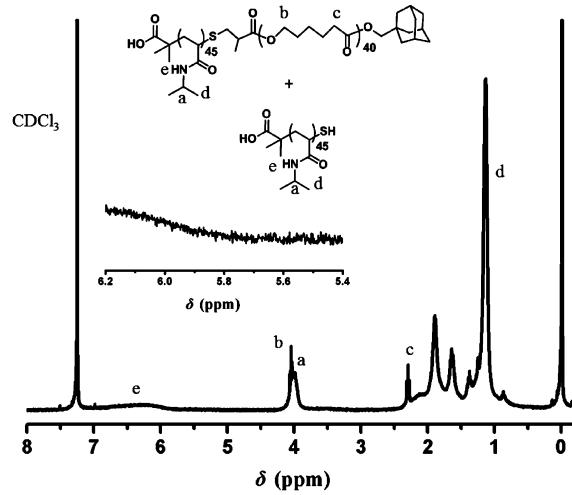
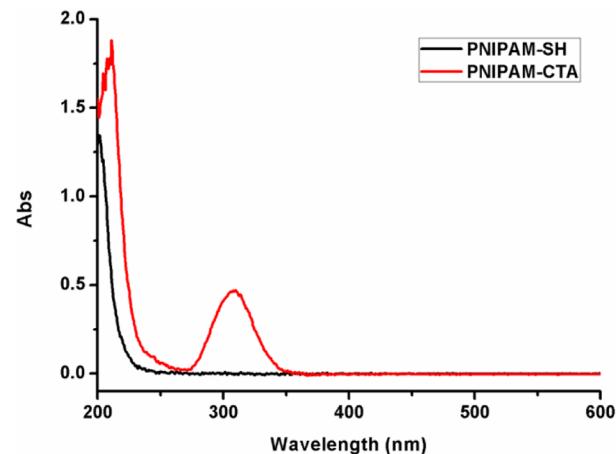
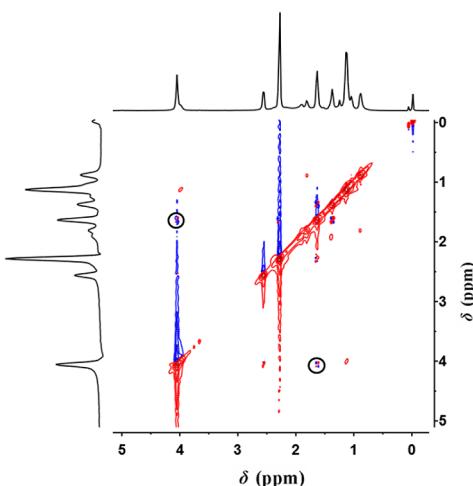
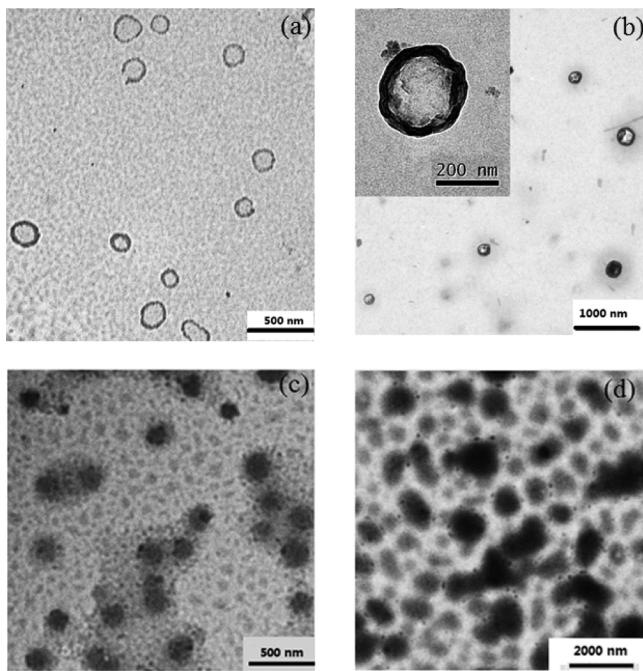
Figure 2.  $^1\text{H}$  NMR spectra of  $\beta\text{-CD-Br}$  (**4**) in  $\text{DMSO-}d_6$ Figure 3.  $^1\text{H}$  NMR spectra of  $\beta\text{-CD-PDMAEMA}$  (**5**) in  $\text{D}_2\text{O}$ Figure 4.  $^1\text{H}$  NMR spectra of (a) Ada-PCL (**6**) and (b) Ada-PCL-MAA (**7**) in  $\text{CDCl}_3$ Figure 5.  $^1\text{H}$  NMR spectra of PCL-*b*-PNIPAM (**10**) in  $\text{CDCl}_3$ 

Figure 6. UV-vis spectra of PNIPAM-SH (black) and PNIPAM-CTA (red)

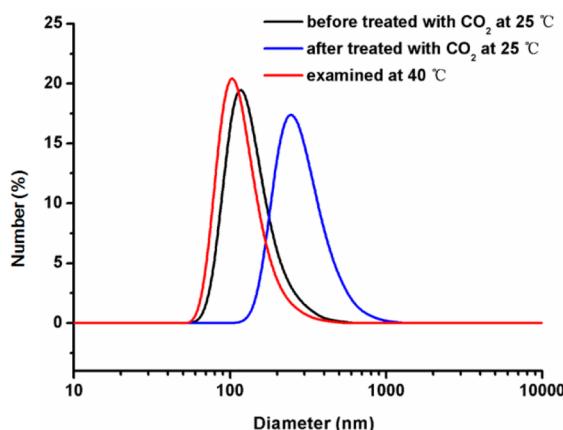
Figure 7. 2D  $^1\text{H}$  NOESY spectrum of PNIPAM-*b*-PCL-*b*-PDMAEMA (**11**) in  $\text{CDCl}_3$ 

(2) clearly exhibits the sharp peak of the characteristic azide absorption at  $2106\text{ cm}^{-1}$ . After click reaction, as shown in the FT-IR spectrum of  $\beta\text{-CD-Br}$  (**4**) (black line) in Figure 1, the

characteristic azide absorption at  $2106\text{ cm}^{-1}$  disappeared completely, confirming the whole consumption of the azide groups.



**Figure 8.** TEM images of PNIPAM-*b*-PCL-*b*-PDMAEMA (**11**) self-assembling aggregates in water before (a) and after (b) being treated with  $\text{CO}_2$  at  $25\text{ }^\circ\text{C}$  (inset: high-resolution TEM image of the vesicle structure); the samples used in parts c and d were prepared at  $40$  and  $80\text{ }^\circ\text{C}$ , respectively. The measurement is at the polymer concentration of  $0.9\text{ mg/mL}$ .



**Figure 9.** DLS measurements of PNIPAM-*b*-PCL-*b*-PDMAEMA (**11**) solutions before (black) and after (blue) treated with  $\text{CO}_2$  at  $25\text{ }^\circ\text{C}$ , as well as the curve examined at  $40\text{ }^\circ\text{C}$  (red) with the polymer concentration of  $0.9\text{ mg/mL}$ .

Moreover, in Figure 2, the multiple peaks of methine proton in 1,2,3-triazole ring (peak a) in the range of  $7.93$ – $7.86\text{ ppm}$  prove the formation of the functional initiator **4**. And all characteristic signals of the  $\beta$ -CD moiety can be observed and the corresponding peaks have been assigned. The peak of the inner methine protons between the oxygen moieties in  $\beta$ -CD ( $1\text{-H}$  protons) at  $4.84\text{ ppm}$  is defined as seven protons. The peak located at  $1.84\text{ ppm}$  is associated with the methyl protons of the 2-bromoisobutyl group (peak b) and the integral ratio of the peaks a and b was calculated to be  $1:6$ .

**Synthesis of  $\beta$ -CD-PDMAEMA (**5**).** Subsequently, the prepared initiator **4** was used to prepare polymer **5** via ATRP of DMAEMA.

The  $^1\text{H}$  NMR spectra of **5** ( $M_{n,\text{NMR}} = 9.2\text{ kDa}$ ,  $M_{n,\text{GPC}} = 9.8\text{ kDa}$ ) are presented in Figure 3, and the characteristic signals of  $\beta$ -CD and PDMAEMA segments are assigned clearly. The broad signals in the region of  $3.35$ – $3.9\text{ ppm}$  (peak b, Figure 3) are associated with the inner methine and methylene protons between the oxygen and carbon moieties ( $\text{O}-\text{CH}-\text{C}$  and  $\text{O}-\text{CH}_2-\text{C}$ , the  $2,3,4,5,6\text{-H}$  protons as described in Figure 2) on the glucose units of  $\beta$ -CD,<sup>59</sup> which are denoted as  $42$  protons. According to the  $^1\text{H}$  NMR analysis, the number-average degree of polymerization (DP) of the PDMAEMA block was determined to be  $50$  from the integral ratio of peak a at  $4.24\text{ ppm}$  (the methylene protons in DMAEMA units adjacent to the oxygen moieties of ester linkages) to peak b.

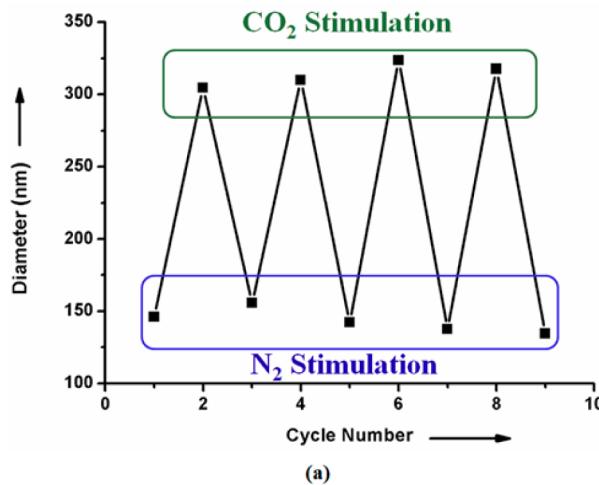
**Synthesis of Ada-PCL (**6**) and Ada-PCL-MAA (**7**).** The polymer **7** with one Ada group and one carbon–carbon double bond at each end via ROP was prepared by two steps (Scheme 2b). The  $^1\text{H}$  NMR spectra of **6** ( $M_{n,\text{NMR}} = 4.7\text{ kDa}$ ,  $M_{n,\text{GPC}} = 5.5\text{ kDa}$ ) and **7** are shown in Figure 4, parts a and b, respectively, and the characteristic signals of Ada and PCL segments were assigned. The signal b at  $3.66\text{ ppm}$  in Figure 4a is assigned as the  $2$  protons of the methylene ( $-\text{CH}_2-\text{OH}$ ) at the end of the PCL block. The number-average DP of PCL was calculated to be  $40$  by  $^1\text{H}$  NMR analysis, determined according to the integral ratio of peak a ( $4.06\text{ ppm}$ , the methylene protons in PCL units adjacent to the oxygen moieties of ester linkages) to peak b mentioned above. Compared with Figure 4a, two peaks (i and h) appeared in the range of  $5.5$  to  $6.2\text{ ppm}$  in Figure 4b related to the two protons at the terminal of the carbon–carbon double bond of **7**, supporting the successful synthesis of **7**. Here, the degree of substitution (DS) was defined as the end-functionalized ratio of the PCL block, which was calculated from the integration ratio of h+i/h+i+b (Figure 4b) to be  $74.9\%$ .

**Synthesis of CTA-PNIPAM (**9**).** The PNIPAM block was yielded through RAFT as shown in Scheme 2c. The  $^1\text{H}$  NMR spectrum of **9** ( $M_{n,\text{NMR}} = 5.4\text{ kDa}$ ,  $M_{n,\text{GPC}} = 6.1\text{ kDa}$ ) is given in Figure S1, Supporting Information, with the corresponding peak assignments. The signal b at  $3.35\text{ ppm}$  originates from the  $2$  protons of the methylene adjacent to the  $-\text{S}-\text{C}(\text{S})-\text{S}-$  segment, and the number-average DP of the PNIPAM block was determined to be  $45$  from the integral ratio of peak a at  $4.00\text{ ppm}$  (the methine protons in NIPAM units adjacent to the nitrogen moieties of amide linkages) to peak b.

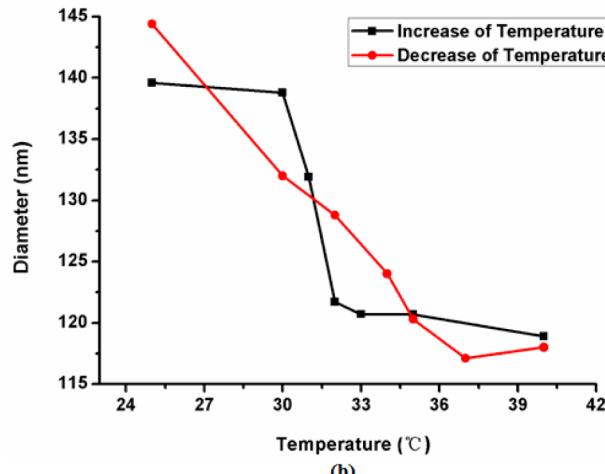
**Synthesis of PNIPAM-*b*-PCL-*b*-PDMAEMA (**11**).** The supramolecular triblock copolymer PNIPAM-*b*-PCL-*b*-PDMAEMA ( $M_{n,\text{GPC}} = 23.1\text{ kDa}$ ) was prepared via thiol–ene Michael addition reaction, as well as the host–guest interaction between  $\beta$ -CD and Ada as presented in Scheme 3.

First, the  $-\text{S}-\text{C}(\text{S})-\text{S}-$  segment in **9** was converted to a  $-\text{SH}$  group, which subsequently reacted with the carbon–carbon double bond in **7** to form the diblock copolymer PNIPAM-*b*-PCL (**10**). The  $^1\text{H}$  NMR spectra of **10** are shown in Figure 5, with the main characteristic signals of PNIPAM and PCL assigned. From the inset in Figure 5, it is clear to see that both the two peaks (i and h) in Figure 4b in the range of  $5.5$  to  $6.2\text{ ppm}$  (the two protons at the terminal of the carbon–carbon double bond in PCL block) and peak b at  $3.35\text{ ppm}$  (Figure S1, Supporting Information, the methylene adjacent to the  $-\text{S}-\text{C}(\text{S})-\text{S}-$  segment of PNIPAM) disappeared, suggesting the successful formation of the diblock copolymer **10**.

Moreover, a blank experiment without the addition of **7** was carried out to further prove the conversion from  $-\text{S}-\text{C}(\text{S})-\text{S}-$  segment in **9** to a  $-\text{SH}$  group. Solids before (red line) and after (black line) the experiment were examined by UV-vis,

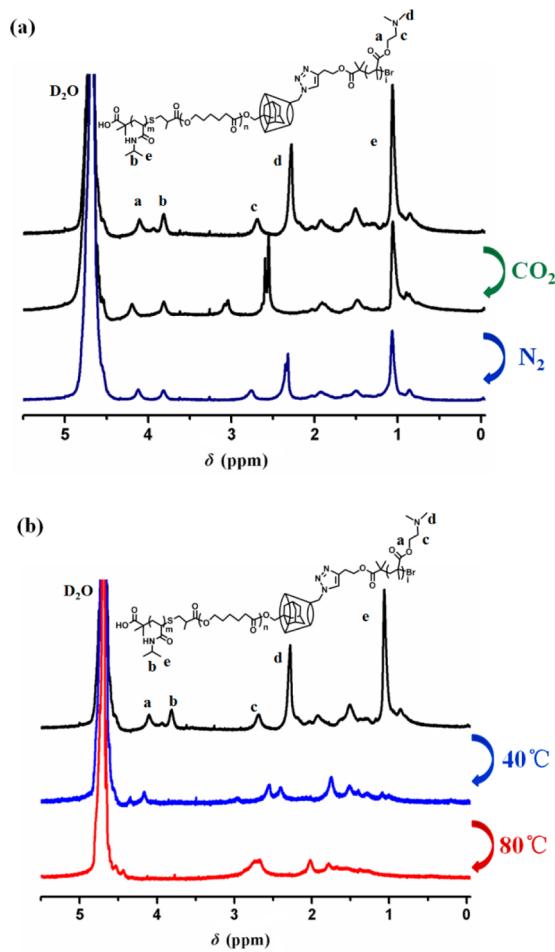


(a)



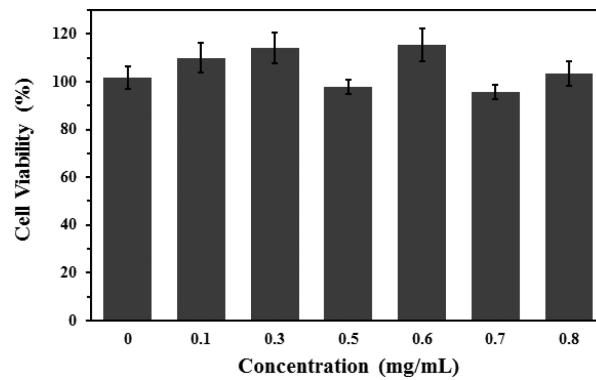
(b)

**Figure 10.** Diameter change of PNIPAM-*b*-PCL-*b*-PDMAEMA (**11**) aggregates under alternating CO<sub>2</sub>/N<sub>2</sub> stimulation (a) and as temperature increases and decreases (b).



**Figure 11.** <sup>1</sup>H NMR spectra of the PNIPAM-*b*-PCL-*b*-PDMAEMA (**11**) aggregates in D<sub>2</sub>O: examined before and after alternating bubbling with CO<sub>2</sub> and N<sub>2</sub> at 25 °C (a), detected at 25 °C, 40 and 80 °C, respectively (b). The measurement is at the polymer concentration of 0.9 mg/mL.

respectively, as depicted in Figure 6. The characteristic absorption at 309.5 nm of the –S–C(S)–S– segment in **9** completely disappeared after the blank experiment, demonstrating the consumption of the –S–C(S)–S– segment. Addition-



**Figure 12.** Cytotoxicity evaluation of PNIPAM-*b*-PCL-*b*-PDMAEMA (**11**).

ally, the color of the reaction mixture gradually faded from yellow to colorless during the reaction, which further supports the formation of the –SH group.

In Figure 7, the 2D <sup>1</sup>H NOESY spectrum of PNIPAM-*b*-PCL-*b*-PDMAEMA (**11**) was displayed, providing a direct evidence for the construction of the supramolecular **11** via the inclusion complexation. Cross-peaks from dipolar interaction between the signals at 4.05 ppm assigned to the inner protons (the 3-, 5-, and 6-H protons) located in the cavities of β-CD and the signals at 1.5–2.0 ppm ascribed to Ada moieties are clearly observed, strongly indicating that Ada moieties have been deeply embedded in the cavities of β-CD, and the supramolecular **11** has been successfully synthesized through host–guest interactions.

The supramolecular PNIPAM-*b*-PCL-*b*-PDMAEMA copolymer with two hydrophilic blocks (PNIPAM and PDMAEMA) and a hydrophobic one (PCL) showed an amphiphilic character, which could spontaneously form aggregated structures. We examined the self-assembly behaviors of the supramolecular PNIPAM-*b*-PCL-*b*-PDMAEMA in water as mentioned above. The critical aggregation concentration (CAC) was 0.68 mg/mL, measured by UV-vis and pyrene fluorescent probe analysis (Figure S2, Supporting Information). To further study the morphology of these aggregates, both TEM and DLS were employed to investigate the nature of the self-assembly, and the results are shown in Figures 8, 9, and 10.

In Figure 8a, the TEM image of the PNIPAM-*b*-PCL-*b*-PDMAEMA aggregates at 25 °C before treated with CO<sub>2</sub> displays quite uniform vesicles. And the hydrodynamic diameter is 139.6 nm with a narrow PDI of 0.173, determined by DLS (Figure 9, black line). Then the aggregates were treated with CO<sub>2</sub> for 10 min (~1 mL/s). From the TEM image in Figure 8b, it was clear to see that the vesicles swelled, with average diameter increased from 139.6 to 299.9 nm (the blue curve in Figure 9). It was affirmed that tertiary amine groups can be protonated by CO<sub>2</sub> bubbled into the water to form a charged ammonium bicarbonate which can be recovered upon CO<sub>2</sub> removal.<sup>70,71</sup> After passing through CO<sub>2</sub> to the system, the repulsion of the surface charges induced the expansion of the aggregates. Additionally, this process is reversible and repeatable at least 4 times under an alternating CO<sub>2</sub> (for 10 min)/N<sub>2</sub> (for 20 min) stimulation, as shown in Figure 10a. Furthermore, to examine the influence of temperature to the aggregates, we prepared two TEM samples at 40 and 80 °C, respectively. From the TEM image in Figure 8c, it was obvious that the vesicles converted to smaller spherical micelles at 40 °C (the red line in Figure 9). To study the thermo-responsiveness in detail, we introduced a heating–cooling cycle to the system. As shown in Figure 10b, the heating run indicates a transition temperature at 32 °C, which corresponds to the LCST (lower critical solution temperature) of PNIPAM in water.<sup>72,73</sup> At 40 °C, the PNIPAM moiety became hydrophobic, resulted in a morphological deformation from vesicle to spherical micelle. Further increasing temperature to 80 °C, which was far beyond the LCST of PDMAEMA in water (about 50 °C),<sup>70,71</sup> leaded to some irregular aggregations, as shown in the TEM image of Figure 8d. Both TEM and DLS observations indicated the formation of the amphiphilic triblock copolymer.

In addition, we carried out the 600 M <sup>1</sup>H NMR measurement to further study the CO<sub>2</sub> and temperature dual stimuli-responsive behavior. Figure 11a presents the <sup>1</sup>H NMR spectra of the PNIPAM-*b*-PCL-*b*-PDMAEMA aggregates in D<sub>2</sub>O alternating bubbling with CO<sub>2</sub>/N<sub>2</sub>. Before treated with CO<sub>2</sub>, the characteristic peaks of the two hydrophilic blocks (PNIPAM and PDMAEMA) can be well observed. After treatment with CO<sub>2</sub> for 10 min, the resonance peaks c and d of PDMAEMA in the range of 2.0 to 3.0 ppm distinctly shifted to low field, indicating the protonation of the tertiary amine groups in PDMAEMA block. Subsequently, after removing CO<sub>2</sub> with N<sub>2</sub> for 20 min, the chemical shift of the peaks c and d moved back, pointing out the deprotonation of the tertiary amine groups. Moreover, temperature also caused a big difference to the <sup>1</sup>H NMR spectrum of the aggregates, as shown in Figure 11b. At 40 °C, the characteristic peaks b and e of PNIPAM block disappeared and the peaks a, c and d of PDMAEMA broadened. Compared to 25 °C, the PNIPAM moiety was trapped from hydrophilic to hydrophobic. Further increasing the temperature to 80 °C, the peaks of PDMAEMA block vanished completely, indicating the chain aggregation of the PDMAEMA block.

#### Cytotoxicity Evaluation of the Nanoparticles Solution.

To evaluate the biocompatibility of PNIPAM-*b*-PCL-*b*-PDMAEMA (**11**), cytotoxicity experiments of the self-assembling solution were carried out on the C26 cell line as shown in Figure 12 at the polymer concentration of 0, 0.1, 0.3, 0.5, 0.6, 0.7, and 0.8 mg/mL, respectively. The results strongly indicate that the self-assembling solution of PNIPAM-*b*-PCL-*b*-PDMAEMA (**11**) has no obvious cytotoxicity. Thus, the synthesized supramolecular copolymer PNIPAM-*b*-PCL-*b*-PDMAEMA with good biocompatibility can be extensively and securely

applied in biological systems. Some preliminary data for controlled release with this kind of vesicles using fluorescent rhodamine B (RB) as a model is given in Figure S5, Supporting Information.

## CONCLUSIONS

In summary, we successfully designed and developed a supramolecular triblock stimuli-responsive copolymer PNIPAM-*b*-PCL-*b*-PDMAEMA. The three blocks PDMAEMA, PCL, and PNIPAM were prepared via ATRP, ROP, and RAFT, respectively. PNIPAM was connected with PCL through thiol–ene Michael addition, while PDMAEMA was linked with PCL by the molecular recognition between β-CD-based host in PDMAEMA and Ada-modified guest in PCL. The reversible sensitivity to CO<sub>2</sub> gas and temperature of the supramolecular triblock copolymer has been studied in detail by TEM, DLS, and NMR. This work provides a feasible strategy for preparing ABC triblock copolymers by the combination of thiol–ene Michael addition reaction and host–guest interactions. Detailed studies on the potential application in biological field, particularly in the area of drug delivery systems of the supramolecular copolymer PNIPAM-*b*-PCL-*b*-PDMAEMA are presently under way, and the relevant results will be reported in due course.

## ASSOCIATED CONTENT

### S Supporting Information

<sup>1</sup>H NMR spectra of PNIPAM-CTA (**9**), CAC measurement, some details for synthesis of PNIPAM-*b*-PCL-*b*-PDMAEMA (**11**), GPC results of the polymers prepared in this paper, and release experiments based on the PNIPAM-*b*-PCL-*b*-PDMAEMA (**11**) assembly. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

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