One-Pot Synthesis of Thermoresponsive Cellulose-Based Miktoarm Graft Copolymer by Simultaneous ATRP and ROP

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ABSTRACT: In this work, we report a one-pot synthesis of amphiphilic miktoarm cellulose graft copolymers, cellulose (-*graft*-oligo(L-lactide))-*graft*-oligo(*N*-isopropylacrylamide) (Cell(-*g*-OLLA)-*g*-ONIPAM), with dual side chains of oligo(L-lactide) and oligo(*N*-isopropylacrylamide) using 2-bromoisobutyl bromide functionalized cellulose (Cell(-OH)-Br) as the macroinitiator, by simultaneously conducting ring-opening polymerization and atom transfer radical polymerization using Cu/CuBr/PMDETA/$Sn(Oct)_2$ as the catalytic system. The chemical structures and thermal properties of Cell(-*g*-OLLA)-*g*-ONIPAMs were characterized with ^{1}H and ^{13}C nuclear magnetic resonance spectroscopy, differential scanning calorimetry and thermal gravimetric analysis. Cell (-*g*-OLLA)-*g*-ONIPAM could self-assemble into micelles in the aqueous solution as confirmed by environmental scanning electron microscopy and dynamic light scattering analyses. The micellar aggregates showed a temperature-responsive property and the sizes of micelles were influenced by the ratio of temperature-responsive ONIPAM side chains. The miktoarm graft copolymers have potential applications as biomedical or intelligent materials.

KEYWORDS: Cellulose, graft copolymer, self-assembly, thermoresponsive

1 INTRODUCTION

With the consumption and depletion of fossil oil, there has been a growing interest in the development of sustainable materials derived from renewable resources in recent years [1]. Cellulose is the most abundant biopolymer on earth and is composed of several hundred to over ten thousand β-1, 4-linked D-glucose units, which impart cellulose with unique physical and chemical properties. It has been widely used in membranes [2] and pharmaceuticals [3] due to the nontoxicity, biocompatibility and mechanical strength; however, the intrinsic disadvantages of cellulose, such as its extremely poor solubility in water and many common organic solvents and poor processability, limit its application. Efforts have been made to overcome these disadvantages and to improve the physical properties of cellulose, e.g., chemical modification [4], enzymatic treatment [5], and blending with other materials [6]. Among these efforts, chemical modification by grating synthetic polymers is an effective method to develop cellulose-based hybrid materials [7]. In general, three widely used grafting approaches have been reported for cellulose modification such as ring-opening polymerization (ROP) [8,9], atom transfer radical polymerization (ATRP) [10] and click chemistry [11].

Recently, amphiphilic graft copolymers with stimuli-responsive properties have attracted great interest because these intelligent macromolecules can respond to external stimuli such as pH value [12,13], temperature [14] and light [15]. Temperature is regarded as the most convenient approach to manipulating the assembly of copolymers and has been a widely used stimulus in drug or gene delivery [16], smart bioactive surfaces [17] and molecular recognition agents [18]. The commonly used temperature-responsive moieties include PNIPAM [19] and oligo(ethylene glycol) [20]. Bokias and coworkers [21] synthesized thermoresponsive graft copolymer, carboxymethylcellulose-*g*-poly(*N*-isopropylacrylamide), which showed a thermothickening property in a very large pH region, ranging from alkaline solutions down to pH=3. When Wei and coworkers [22] connected the PNIPAM to the surface of hydroxyapatite (HA) nanoparticles (PNIPAM-*g*-HA) by ATRP,

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the particle size reversibly changed with the change of temperature, which was around 1100 nm at 25°C following by a decrease to 300 nm at 40°C. Yuan and coworkers [23] prepared an ethyl cellulose (EC) graft copolymer, EC-*graft*-poly(2-(2-methoxyethoxy)ethyl methacrylate)-co-oligo(ethylene glycol) methacrylate), which showed response to the change of temperature and with a cloud point of about 37.4°C. Chen and coworkers [24] prepared a new thermoresponsive pegylated poly-L-glutamate (poly-L-EG_xGlu), where x (= 2, and 3) represents the repeat unit oligoethylene glycol at the side chain. The results suggested that the poly-L-EG_2Glu and poly-L-EG_3Glu had a lower critical solution temperature (LCST) of about 32 and 57°C, respectively.

In this article, the aim of the study was to develop a system where cellulose could be grafted by one-pot synthesis that could simplify experimental procedure. We designed and synthesized an amphiphilic miktoarm cellulose graft copolymer, cellulose(-*graft*-oligo(L-lactide))-*graft*-oligo(N-isopropylacrylamide) (Cell(-*g*-OLLA)-*g*-ONIPAM), using Cell(-OH)-Br as the macroinitiator at 120°C (Scheme 1) in one pot via simultaneous ATRP and ROP. We studied the assembly behavior of Cell(-*g*-OLLA)-*g*-ONIPAM in a selective solvent by SEM and DLS. Cell(-*g*-OLLA)-*g*-ONIPAM micellles showed a temperature-responsive behavior and the sizes of micelles reversibly changed with the change of temperature.

2 EXPERIMENTAL

2.1 Materials

Cellulose (powder, cotton linters) was obtained from Sigma-Aldrich (product no. C6288) and dried at 140°C for 2 h under vacuum before use. *N*-isopropylacrylamide (NIPAM) was purchased from Sigma-Aldrich, recrystallized in hexane, and dried under vacuum before use. 2-bromoisobutyl bromide, *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMDETA), copper(I) bromide and stannous octoate ($Sn(Oct)_2$, 95%) were purchased from Aladdin and used as received. *N*,*N*′-dimethylacetamide (DMAc), triethylamine and dioxane were distilled after drying with CaH_2. L-Lactide (L-LA) was purchased from Purac, Holland. All other materials were used without further purification.

2.2 Measurement

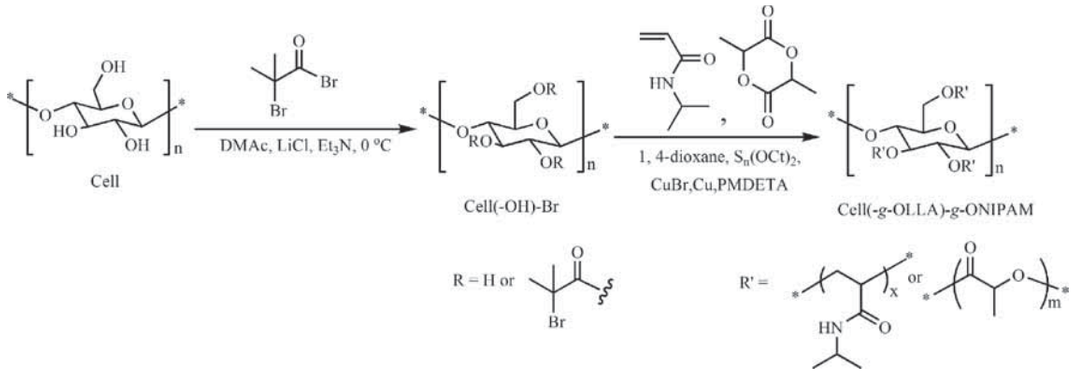
The ^1H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AV300 NMR spectrometer in chloroform-d ($CDCl_3$) and dimethyl sulfoxide-d_6 (DMSO-d_6). Gel permeation chromatography (GPC) measurements were carried out at 35°C with a Waters 1515 GPC instrument and Waters 2414 refractive index detector. THF was used as the eluent at a flow rate of 1 mL·min^{-1}. The molecular weights were calibrated with polystyrene standards. The thermal stability was estimated by thermal gravimetric analysis (TGA) (TA Instrument Q500) under nitrogen atmosphere. The measurements were performed incrementally (10°C/min) from 50°C up to 600°C. Differential scanning calorimetry (DSC) was carried out on a TA Instrument Q100 under nitrogen atmosphere. The samples were heated to 200°C followed by cooling to 0°C in the first cycle and then heated to 200°C at 10°C/min. The size distribution of micelles was determined by dynamic light scattering (DLS) techniques. The experiments were performed on a DLS (Wyatt-QUELS) equipped with a vertically polarized He–Ne laser (DAWN EOS, Wyatt Technology). Environmental scanning electron microscopy (SEM) was performed using an XL 30 ESEM FEG scanning electron microscope (Micron FEI Philips).

2.3 Synthesis of Difunctional Cellulose-Based Macroinitiator (Cell(-OH)-Br) (Scheme 1)

Dry cellulose (0.5 g, AUG 3.09 mmol) was suspended in 30 mL of DMAc, and the mixture was heated at 150°C for 2 h. After the slurry was cooled to 80°C, 1.9 g of anhydrous LiCl was added and the mixture was stirred at 80°C for 12 h. Cellulose was completely dissolved after the mixture was cooled down to room temperature under stirring. After the addition of triethylamine (0.69 g, 6.79 mmol) into the cellulose solution at room temperature, the mixture was cooled below 10°C in an ice/water bath. Subsequently, 2-bromoisobutyryl bromide (1.42 g, 6.17 mmol) in anhydrous DMAc (10 mL) was added dropwise into the mixture within 30 min. After addition, the mixture was stirred for an additional 24 h at room temperature and then precipitated into deionized water. The precipitate was dissolved in DMAc and reprecipitated into deionized water. The precipitation process was repeated three times and the Cell(-OH)-Br was obtained after filtration and dried in 50°C under vacuum to give 0.9 g. The degree of substitution (DS) of Cell(-OH)-Br was determined by ^1H NMR according to our previous work [13]. DS_{Br} and DS_{OH} were 1.31 and 1.69, respectively.

2.4 One-Pot Synthesis of Cell(-*g*-OLLA)-*g*-ONIPAM Miktoarm Graft Copolymer (Scheme 1)

The target miktoarm graft copolymer, Cell(-*g*-OLLA)-*g*-ONIPAM, was obtained in a one-pot manner by simultaneously conducting ATRP of NIPAM and ROP of L-LA using Cu/CuBr/PMDETA/$Sn(Oct)_2$ as the catalyst



Scheme 1 One-pot synthesis of amphiphilic miktoarm graft copolymer via simultaneous ATRP and ROP.

system. The procedure for the synthesis of Cell(-*g*-OLLA)-*g*-ONIPAM-1 was given as an example (Scheme 1). Cell (-OH)-Br (0.3 g, Br 0.81 mmol, OH 1.04 mmol), NIPAM (1 g, 8.84 mmol), L-LA (1 g, 6.94 mmol) and PMDETA (0.41 g, 2.43 mmol) were dissolved in 10 mL of dry dioxane. The mixed solution was degassed by three freeze-thaw cycles. CuBr (0.12 g, 0.81 mmol) and $Sn(Oct)_2$ (5 mg/mL in dry dioxane, 1 mL, 0.01 mmol) were introduced into the mixed solution under the protection of N_2 flow. The polymerization was performed at 120°C for 12 h under nitrogen. After filtration, the filtrate was precipitated into deionized water with vigorous stirring. The precipitate was dissolved in THF and dialyzed against tetrahydrofuran (THF) for 4 days using the dialysis membrane (cut-off M_w = 3500 g/mol). The solution was concentrated and precipitated into deionized water to yield a white powder (1.2 g).

2.5 Self-Assembly of Cell(-*g*-OLLA)-*g*-ONIPAM Graft Copolymers

Cell(-*g*-OLLA)-*g*-ONIPAM powders (1 mg) were dissolved in THF (25 mL). Deionized water (25 mL) was added dropwise to the solution under stirring and the solution was sequentially stirred for 24 h. Samples for SEM characterization were prepared by spin-coating from the above solution at two temperatures: 25 and 40°C. DLS measurements were performed at 25 and 40°C.

3 RESULTS AND DISCUSSION

3.1 Synthesis and Characterization of Cell(-*g*-OLLA)-*g*-ONIPAM by ATRP and ROP

The procedure for the synthesis of Cell(-*g*-OLLA)-*g*-ONIPAM is shown in Scheme 1. Difunctional macroinitiator, Cell(-OH)-Br, was synthesized by coupling hydroxyl groups on cellulose with 2-bromoisobutyryl bromide [25]. Cell(-OH)-Br bears hydroxyl groups and bromine moieties that can be employed for ROP and ATRP, respectively. The successful attachment of the 2-bromoisobutyryl group on cellulose was confirmed by ^{1}H NMR and ^{13}C NMR spectra. As shown in Figure 1a, the formation of 2-bromoisobutyryl ester on cellulose was confirmed with the emergence of a broad peak around 1.75 ppm, attributed to the methyl groups of 2-bromoisobutyryl group. In addition, the ^{13}C NMR spectrum of Cell(-OH)-Br is shown in Figure 1b. Signals corresponding to the carbons of 2-bromoisobutyryl group (Figure 1b, signal "7–9") and the cellulose carbons (Figure 1b, signal "1–6") were oberserved in the spectrum of Cell(-OH)-Br. The amount of bromine in Cell(-OH)-Br was determined by ^{1}H NMR analysis according to the reported procedure [13]. The DS_{Br} of the Cell(-OH)-Br was measured to be 1.31.

The target miktoarm graft copolymer, Cell(-*g*-OLLA)-*g*-ONIPAM, was then synthesized in one-pot by simultaneously conducting ATRP of NIPAM and ROP of L-LA. Cu/CuBr/PMDETA and $Sn(Oct)_2$ have been widely used as catalysts for ATRP and ROP, respectively. Zhang and coworkers combined ATRP and ROP in one-pot to synthesize ABC miktoarm PS(-*b*-PCL)-*b*-PDMA copolymers using Cu/CuBr/PMDETA and $Sn(Oct)_2$ cocatalyst system [26], suggesting that these two catalysts are compatible. We performed ATRP of NIPAM and ROP of L-LA from Cell(-OH)-Br dual initiators using the Cu/CuBr/PMDETA/$Sn(Oct)_2$ catalytic system at 120°C under a nitrogen atmosphere. ATRP of NIPAM did not interfere with ROP of L-LA, which allows simultaneous controlled polymerization of these two monomers to provide well-defined graft copolymers. Two Cell(-*g*-OLLA)-*g*-ONIPAMs were synthesized with different monomer feed ratios. Figure 2 shows the ^{1}H NMR spectrum of Cell(-*g*-OLLA)-*g*-ONIPAM-2 graft copolymer. In the ^{1}H NMR spectrum, the broad peaks at

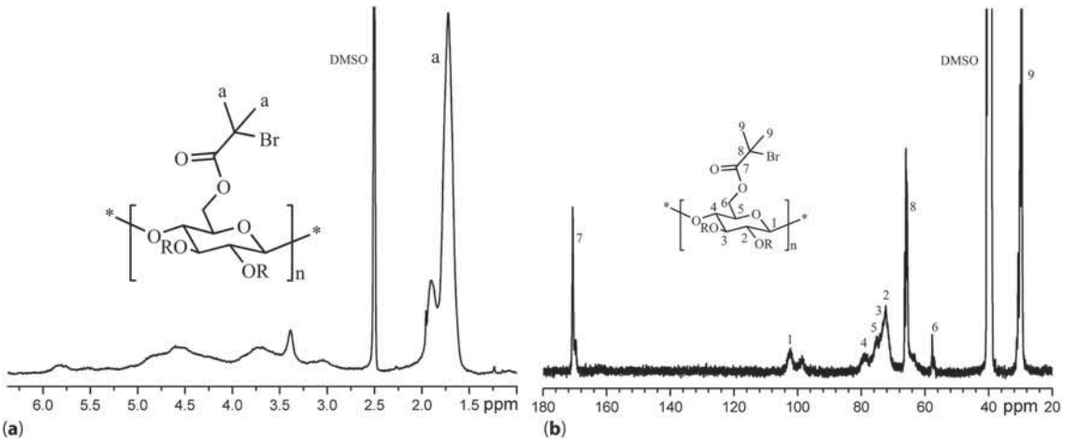


Figure 1 (**a**) ^{1}H NMR and (**b**) ^{13}C NMR spectra of Cell(-OH)-Br.

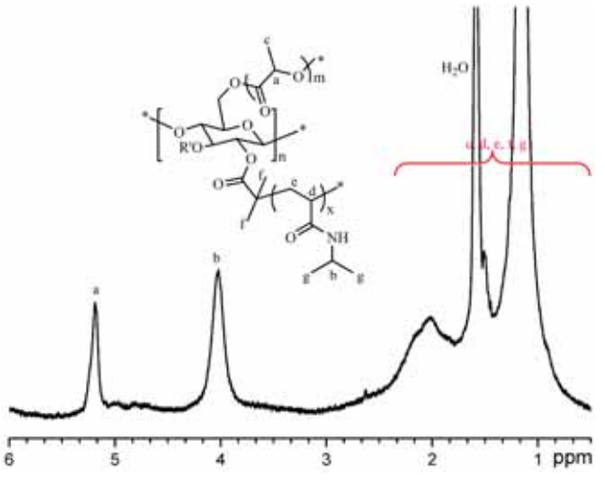


Figure 2 ^{1}H NMR spectrum of Cell(-*g*-OLLA)-*g*-ONIPAM-2 graft copolymers.

5.3 and 4.0 ppm were assigned to the methine protons in OLLA and ONIPAM, respectively. The molar ratio of the lactyl unit from OLLA to the amide group from ONIPAM was calculated using:

$$\frac{\text{mole}(\text{lactyl unit})}{\text{mole}(\text{amide group})} = \frac{I_a}{I_b}$$

where I_a is the integration area of the methine proton in OLLA side chains, and I_b is the integration area of the methine proton of the amide group in ONIPAM side chains. The molecular weights of OLLA and ONIPAM side chains were calculated based on their mass ratios to cellulose and DS. The characterization data of Cell(-*g*-OLLA)-*g*-ONIPAMs are summarized in Table 1. The molecular weights of Cell(-*g*-OLLA)-*g*-ONIPAM were measured by GPC and the results are summarized in Table 1.

3.2 Thermal Properties of the Cell (-*g*-OLLA)-*g*-ONIPAM Copolymers

The glass transition temperature (T_g) of Cell(-*g*-OLLA)-*g*-ONIPAM copolymers was characterized using DSC, as shown in Figure 3. Both Cell(-*g*-OLLA)-*g*-ONIPAMs had one T_g around 110°C, which is significantly lower than the Tg of high molecular weight PNIPAM (130°C), for ONIPAM side chains. We did not observe the T_g of OLLA chains because they were too small.

The thermal stability of Cell(-*g*-OLLA)-*g*-ONIPAM copolymers, Cell(-OH)-Br and cellulose was characterized by TGA (Figure 4). The onset degradation temperature of pure cellulose was 330°C. Compared with pure cellulose, the thermal stability of Cell(-OH)-Br decreased significantly and its onset degradation temperature was 262°C, which resulted from the introduction of relatively unstable 2-bromoisobutyryl groups. The Cell(-*g*-OLLA)-*g*-ONIPAM copolymers clearly had two decomposition stages. The first weight loss step started at 205°C, which is attributed to the degradation of cellulose main chains and OLLA side chains. The subsequent weight loss step started at 313°C, which is attributed to the degradation of the ONIPAM side chains.

3.3 Self-Assembly of Cell(-*g*-OLLA)-*g*-ONIPAM Graft Copolymers

The assembly behaviors of Cell(-*g*-OLLA)-*g*-ONIPAM in solutions were studied at two different temperatures by SEM and DLS. Cell(-*g*-OLLA)-*g*-ONIPAM self-assembled into micelles when deionized water was added into its THF solution. The hydrophobic cellulose backbone and OLLA side chains were mainly in the core of the micelles, whereas the hydrophilic ONIPAM side chains were in the corona of the

Table 1 Summary of structure parameters of Cell(-OH)-Br and grafted copolymers.

Samples	Feed mole ratio [L-LA]/[NIPAM]	Molar ratio of lactyl units/amide groups in polymers[a]	$M_{n,OLLA}$ (Da)[b]	$M_{n,OPNIPAM}$ (Da)[b]	$M_{n,GPC}$ (kDa)[c]	M_w/M_n[c]
Cell(-OH)-Br	-	-	-	-	45.1	2.7
Cell(-*g*-OLLA)-*g*-ONIPAM-1	1.6:1	2.1:1	500	400	11.8	2.2
Cell(-*g*-OLLA)-*g*-ONIPAM-2	1:1.3	1:1.9	500	1400	8.5	1.8

[a] Determined by ^{1}H NMR.
[b] The molecular weights of OLLA and ONIPAM side chains were calculated based on their mass ratios to cellulose and DS.
[c] Determined by GPC in THF, relative to polystyrene standards.

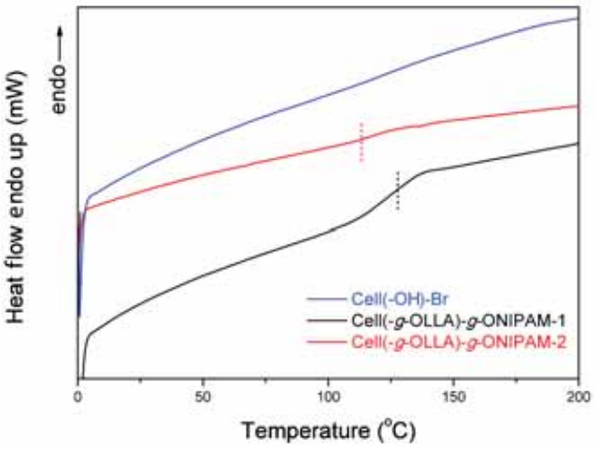


Figure 3 DSC curves of the second heating run of Cell (-OH)-Br and Cell(-*g*-OLLA)-*g*-ONIPAM copolymers.

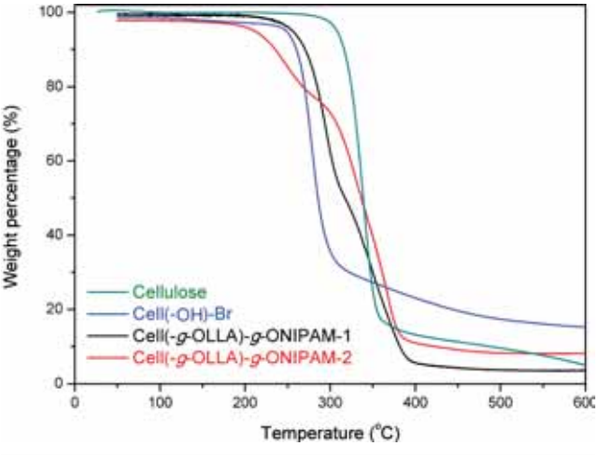


Figure 4 TGA curves of cellulose, Cell(-OH)-Br and Cell(-*g*-OLLA)-*g*-ONIPAM copolymers.

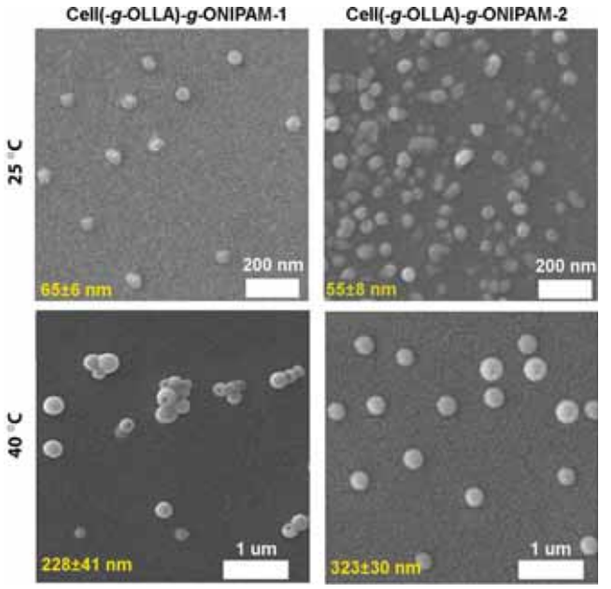


Figure 5 SEM images of Cell(-*g*-OLLA)-*g*-ONIPAM-1 and Cell(-*g*-OLLA)-*g*-ONIPAM-2 at different temperatures.

micelles. The sizes of the micelles were measured to be 65±6 nm and 55±8 nm by SEM for Cell(-*g*-OLLA)-*g*-ONIPAM-1 and Cell(-*g*-OLLA)-*g*-ONIPAM-2, respectively, at 25°C (Figure 5). Their corresponding hydrodynamic radii (R_h) were 128±46 nm and 112±24 nm at 25°C (Figure 6a). At this temperature, ONIPAM side chains existed in random coil conformation in the solution owing to the hydrogen-bonding interaction between water molecules and amido bonds of ONIPAM. Upon spin-coating on silicon wafer for SEM measurement, the corona collapsed and the size of micelles decreased.

The PNIPAMs are widely used as intelligent materials due to their temperature-sensitive characteristics [27]

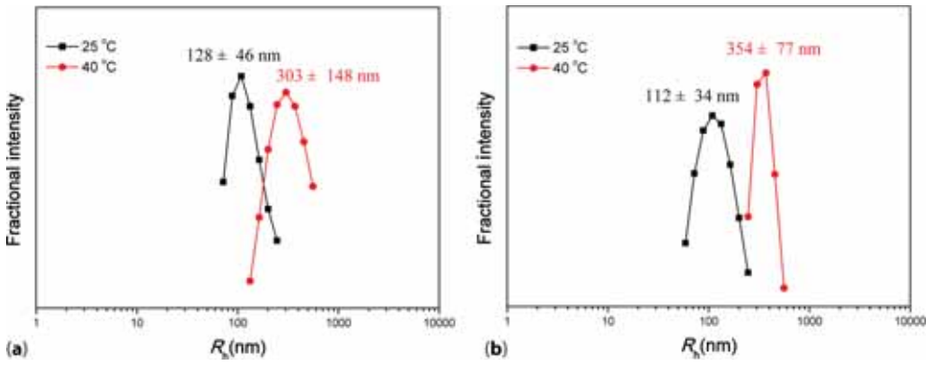


Figure 6 Size-distribution of (**a**) Cell(-*g*-OLLA)-*g*-ONIPAM-1 and (**b**) Cell(-*g*-OLLA)-*g*-ONIPAM-2 at different temperatures.

and lower critical solution temperature (LCST) of about 32°C, close to body temperature [28]. When the temperature is increased to 40°C, above LCST, the sizes of the micellar aggregates increased to 228±41 and 323±30 nm for Cell(-*g*-OLLA)-*g*-ONIPAM-1 and Cell(-*g*-OLLA)-*g*-ONIPAM-2, respectively, consistent with the experimental results from DLS (Figure 6). At the temperature above LCST, hydrogen bonding between water molecules and amido bonds of PNIPAM will break and PNIPAM chains become hydrophobic and collapse. The hydrophilic/hydrophobic balance of originally formed micelles at lower temperatures is broken. The intermolecular hydrophobic attractions are thermodynamically favored and aggregation of micelles might occur, which results in the formation of large particles.

4 CONCLUSION

The miktoarm graft copolymers (Cell(-*g*-OLLA)-*g*-ONIPAM) were synthesized in one-pot by simultaneously conducting ATRP and ROP using Cu/CuBr/PMDETA/$Sn(Oct)_2$ as the catalyst system and Cell(-OH)-Br as the difunctional macroinitiator. Cell(-*g*-OLLA)-*g*-ONIPAM self-assembled into micelles in a mixed THF/water solution. The self-assembly behavior and tunable temperature-responsive properties of Cell(-*g*-OLLA)-*g*-ONIPAM were investigated by DLS and SEM. The results showed that the sizes of Cell(-*g*-OLLA)-*g*-ONIPAM micelles increased when the temperature was increased above LCST. The miktoarm graft copolymers with tunable temperature-responsive behavior have potential applications as biomedical and smart materials.

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