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The Doubly Thermo-responsive Triblock Copolymer Nanoparticles Prepared through Seeded RAFT Polymerization*

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Abstract The doubly thermo-responsive triblock copolymer nanoparticles of polystyrene-block-poly(*N*-isopropylacrylamide)-block-poly[*N,N*-(dimethylamino) ethyl methacrylate] (PS-*b*-PNIPAM-*b*-PDMAEMA) are successfully prepared through the seeded RAFT polymerization *in situ* by using the PS-*b*-PNIPAM-TTC diblock copolymer nanoparticles as the seed. The seeded RAFT polymerization undergoes a pseudo-first-order kinetics procedure, and the molecular weight increases with the monomer conversion linearly. The hydrodynamic diameter (D_h) of the triblock copolymer nanoparticles increases with the extension of the PDMAEMA block. In addition, the double thermo-response behavior of the PS-*b*-PNIPAM-*b*-PDMAEMA nanoparticles is detected by turbidity analysis, temperature-dependent ^{1}H-NMR analysis, and DLS analysis. The seeded RAFT polymerization is believed as a valid method to prepare triblock copolymer nanoparticles containing two thermo-responsive blocks.

Keywords Thermo-responsive; Seeded RAFT polymerization; Block copolymers

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INTRODUCTION

Over the past decades, block copolymer nanoparticles with thermo-responsive chains have aroused great interest, since they can be potentially used in biological separation, drug delivery, smart surfaces and regulating enzyme activity *et al*[1, 2]. In recent years, the doubly thermo-responsive block copolymer nanoparticles, which contain two thermo-responsive blocks, have attracted much attention[3−13]. Based on the topology of the block copolymer nanoparticles, four kinds of doubly thermo-responsive block copolymer nanoparticles were synthesized and clarified in our previous contributions[5]. So far, micellization in the selective solvent for a certain block is frequently used and becomes the main method to synthesize (thermo-responsive) block copolymer

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nanoparticles[6–14], but it suffers from many disadvantages, including low polymer concentration, uncontrollable size or morphology, *etc*.

Recently, much effort has been made to explore a convenient and valid method to synthesize the doubly thermo-responsive block copolymer nanoparticles[3–13]. It has been found that the macro-RAFT agent containing two thermo-responsive blocks mediated dispersion RAFT polymerization is a good method to synthesize doubly thermo-responsive nanoparticles, in which a diblock copolymer with two thermo-responsive blocks[3, 4] or two homopolymers[5] can be used as the macro-RAFT agent.

The seeded polymerization is another strategy to *in situ* prepare the concentrated block copolymer nanoparticles with tunable structures[15–18]. Various nanoparticles were used as the intermediate (seed) to prepare the novel nano-objects. However, few reports have been found to describe the synthesis of thermo-responsive nanoparticles or even doubly ones through the seeded polymerization[19]. By introducing the RAFT polymerization into seeded polymerization, the strategy named seeded RAFT polymerization could overcome the shortcomings of the micellization strategy, which is expected to be another valid method to synthesize doubly thermo-responsive nanoparticles.

In this contribution, the seeded RAFT polymerization was employed to synthesize doubly thermo-responsive triblock copolymer nanoparticles of polystyrene-block-poly(*N*-isopropylacrylamide)-block-poly[*N,N*-(dimethylamino) ethyl methacrylate] (PS-*b*-PNIPAM-*b*-PDMAEMA). The results demonstrated that the synthesized triblock copolymer nanoparticles were narrowly distributed both in molecular and average diameter. After transferring the nanoparticles from ethanol to neat water, the triblock copolymer nanoparticles exhibit two distinct and separate phase transition process with increasing temperature, during which the corona-core nanoparticles firstly convert into the corona-shell-core structure, and then further convert into shell-shell-core structure.

EXPERIMENTAL

Materials

N-isopropylacrylamide (NIPAM, > 99%) was purchased from Acros Organics and purified by recrystallization in the *n*-hexane/acetone mixture (50:50 by volume). *N*,*N*-(dimethylamino) ethyl methacrylate (DMAEMA, 98%) monomer was purchased from Alfa, dried with CaH_2 overnight and distilled under reduced pressure. Styrene (St, > 98%) was purchased from Tianjin Chemical Company, distilled under vacuum and stored in the icebox at −5 °C. 2,2′-Azodiisobutyronitrile (AIBN, > 99%) was recrystallized from ethanol. The small molecular RAFT agent of 4-cyano-4-(ethylsulfanylthiocarbonyl) sulfanyl pentanoic acid (ECT) was synthesized as reported elsewhere[20]. Other chemical reagents were analytic grade and used as received. Distilled water was used in the experiments.

Synthesis of PS-b-PNIPAM-TTC Diblock Copolymer

The polystyrene-*b*-poly(*N*-isopropylacrylamide) trithiocarbonate (PS-*b*-PNIPAM-TTC) diblock copolymer was synthesized by a two-step solution RAFT polymerization. In a 50 mL Schlenkflask with a magnetic bar, St (20.0 g, 0.193 mol), ECT (84.4 mg, 0.321 mmol), and AIBN (17.6 mg, 0.107 mmol) dissolved in 1,4-dioxane (10.0 g) were added. The solution was initially degassed with nitrogen in ice-water bath for 30 min, and then the polymerization was carried out at 70 °C for 20 h. The monomer conversion was 48.2%, which was determined by ^{1}H-NMR analysis in the presence of the internal standard of 1,3,5-trioxane after the polymerization. The synthesized polymer was then precipitated in excess methanol, collected by three precipitation/filtration cycles to remove the residual monomer, and then the polymer was dried at 25 °C under vacuum to afford the pale yellow PS-TTC powder.

The synthesized macro-RAFT agent of PS-TTC (5.00 g, 0.165 mmol), NIPAM (2.797 g, 24.7 mmol), and AIBN (9.03 mg, 0.055 mmol) dissolved in 1,4-dioxane (10 g) were added into a 25 mL Schlenkflask with a magnetic bar. The solution was degassed with nitrogen, and then the polymerization was carried out in the preheated oil bath at 70 °C. After 6 h, the polymerization was quenched by rapid cooling upon immersion of the flask into iced water and exposing to the air with the monomer conversion of 85.2%, which was determined by ^{1}H-NMR analysis in the presence of 1,3,5-trioxane. The synthesized polymer was then precipitated into the iced mixture of methanol and diethyl ether (5:3 by weight), collected by three precipitation/filtration cycles, washed twice with methanol, and dried under vacuum at room temperature to afford the PS-*b*-PNIPAM-TTC diblock copolymer.

Preparation of the PS-b-PNIPAM-TTC Seed Nanoparticles

Into a 50 mL Schlenkflask with a magnetic bar, the synthesized diblock copolymer macro-RAFT agent of PS-*b*-PNIPAM-TTC (2.00 g, 0.045 mmol) and ethanol (16.5 g), were added, and then the mixture was dispersed by means of an ultrasonic bath for 30 min (Kc-Y1000, 28 kHz, 1000 W, Keyuan, China). Subsequently, the DMAEMA monomer (2.12 g, 13.5 mmol) was added, and the dispersion was vigorously stirred for over 30 min to obtain an opalesque dispersion of the PS-*b*-PNIPAM-TTC seed nanoparticles at the concentration of 20 wt%. The seed nanoparticles were stored at −5 °C prior to use in the subsequent seeded RAFT polymerization.

Seeded RAFT Polymerization and Synthesis of the Thermo-responsive Triblock Copolymer Nanoparticles

The seeded RAFT polymerization of DMAEMA was performed under the molar ratio of $[\text{DMAEMA}]_0$:$[\text{PS-}b\text{-PNIPAM-TTC}]_0$:$[\text{AIBN}]_0$ = 900:3:1 with the weight percent of the feed PS-*b*-PNIPAM-TTC seed nanoparticles plus the monomer 15 wt% in ethanol at 70 °C. Typically, into the freshly prepared dispersion of the PS-*b*-PNIPAM-TTC seed nanoparticles (2.00 g containing 0.194 g or 0.00433 mmol of PS-*b*-PNIPAM-TTC), DMAEMA (0.206 g, 1.31 mmol), AIBN (0.237 mg, 0.0032 mmol) dissolved in ethanol (3.58 g), and the internal standard of 1,3,5-trioxane (11.8 mg, 0.131 mmol) dissolved in ethanol (0.665 g) were added. The mixture was degassed with nitrogen, and then the polymerization was carried out in a preheated oil bath at 70 °C. After a given time, the polymerization was quenched by immersing the flask in iced water. The monomer conversion was also detected by ^{1}H-NMR analysis according to the Eq. (S1) in the supporting information.

To detect the morphology of the PS-*b*-PNIPAM-*b*-PDMAEMA triblock copolymer nanoparticles synthesized through the seeded RAFT polymerization, the colloidal dispersion was diluted with suitable ethanol, and a small drop of the diluted dispersion was deposited onto a piece of copper grid, dried at room temperature, and then observed through a transmission electron microscope (TEM). To collect the PS-*b*-PNIPAM-*b*-PDMAEMA triblock copolymer for the ^{1}H-NMR and gel permeation chromatography (GPC) measurements, part of the dispersion of the PS-*b*-PNIPAM-*b*-PDMAEMA triblock copolymer nanoparticles was precipitated into iced *n*-hexane, washed twice with *n*-hexane, and finally dried at room temperature to afford the pale-yellow triblock copolymer.

Characterization

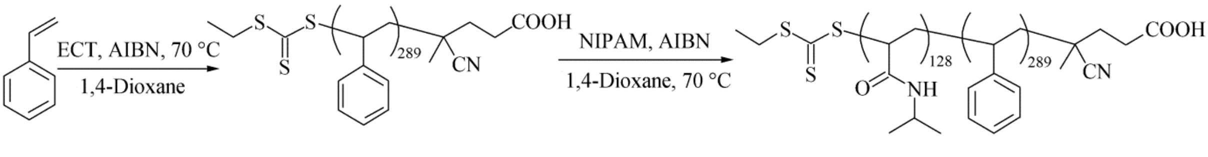
The ^{1}H-NMR measurement was performed on a Bruker Avance III 400 MHz NMR spectrometer using $CDCl_3$ or D_2O as solvent. The GPC measurement was performed on a Waters 600E GPC system equipped with three TSK-GEL columns and a Waters2414 refractive index detector, where THF was used as an eluent at a flow rate of 0.5 $\text{mL}\cdot\text{min}^{-1}$ at 30 °C and polystyrene with the narrow-polydispersity was used as the calibration standard. Triethylamine was added in the eluent of THF to reduce the interaction of the nitrogen-containing polymer with the GPC columns as discussed elsewhere[21]. TEM observation was performed using a JEOL 100CX-Pelectron microscope at an acceleration of 100 kV. The dynamic light scattering (DLS) was performed on a NanoZS90 (Malvern) laser light scattering spectrometer with He-Ne laser at the wavelength of 633 nm at 90°. The phase transition temperature (PTT) of the thermo-responsive polymers was determined by turbidity analysis on a Varian 100 UV-Vis spectrophotometer equipped with a thermo-regulator (± 0.1 °C) at the wavelength of 500 nm. The PTT was determined at the middle point of the transmittance change.

RESULTS AND DISCUSSION

Synthesis of the PS-b-PNIPAM-TTC Diblock Copolymer Macro-RAFT Agent

Scheme 1 shows the synthesis of the diblock copolymer macro-RAFT agent of PS-*b*-PNIPAM-TTC. The PS-

TTC was synthesized by the solution RAFT polymerization of St with a molar ratio of $[\mathrm{St}]_0$:$[\mathrm{ECT}]_0$:$[\mathrm{AIBN}]_0$ = 1800:3:1, and subsequently the PS-*b*-PNIPAM-TTC was synthesized by the solution RAFT polymerization of NIPAM in the presence of PS-TTC macro-RAFT agent with a molar ratio of $[\mathrm{NIPAM}]_0$:$[\mathrm{PS\text{-}TTC}]_0$:$[\mathrm{AIBN}]_0$ = 450:3:1.



Scheme 1 Synthesis of the diblock copolymer macro-RAFT agent of PS_{289}-*b*-PNIPAM_{128}-TTC

The PS-TTC macro-RAFT agent was synthesized *via* the RAFT polymerization of St using ECT as the RAFT agent with a molar ratio of $[\mathrm{St}]_0$:$[\mathrm{ECT}]_0$:$[\mathrm{AIBN}]_0$ = 1800:3:1. The solution RAFT polymerization of St was quenched in 20 h with the monomer conversion of 48.0%. The theoretical number-average molecular weight ($M_{\mathrm{n,th}}$) of PS-TTC is 30.3 kg/mol, corresponding to the degree of polymerization (DP) of 289, in which $M_{\mathrm{n,th}}$ is calculated following Eq. (1) as discussed elsewhere[22]. The molecular weight $M_{\mathrm{n,GPC}}$ of the synthesized PS-TTC is 29.1 kg/mol, which is very close to $M_{\mathrm{n,th}}$. The low PDI value or $Đ$ of 1.11 indicates that the solution polymerization is well controlled (Fig. 1). The ^{1}H-NMR spectrum of PS-TTC is shown in Fig. 2(A). Based on the characteristic proton signals at δ = 7.22−6.26 (the phenylgroup in the backbone of PS-TTC), and the proton signal at δ = 0.88 (the RAFT terminal group), the molecular weight $M_{\mathrm{n,NMR}}$ of the synthesized PS-TTC is calculated to be 33.6 kg/mol. In the subsequent paragraphs, the synthesized PS-TTC is labeled as PS_{289}-TTC, in which the DP 289 is calculated through the theoretical number-average molecular weight $M_{\mathrm{n,th}}$.

$$M_{\mathrm{n,th}} = \frac{[\mathrm{monomer}]_0 \times M_{\mathrm{monomer}}}{[\mathrm{RAFT}]_0} \times \mathrm{conversion} + M_{\mathrm{RAFT}} \tag{1}$$

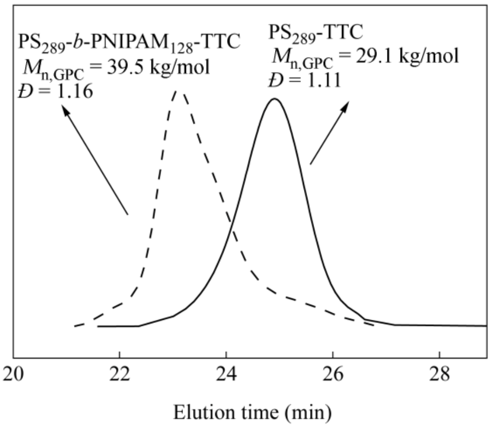


Fig. 1 The GPC traces of the PS_{289}-TTC and PS_{289}-*b*-PNIPAM_{128}-TTC macro-RAFT agents

The PS-*b*-PNIPAM-TTC diblock copolymer macro-RAFT agent was synthesized by the RAFT polymerization of NIPAM in 1,4-dioxane using the above synthesized PS-TTC as the macro-RAFT agent. The PS-*b*-PNIPAM-TTC macro-RAFT agent was characterized by GPC (Fig. 1) and ^{1}H-NMR measurements (Fig. 2). The $M_{\mathrm{n,th}}$ of PS-*b*-PNIPAM-TTC is 44.8 kg/mol, corresponding to DP128. The $M_{\mathrm{n,NMR}}$ of the synthesized PS-*b*-PNIPAM-TTC was calculated by comparing the proton resonance signals at δ= 7.22−6.26 (the phenyl group in the PS block) and the proton resonance signal at δ = 4.00 (the single proton of the isopropyl group) in the PNIPAM block according to the Eq. (S2). The molecular weight $M_{n,GPC}$ and $M_{n,NMR}$ of the synthesized PS-*b*-PNIPAM-TTC are 39.5 and 46.3 kg/mol, respectively. However, the $M_{n,GPC}$ of the synthesized PNIPAM-TTC is lower than $M_{n,th}$ and $M_{n,NMR}$. The reason is possibly due to the adsorption between the PNIPAM block and the GPC columns, although triethylamine is added to the eluent of THF[21]. This diblock copolymer is labeled as PS_{289}-*b*-$PNIPAM_{128}$-TTC, in which the subscripts 289 and 128 calculated by monomer conversion represent the DP of the corresponding blocks.

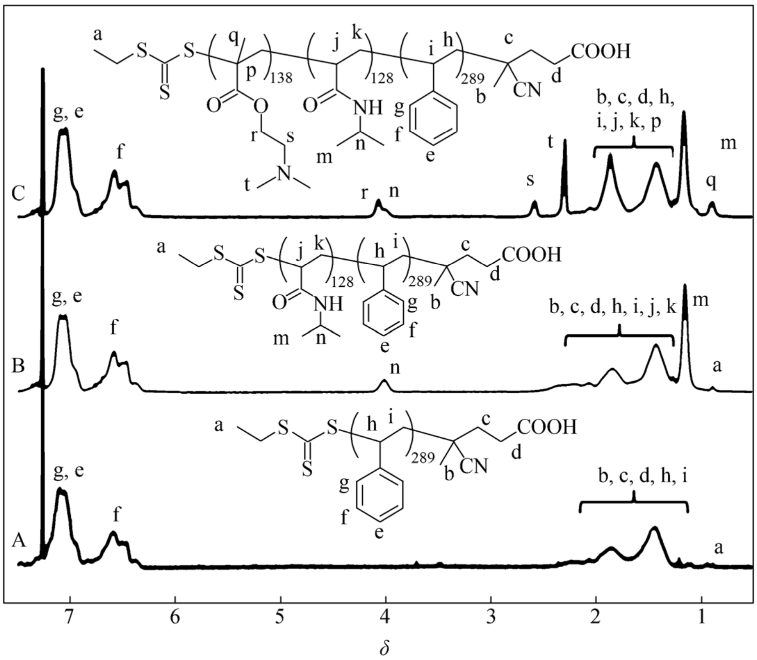


Fig. 2 The ^{1}H-NMR spectra of the PS_{289}-TTC (A), PS_{289}-*b*-$PNIPAM_{128}$-TTC (B) macro-RAFT agents, and PS_{289}-*b*-$PNIPAM_{128}$-*b*-$PDMAEMA_{138}$ triblock copolymer (C)

Preparation of the PS-b-PNIPAM-TTC Seed Nanoparticles

The seed nanoparticles of the PS_{289}-*b*-$PNIPAM_{128}$-TTC diblock copolymer macro-RAFT agent were prepared similarly as discussed elsewhere[21]. The dispersion of the PS_{289}-*b*-$PNIPAM_{128}$-TTC seed nanoparticles at 9.7 wt% can be prepared by dispersing the PS_{289}-*b*-$PNIPAM_{128}$-TTC diblock copolymer in the binary mixture of ethanol/DMAEMA (80/10.3 by weight). The TEM images in Figs. 3(a) and 3(b) show that the diameter of freshly prepared seed nanoparticles is 43 nm on average, which is narrowly distributed. The narrowly distributed seeded nanoparticles are essential to prepare the triblock copolymer with narrowly distributed molecular weight and low *Đ* value in the next seeded RAFT polymerization. Based on the solubility of the PNIPAM block and the PS block in the ethanol/DMAEMA binary mixture, the PS_{289}-*b*-$PNIPAM_{128}$-TTC seed nanoparticles are believed to contain a PNIPAM corona and a PS core, which is shown in Fig. 3(c). Based on the structure of the PS_{289}-*b*-$PNIPAM_{128}$-TTC diblock copolymer (Scheme 1), the Z-group of RAFT terminal/end is located on the outside of the PNIPAM block as shown in Fig. 3(c). Therefore, the soluble PDMAEMA block further extends at the outside of the soluble PNIPAM block, and the PS-*b*-PNIPAM-*b*-PDMAEMA triblock copolymer nanoparticles can be prepared in the seeded RAFT polymerization.

Synthesis of the Thermo-responsive Triblock Copolymer Nanoparticles through the Seeded RAFT Polymerization

The seeded RAFT polymerization of DMAEMA was carried out in ethanol with a molar ratio of $[DMAEMA]_0$:$[PS_{289}$-*b*-$PNIPAM_{128}$-$TTC]_0$:$[AIBN]_0$ = 900:3:1. As discussed previously, the soluble PDMAEMA block further extends on the outside of the soluble PNIPAM block and the RAFT polymerization only takes place in the ethanol solvent, and therefore the seeded RAFT polymerization in this study is similar to the generally homogeneous RAFT polymerization, although the colloidal dispersion is heterogeneous. With increasing monomer conversion during the RAFT polymerization, the newly formed PNIPAM block extends at the homogeneous condition (Scheme 2), and the diblock copolymer seed nanoparticles with a PNIPAM corona convert into triblock copolymer nanoparticles with a diblock PNIPAM-*b*-PDMAEMA corona.

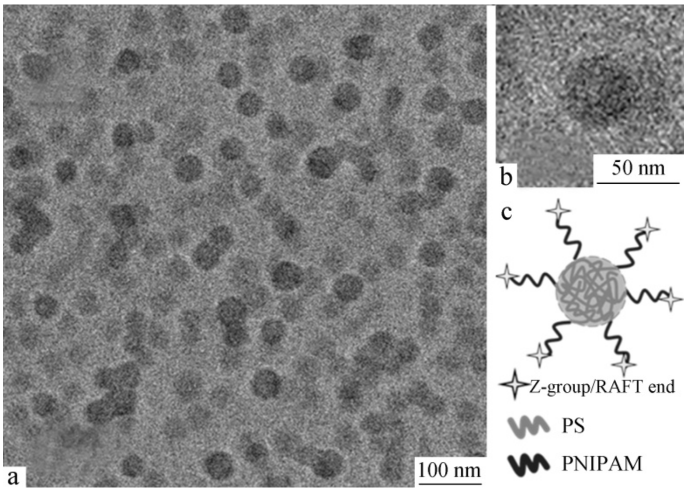
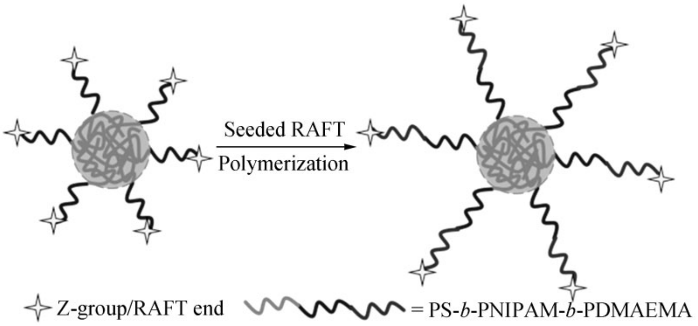
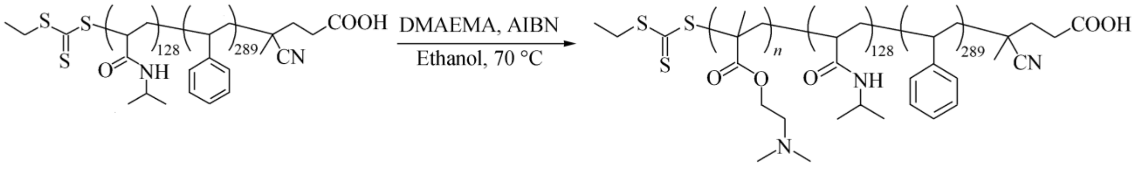


Fig. 3 The TEM images (a, b) and the expected schematic structure (c) of the PS_{289}-*b*-$PNIPAM_{128}$-TTC seed nanoparticles dispersed in the ethanol/DMAEMA binary mixture



Scheme 2 Schematic illustration of the *in situ* synthesis of the PS-*b*-PNIPAM-*b*-PDMAEMA triblock copolymer nanoparticles through the seeded RAFT polymerization

The kinetics of the seeded RAFT polymerization of DMAEMA in ethanol was carried out as shown in Scheme 3. The results are shown in Figs. 4(a) and 4(b). Figure 4(a) shows the relationship of monomer conversion versus polymerization time for the typical seeded RAFT polymerization in the presence of the macro-RAFT agent of PS_{289}-*b*-$PNIPAM_{128}$-TTC. The monomer conversion increased with the polymerization time and it finally reached 64.2% in 20 h, and further increasing the polymerization time only led to a slight increase in the monomer conversion. In Fig. 4(b), the seeded RAFT polymerization exhibits a pseudo-first-order kinetics similar to the other homogeneous RAFT polymerization as reported elsewhere[23, 24]. Figure 4(c) shows the GPC traces of the PS_{289}-*b*-$PNIPAM_{128}$-*b*-PDMAEMA triblock copolymers synthesized at different monomer conversion in the seeded RAFT polymerization. Based on the GPC analysis, the $M_{n,GPC}$ and $Đ$ value of the PS_{289}-*b*-$PNIPAM_{128}$-*b*-PDMAEMA triblock copolymers are obtained and the values are summarized in Fig. 4(d). It is found that the $M_{n,GPC}$ of the PS-*b*-PNIPAM-*b*-PDMAEMA triblock copolymer increases with the monomer conversion and the $Đ$ values of the triblock copolymer are all below 1.35. The PS-*b*-PNIPAM-*b*-PDMAEMA triblock copolymers are characterized by ^{1}H-NMR analysis as well, and Fig. 2(C) shows the spectrum of the typical PS_{289}-*b*-$PNIPAM_{128}$-*b*-$PDMAEMA_{138}$ triblock copolymer. The $M_{n,NMR}$ of the PS-*b*-PNIPAM-*b*-PDMAEMA triblock copolymer was calculated by comparing the proton resonance signals at $\delta = 7.22–6.26$ and 4.22–3.88 according to the Eq. (S3) in the supporting information. It is found that $M_{n,NMR}$ of the triblock copolymer is larger than $M_{n,GPC}$ by GPC analysis (Fig. 4d). This is due to the strong interaction between the triblock copolymer and the GPC columns, although triethylamine is added to the THF eluent.



Scheme 3 Seeded RAFT polymerization of DMAEMA monomer to synthesize the PS-*b*-PNIPAM-*b*-PDMAEMA triblock copolymer nanoparticles

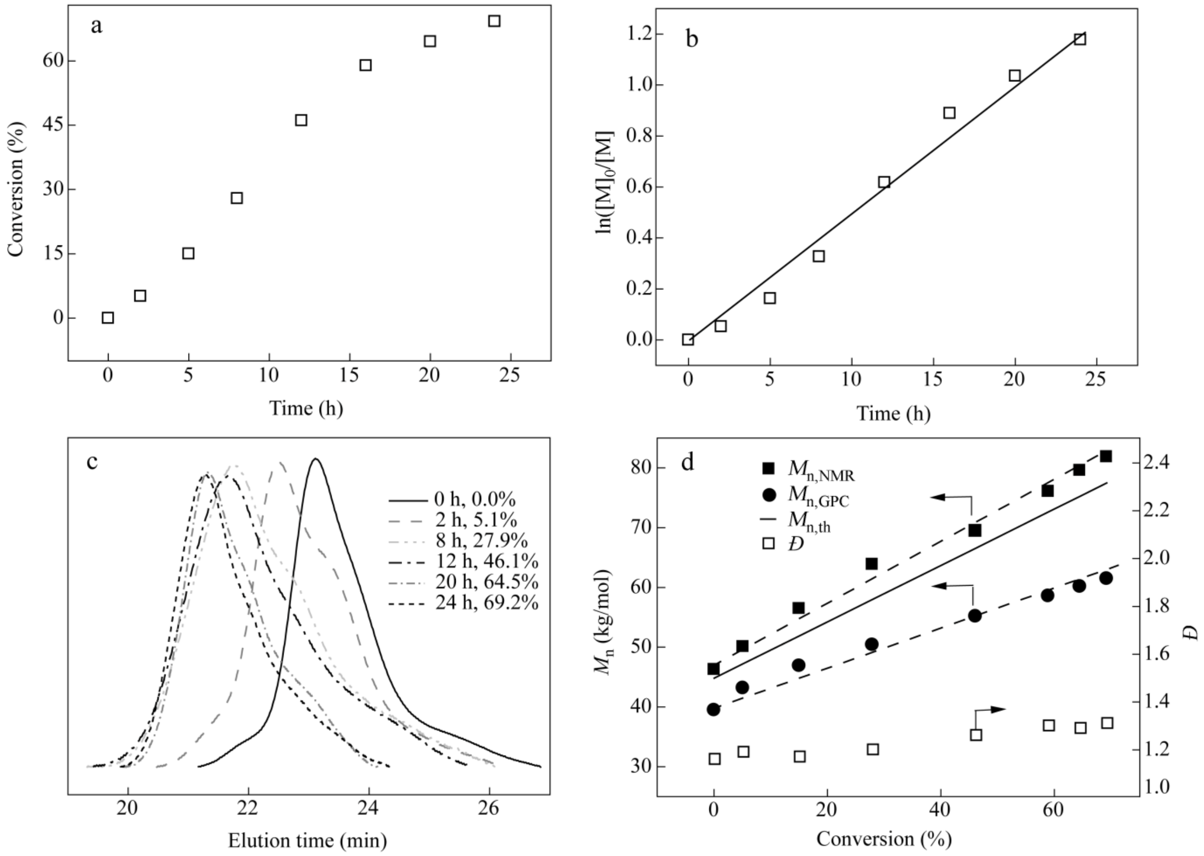


Fig. 4 The monomer conversion-time plot (a), and the ln($[M]_0$/[M])-time plot (b) for the seeded RAFT polymerization of DMAEMA in the presence of the seed-nanoparticles of PS_{289}-*b*-$PNIPAM_{128}$-TTC; the GPC traces (c) and the evolution of molecular weight and *Đ* value (d) of the synthesized PS-*b*-PNIPAM-*b*-PDMAEMA triblock copolymers

To view the morphology of the PS-*b*-PNIPAM-*b*-PDMAEMA triblock copolymer nanoparticles, the triblock copolymer nanoparticles synthesized in ethanol were transferred into water by dialysis against water for three days (molecular weight cutoff: 12–14 kDa). It has been reported[3–5] previously that the transformation of the triblock copolymer nanoparticle from ethanol into water does not change the morphology of the corona-core triblock copolymer nanoparticles, since they may be somewhat frozen in ethanol or neat water at room temperature.

The seeded RAFT polymerization of DMAEMA in the presence of PS-*b*-PNIPAM-TTC seed nanoparticles allows the *in situ* preparation of the PS-*b*-PNIPAM-*b*-PDMAEMA triblock copolymer nanoparticles at a high concentration. These triblock copolymer nanoparticles can stably dispersed in ethanol and neat water for a long time. Figure 5 shows the TEM images of the PS-*b*-PNIPAM-*b*-PDMAEMA triblock copolymer nanoparticles synthesized through the seeded RAFT polymerization at different polymerization time, in which uniform nanospheres can be observed. By statistical analysis of over 100 nanoparticles in the TEM images, the average diameter D_{TEM} of the triblock copolymer nanoparticles is evaluated. It is found that the average diameter D_{TEM} of the PS-*b*-PNIPAM-*b*-PDMAEMA triblock copolymer nanoparticles are within 44–47 nm, and there seems no influence from the length of the third PDMAEMA block on D_{TEM}. As discussed elsewhere[25–30], for the general corona-core nanoparticles in the TEM images, only the insoluble core could be observed and the soluble corona of the solvophilic block was usually hard to be detected. As shown in Scheme 2, in the structure of PS-*b*-PNIPAM-*b*-PDMAEMA nanoparticles, the insoluble PS block forms the core and the soluble PNIPAM-*b*-PDMAEMA diblock forms the corona. Thus, the TEM images shown in Fig. 5 reflect the solvophobic PS core in the PS-*b*-PNIPAM-*b*-PDMAEMA corona-core nanoparticles. The PS-*b*-PNIPAM-*b*-PDMAEMA triblock copolymer nanoparticles are also characterized by DLS analysis. As shown in Fig. 6, the hydrodynamic diameter D_{h} of the PS-*b*-PNIPAM-*b*-PDMAEMA nanoparticles increases from 151 nm to 261 nm with different polymerization time. Based on the constant D_{TEM} of the solvophobic core and the increasing D_{h} of the nanoparticles with extending of third solvophilic PDMAEMA block, the corona-core structure of the PS-*b*-PNIPAM-*b*-PDMAEMA nanoparticles are proposed and shown in Scheme 2. The *D* of the triblock copolymer nanoparticles by DLS analysis was much larger than that from the TEM observation. This is because DLS analysis detects the solvated nanoparticles, while TEM detects the nanoparticles in the dry state as discussed elsewhere[3–5].

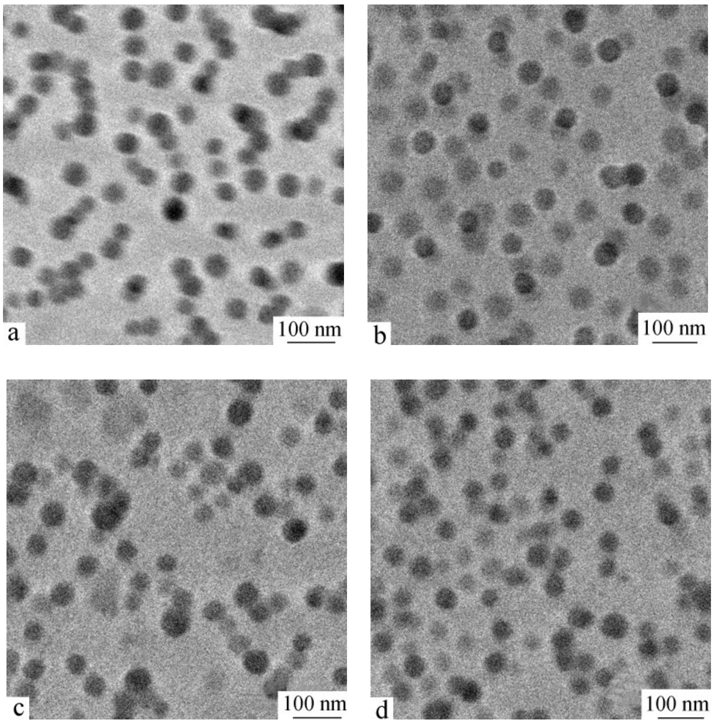


Fig. 5 TEM images of the triblock copolymer nanoparticles of PS_{289}-*b*-$PNIPAM_{128}$-*b*-$PDMAEMA_{15}$ (a), PS_{289}-*b*-$PNIPAM_{128}$-*b*-$PDMAEMA_{84}$ (b), PS_{289}-*b*-$PNIPAM_{128}$-*b*-$PDMAEMA_{177}$ (c), and PS_{289}-*b*-$PNIPAM_{128}$-*b*-$PDMAEMA_{208}$ (d) at polymerization time of 2, 8, 16 and 24 h, respectively

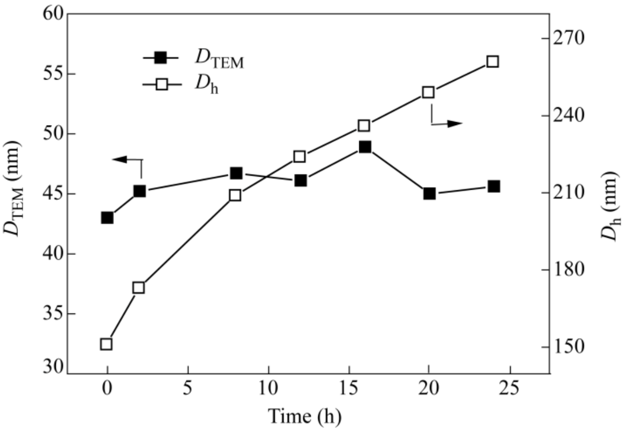


Fig. 6 Evolution of the average diameter D_{TEM} by TEM observation and the average diameter D_h by DLS analysis of the PS_{289}-*b*-$PNIPAM_{128}$-*b*-PDMAEMA nanoparticles synthesized at different polymerization time

Double Thermo-response of the PS-b-PNIPAM-b-PDMAEMA Triblock Copolymer Nanoparticles

The PS-*b*-PNIPAM-*b*-PDMAEMA nanoparticles contain two thermo-responsive blocks of PNIPAM and PDMAEMA, and therefore it is expected that the nanoparticles can exhibit a double temperature-sensitive response in aqueous solution. The solution containing nanoparticles were diluted with distilled water to about 0.1 wt% polymer concentration, and then the transmittance of the aqueous dispersion of the PS-*b*-PNIPAM-*b*-PDMAEMA triblock copolymer nanoparticles was detected at a given temperature.

Figure 7 shows the thermo-response behaviour of the aqueous solutions of the reference $PNIPAM_{92}$ and $PDMAEMA_{96}$ homopolymers (See the synthesis in the supporting information) and the aqueous dispersion of the PS_{289}-*b*-$PNIPAM_{128}$-*b*-$PDMAEMA_{138}$ nanoparticles. (Note: herein the pH value of the aqueous solution or dispersion was set at pH = 8). As shown in Figs. 7(A) and 7(B), at low temperatures, a relatively high transmittance is observed, then followed by a sharp decrease in the transmittance at 29.7 °C for the $PNIPAM_{92}$ homopolymer and at 34.0 °C for the $PDMAEMA_{96}$ homopolymer, respectively, indicating the sharp phase transitions. For the aqueous dispersion of the PS_{289}-*b*-$PNIPAM_{128}$-*b*-$PDMAEMA_{138}$ nanoparticles shown in Fig. 7(C), two separate phase transition temperatures (PTTs) are clearly observed. The two PTTs at 37 and 52 °C corresponding to the PNIPAM block and the PDMAEMA block, respectively. Further increasing the temperature leads to the precipitation of the nanoparticles. Compared with the reference homopolymers of $PNIPAM_{92}$ (29.7 °C) and $PDMAEMA_{96}$ (37 °C), the first PTT of the PNIPAM block (37 °C) and the second PTT of the PDMAEMA block (52 °C) attached on the PS core of the triblock copolymer nanoparticles shift to high values. Besides, the thermo-responsive transition of the PNIPAM and PDMAEMA blocks in the triblock copolymer nanoparticles takes place within a relatively broad temperature range. The reason is possibly due to the steric-hindrance effect among the crowded PNIPAM and PDMAEMA chains attached on the PS core of the triblock copolymer nanoparticles[3, 5].

The thermo-responsive behaviour of the PS_{289}-*b*-$PNIPAM_{128}$-*b*-$PDMAEMA_{138}$ triblock copolymer nanoparticles was further studied by the variable temperature ^{1}H-NMR analysis. As shown by the ^{1}H-NMR spectra in Fig. 8, the characteristic proton signals ascribed to the two thermo-responsive blocks of PNIPAM and PDMAEMA are clearly observed at 30 °C, suggesting that both of the PNIPAM and PDMAEMA blocks are soluble at this temperature below the PTT of the PNIPAM block. (Note: the PS block is solvophobic in D_2O and a very weak signal can be detected, which is not discussed herein). From Fig. 8, it can be clearly seen that, when the temperature increases from 30 °C to 45 °C, the signals ascribed to the PNIPAM block almost disappear, while the signals ascribed to the PDMAEMA block remain unchanged or slightly decrease, indicating the shrinkage of the PNIPAM block. When the temperature increases from 45 °C to 65 °C, the signals ascribed to the PDMAEMA block become weaken, suggesting the soluble-to-insoluble phase transition of the PDMAEMA block. This result confirms the two-step phase transition of the PNIPAM block and the PDMAEMA block in the

PS_{289}-*b*-$PNIPAM_{128}$-*b*-$PDMAEMA_{138}$ triblock copolymer nanoparticles.

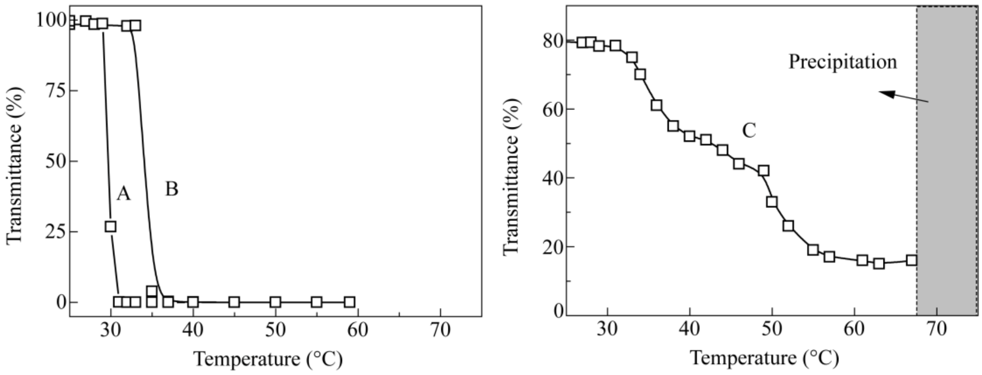


Fig. 7 Temperature dependent transmittance of the 0.1 wt% aqueous solution (pH = 8) of the homopolymers of $PNIPAM_{92}$ (A) and $PDMAEMA_{96}$ (B), and the 0.1 wt% aqueous dispersion (pH = 8) of the PS_{289}-*b*-$PNIPAM_{128}$-*b*-$PDMAEMA_{138}$ triblock copolymer nanoparticles (C)

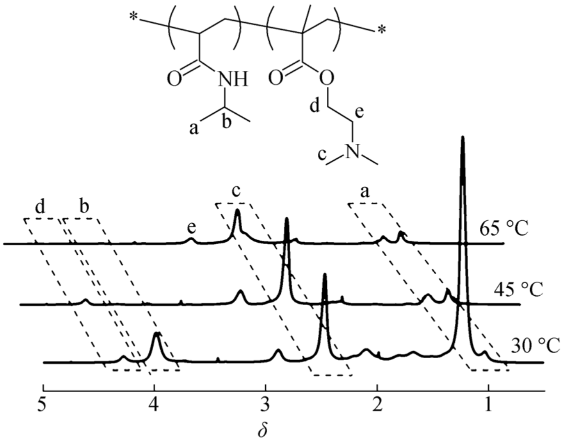


Fig. 8 Temperature-dependent ^{1}H-NMR spectra of the PS_{289}-*b*-$PNIPAM_{128}$-*b*-$PDMAEMA_{138}$ nanoparticles dispersed in D_2O

The thermo-responsive behaviour of the PS_{289}-*b*-$PNIPAM_{128}$-*b*-$PDMAEMA_{138}$ triblock copolymer nanoparticles in water was further detected by DLS analysis. Before the DLS analysis, the dispersion of the nanoparticles were diluted with water to about 0.01 wt% polymer concentration to avoid the formation of nanoparticle-clusters or inter-nanoparticle aggregation during temperature increasing. Figure 9 shows the hydrodynamic diameter (D_h) of the synthesized PS_{289}-*b*-$PNIPAM_{128}$-*b*-$PDMAEMA_{138}$ nanoparticles at 30 °C (below the first PTT), 45 °C (above the first PTT) and 65 °C (above the second PTT). It is found that the nanoparticles in water are also distributed narrowly at the set temperatures. The hydrodynamic diameter D_h decreases when the temperature increases above the first PTT, and further decreases at the temperature above the second PTT. This result confirms the existence of the two-step phase transition/shrinkage during temperature increasing.

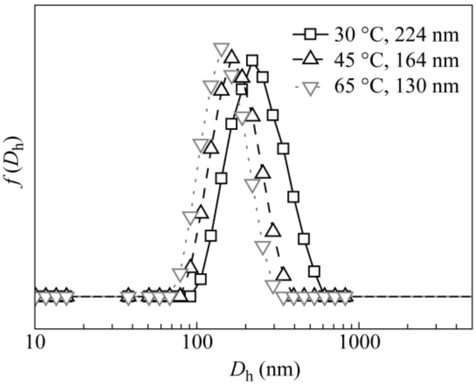
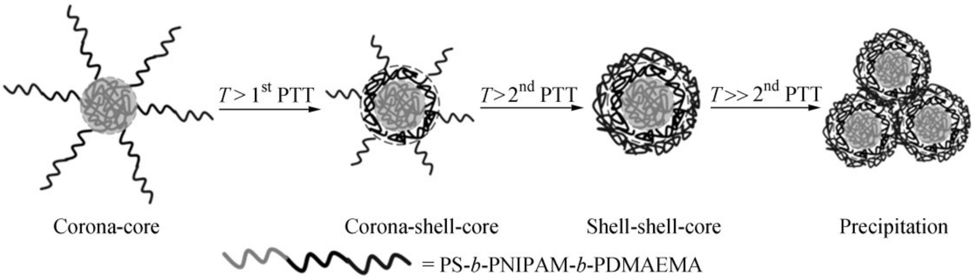


Fig. 9 Hydrodynamic diameter distribution $f(D_h)$ of the PS_{289}-*b*-$PNIPAM_{128}$-*b*-$PDMAEMA_{138}$ nanoparticles dispersed in water at 30, 45 and 65 °C, respectively

Based on the results obtained from turbidity, ^{1}H-NMR and DLS analysis, the two-step shrinkage/phase transition behaviour with increasing temperature can be illustrated as shown in Scheme 4. That is, when the temperature increases above the first PTT corresponding to the PNIPAM block, the middle PNIPAM block becomes dehydrated and collapses onto the PS core to form the nanoparticles with a corona-shell-core structure with the solvophobic PS block as the core, the dehydrated PNIPAM block as the shell and the outer PDMAEMA block as the corona. When the temperature increases above the second PTT corresponding to the PDMAEMA block, the PDMAEMA block further collapses onto the PNIPAM shell to form a shell-shell-core structure. With further increasing the temperature, the shell-shell-core nanoparticles aggregate and the precipitation occurs. The thermo-responsive behavior of the PS-*b*-PNIPAM-*b*-PDMAEMA triblock copolymer nanoparticles matches well with the PNIPAM-*b*-PDMAEMA-*b*-PS triblock copolymer nanoparticles as reported elsewhere[3, 5].



Scheme 4 Schematic illustration of the double thermo-responsive behaviour of the PS-*b*-PNIPAM-*b*-PDMAEMA nanoparticles dispersed in water during the temperature increasing

CONCLUSIONS

The seeded RAFT polymerization is successfully employed as a method to synthesize the doubly thermo-responsive nanoparticles, in which the PS-*b*-PNIPAM-TTC diblock copolymer nanoparticles are used as the seed. In the seeded RAFT polymerization, the third thermo-responsive PDMAEMA block is successfully introduced, and the triblock copolymer nanoparticles of PS-*b*-PNIPAM-*b*-PDMAEMA containing two thermo-responsive blocks are prepared. The seeded RAFT polymerization shows a pseudo-first-order kinetics, and the molecular weight of the synthesized triblock copolymers increases linearly with the monomer conversion. The synthesized nanoparticles are characterized by TEM and DLS, and the corona-core structure containing a solvophobic PS core and a solvophilic corona of PNIPAM-*b*-PDMAEMA block is confirmed. The double thermo-response behavior of the nanoparticles is confirmed by turbidity analysis, variable temperature ^{1}H-NMR analysis, and DLS analysis, from which the two-step shrinkage process during the temperature increasing is proposed. This strategy is believed to be a valid method to prepare the doubly thermo-responsive triblock copolymer nanoparticles.

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