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Regulation of the thermal sensitivity of hydroxypropyl cellulose by poly(*N*-isopropylacryamide) side chains

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ABSTRACT

Hydroxyproyl cellulose graft poly(*N*-isopropylacryamide) (HPC-*g*-PNIPAm) copolymers were synthesized by single-electron transfer living radical polymerization (SET-LRP) in water and THF mixture solvent and characterized. The controllability and polymerization rate of SET-LRP can be adjusted by the water/THF ratio in the mixture solvent. The monomer conversion rate is relatively low in the solvent with low water content. The thermal responsive property of HPC-*g*-PNIPAm copolymers in aqueous solution depends on the length of the graft chains. The relatively short PNIPAm side chains (<150 repeat units) can effectively regulate the low critical solution temperature (LCST) of the HPC-*g*-PNIPAm copolymers in aqueous solution due to the hydrophilic properties of the short PNIPAm chains. This work provides an approach for the regulation of the LCST to body temperature region by graft copolymerization.

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1. Introduction

Cellulose is the most abundant and renewable carbon source in nature and has attracted increasing attention in both scientific and industrial aspects (Klemm, Heublein, Fink, & Bohn, 2005; Kim, Yun, & Ounaies, 2006; Repka et al., 2007). Cellulose and its derivatives have been widely used in many fields including pharmaceutical, medical, food and painting industries. Among the cellulose derivatives, hydroxypropyl cellulose (HPC) has the unique advantages of good water solubility, non-toxicity, amphiphilicity and thermal sensitivity (Kim, Yun, & Lee, 2008) and has been widely applied pharmaceutical field (Repka et al., 2007). The thermal sensitivity of HPC is attractive. However, the lower critical solution temperature (LCST) of HPC is around 42 °C in aqueous solution and there is a gap to the physiological temperature (25–38 °C) (Crespy & Rossi, 2007), which limited the applications of HPC as a promising biomaterial. Efforts have been tried to regulate the LCST of HPC to the physiological temperature region or even to body temperature (Xu et al., 2010), among which graft modification of HPC seems more effective (Ma, Kang, Liu, & Huang, 2010; Ma, Liu, et al., 2010).

Many synthetic thermal sensitive polymers, such as poly(*N*-isopropylacrylamide) (PNIPAm), poly(ethylene glycol) (PEG), and poly(oligo(ethylene glycol) methacrylate) have been reported and investigated extensively. The most popular thermal sensitive polymer is PNIPAm, which has a LCST in water around 32 °C and has been studied extensively in both of its phase transition behaviors and bio-applications (Lutz, Akdemir, & Hoth, 2006; Wu & Zhou, 1995a; Wu & Zhou, 1995b). However, it is not really the fact that any of the available homopolymer has a LCST close to the body temperature. The feasible approach for adjusting the LCST of the polymers is copolymerization. The precise regulation of LCST of polymers in aqueous solution has been achieved by the copolymerization of 2-(2-methoxyethoxy)ethyl methacrylate and oligo(ethylene glycol) methacrylate (Han, Hagiwara, & Ishizone, 2003; Lutz et al., 2006; Lutz & Hoth, 2006), which has attracted increasing attention in recent years. Compared with the copolymerization approach, methods for regulating the LCST of polymeric material by graft copolymerization, especially from the polysaccharides, are somewhat overlooked.

For the purpose of regulating the LCST of polysaccharides by graft copolymerization, the graft density and the side chains length must be well-defined and controlled. Traditional graft copolymerization was generally carried out using free radical polymerizations (grafting from) or by polymeric reactions (grafting to). However,

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the graft density and side chains length are uncontrollable and the formation of homopolymers is unavoidable for traditional free radical polymerization. The "grafting to" approach has a low reaction efficiency and is uncontrollable for the graft copolymer architecture (Li, Liu, & Huang, 2008). In last decade, the application of atom transfer radical polymerization (ATRP) on the synthesis of cellulosic graft copolymers with well-defined architecture have been investigated extensively (Kang, Liu, Liu, & Huang, 2008; Kang, Liu, & Huang, 2013a; Li, Liu, Liu, et al., 2008; Li, Kang, Liu, & Huang, 2012; Lindqvist et al., 2008; Ma, Kang, et al., 2010; Ma, Liu, et al., 2010; Meng et al., 2009; Ostmark, Harrisson, Wooley, & Malmstrom, 2007; Ostmark, Lindqvist, Nystrom, & Malmstrom, 2007; Shen & Huang, 2004; Shen, Yu, & Huang, 2005; Vlcek et al., 2006; Wang et al., 2011; Yan et al., 2009; Yuan, Zhang, Zou, Shen, & Ren, 2012). The graft copolymers could have the properties of pH or/and thermal sensitivities depending on the properties of the cellulosic backbones and the side chains as well (Li, Liu, Liu, et al., 2008; Ma, Kang, et al., 2010; Ma, Liu, et al., 2010; Tan et al., 2010; Wang et al., 2011). Recently, single-electron transfer living radical polymerization (SET-LRP) has been founded in the polar media (Percec et al., 2006), which offers an optimistic approach for synthesis bio-functional polymer materials due to that most of the biopolymers have a good solubility in polar solvent. SET-LRP is a robust methodology that allows for the ultrafast synthesis of linear vinyl polymer with ultrahigh molecular weight at room temperature or below. Polymers synthesized by SET-LRP have the predictable molecular weight and distribution, perfect retention of chain functionality, and no detectable structural defects, and they are colorless without any purification (Rosen & Percec, 2009). SET-LRP has been successfully used for the synthesis of block and graft copolymers with well-defined architecture (Feng et al., 2009; Kang, Liu, & Huang, 2013b; Tang et al., 2009; Zhai et al., 2010; Zoppe et al., 2010).

In this work, SET-LRP was used to synthesize hydroxypropyl cellulose graft poly(*N*-isopropylacrylamide) (HPC-*g*-PNIPAm) copolymers in water/tetrahydrofuran (H_2O/THF) mixture solvent. The effect of the H_2O/THF ratio on SET-LRP was investigated. The length of the PNIPAm side chains on thermal sensitivity of the resultant HPC-*g*-PNIPAm copolymers was investigated.

2. Experimental

2.1. Materials

Hydroxylpropyl cellulose (HPC, Sigma Aldrich, $M_n = 1.0 \times 10^5$ g/mol, the degree of substitution hydroxylpropyl groups is 3.56 per glucose unit, estimated by ^{1}H NMR) was vacuum dried at 40 °C for 3 days before use. *N*-isopropylacrylamide (NIPAm) (>99%, Sigma Aldrich) was recrystallized in hexane for 3 times before use. 2-Bromoisobutyryl bromide (BIBB, 98%), copper(I) bromide (CuBr, 99%), *N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine (PMEDTA, >99%) were purchased from Sigma Aldrich and used as received.

2.2. Synthesis of HPC-g-PNIPAm via SET-LRP and the solvent effects

The synthesis route of HPC-*g*-PNIPAm copolymers is shown in Scheme 1. The macro-initiator HPC-Br for SET-LRP graft copolymerization was synthesized according to our previous works (Ma, Kang, et al., 2010; Ma, Liu, et al., 2010). Briefly, HPC (5.0 g) was dissolved in 100 mL anhydrous tetrahydrofuran (THF) with continuous stirring overnight. The solution was then cooled down to 0 °C in an ice bath, and then 0.5 mL 2-bromoisobutyryl bromide (BIBB) in 5 mL anhydrous THF was added dropwise into the flask over a period of 30 min. The flask was then sealed and allowed to react at room temperature for another 3 h. The final reaction mixture was condensed by rotary evaporation and then dialysis against water. The resultant solution was lyophilized to result purified macro-initiator HPC-Br. The degree of substitution of the bromide groups can be tailored via varying the feeding molar ratio of BIBB and hydroxyl groups of HPC. In present work, HPC-Br with a relatively low degree of substitution of bromide groups ($DS_{-Br} = 0.1$, about one bromide group per ten glucose units of HPC) was selected as the initiator for the purpose to preserve the properties of HPC.

HPC-*g*-PNIPAm copolymers were synthesized according to the following protocols. The feeding ratio [monomer]:[Br]:[CuBr]:[PMDETA] = 200:1:5:10. H_2O/THF mixed solvents with volume ratio from 1/3 to 2 were used as reaction solvents, and the polymerizations were conducted at 25 °C for desired time. Typically, NIPAm and HPC-Br were first completely dissolved in 20 mL H_2O/THF mixed solvent with continuous stirring. The solutions were then deoxygenated through bubbling with nitrogen for 30 min, and PMDETA and CuBr were added under the nitrogen atmosphere. The reaction mixtures were deoxygenated with purge of nitrogen for another 10 min. The flask was sealed and the polymerization was allowed to process at 25 °C. After the polymerization was performed for a desired time, the reaction mixtures were exposed to air to stop the reaction. The reaction mixtures were allowed to pass through an aluminum oxide column to remove complex of ligand with CuBr and then dialyzed against water for further purification. The resulted solutions were lyophilized to obtain purified graft copolymers.

2.3. Characterization

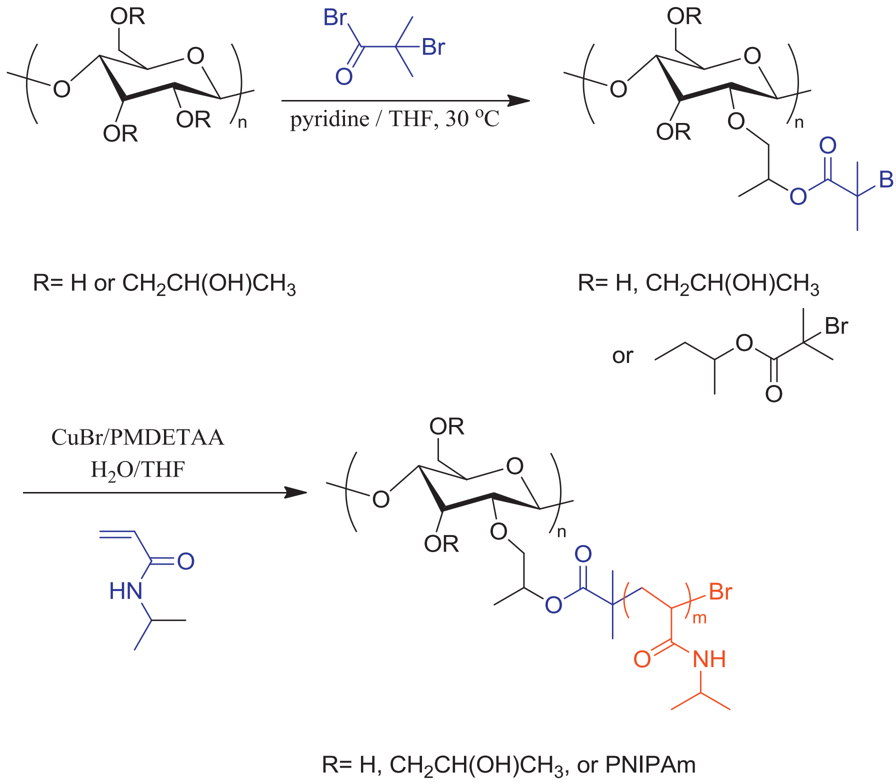
Fourier transforms infrared (FTIR) spectra were measured on a Bio-Rad FTS 135 FT-IR spectrophotometer using KBr pellets. Each spectrum was collected by cumulating 64 scans. Proton nuclear magnetic resonance (^{1}H NMR) spectra were measured on a Bruker ARX 400 MHz spectrometer. Deuterated chloroform (CCl_3D) was used for the structure characterization of the graft polymers and deuteroxide (D_2O) was used as the solvent for characterization of the thermal sensitivity of the HPC-*g*-PNIPAm in water. The monomer conversion was determined by weighing method, from which the side chain length was calculated based on the assumption of complete initiation and even distribution of side chains.

The LCST of the HPC-*g*-PNIPAm samples was determined by transmittance and differential scanning calorimetry (DSC). The transmittance of the graft copolymer PBS solutions (pH 7.4) as a function of temperature was determined on (TENSOR-27) at then wavelength of 500 nm. DSC measurements were carried out on Q2000 V24.4 Build 116 at a heating rate of 2 °C/min in the temperature range 20–70 °C under a nitrogen flow rate of 40 mL/min.

3. Results and discussion

3.1. Synthesis of graft-copolymers HPC-g-PNIPAm

The synthesis route of HPC-*g*-PNIPAm copolymers is shown in Scheme 1. The first step is to synthesize the macro-initiator HPC-Br via the esterification between hydroxyl groups on HPC backbone and 2-bromoisobutyryl bromide. The resultant HPC-Br macro-initiators were characterized by FT-IR and ^{1}H NMR spectroscopies. On the FT-IR spectrum of HPC-Br, the absorbance peak at 1735 cm^{-1} comes from the C=O stretching vibration of the ester (Fig. 1b), which is unavailable on the spectrum of HPC (Fig. 1a). On the ^{1}H NMR spectra, a new single peak at $\delta = 1.90$ ppm (***d***) appears on the ^{1}H NMR spectrum of HPC-Br, which comes from the methyl protons in the ester group (Fig. 2b). Both FT-IR and ^{1}H NMR results confirm the success of the esterification. The substitution degree



Scheme 1. Synthesis route of HPC-g-PNIPAm copolymer.

of the 2-bromoisobutyryl groups (DS_{-Br}, defined as the number of bromide groups per glucose ring) on the HPC backbone was estimated by comparing the integral area of the signal for the methyl group of HPC around $\delta = 1.10$ ppm (***a***) to that of the methyl proton of the 2-bromoisobutyryl group around $\delta = 1.90$ ppm (***d***). In present work, macro-initiator with $DS_{-Br} = 0.1$ was used for the initiation of graft copolymerization. At low DS_{-Br}, the properties of the HPC has less influenced by substitution of hydroxyl groups.

The PMDETA/CuBr complex in water is of high instability, which leads to fast disproportionation reaction (Tsarevsky, Braunecker, & Matyjaszewski, 2007; Tsarevsky & Matyjaszewski, 2007). It is a crucial process for this SET-LRP polymerization process (Percec et al., 2006). In situ disproportionation process generates Cu(I), Cu(0) and Cu(II), providing catalyst and anti-catalyst at the same time (Tang et al., 2009). Among them, Cu(0) plays the lead role that it catalyzes initiator HPC-Br to form free radical ionic

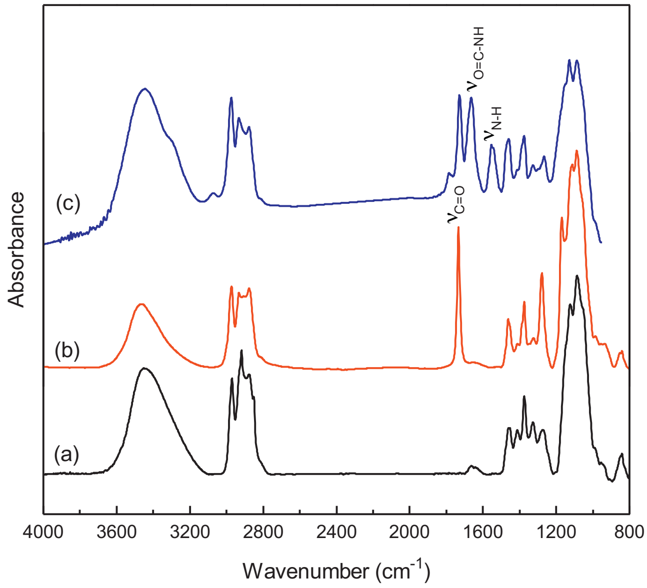


Fig. 1. FTIR spectra of (a) HPC, (b) HPC-Br and (c) HPC-g-PNIPAm (band 1730 cm^{-1}, $\upsilon_{O=C-O}$; band 1650 cm^{-1}, $\upsilon_{O=C-NH}$; band 1540 cm^{-1}, υ_{N-H}).

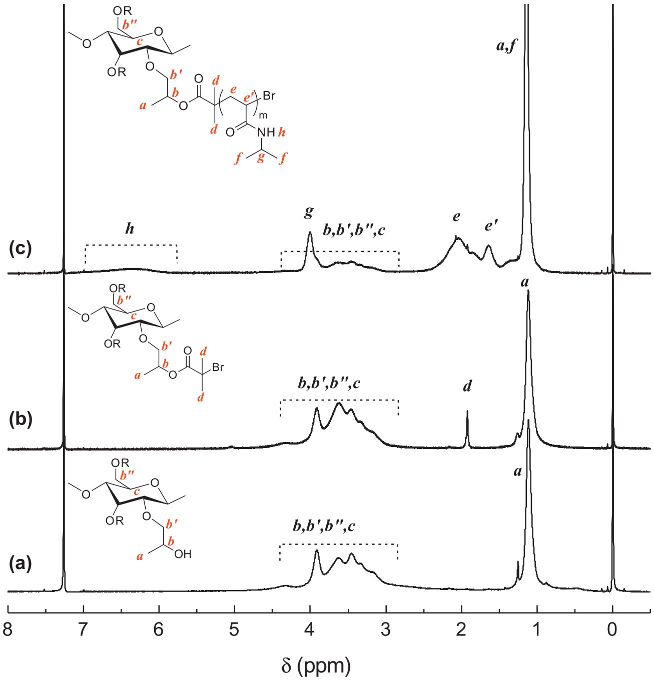


Fig. 2. 400 MHz ^{1}H NMR spectra of (a) HPC, (b) HPC-Br and (c) HPC-g-PNIPAm in CCl_3D.

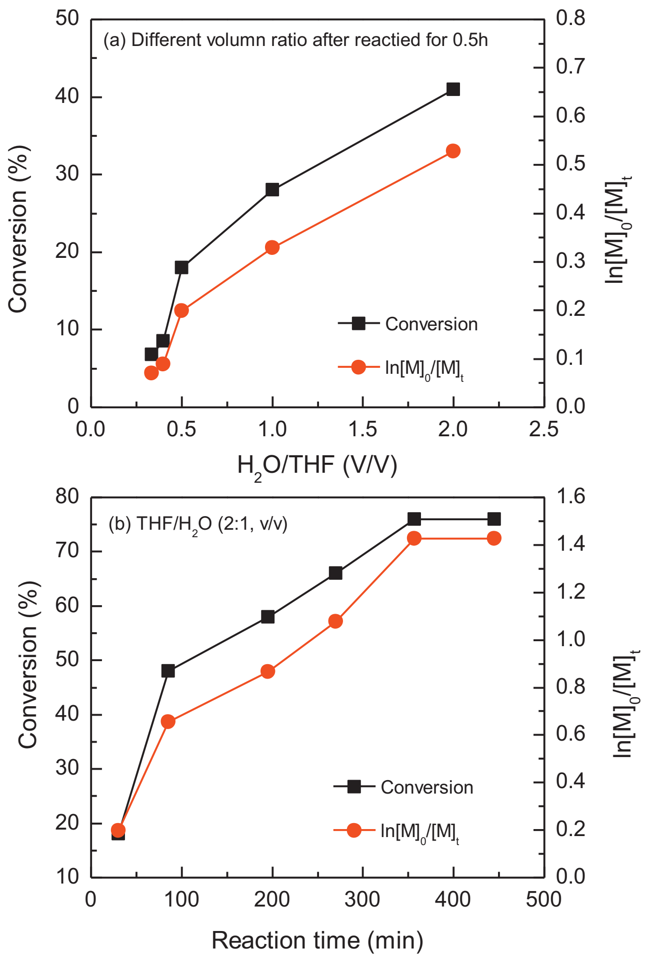


Fig. 3. Kinetics and polymerization data comparison of solvent effects of SET-LRP process (a) SET-LRP reaction rate comparison of water vs THF volume ratio from 1/3 to 2; (b) kinetics of SET-LRP with water/THF volume ratio of 1:2.

[HPC-Br]$^-$ through outer shell electron transfer (OSET), which dissociates into free radical HPC, turning on the polymerization propagation. The graft copolymerization can be carried out a low temperature (25 °C in this work), which is very important for the synthesis of HPC-g-PNIPAm copolymers. At low reaction temperature, both reactant HPC and the HPC-*g*-PNIPAm copolymer have good solubility in the reaction media. Moreover, environmental-friendly solvents can be used and it is easy to remove the catalyst from the graft copolymers. The polymerization was conducted by varying the volume ratio of water and THF, and the reaction was monitored by reaction kinetics. Firstly, polymerization rate with different water ratios are compared (Fig. 3a) and results show that conversions increase with the increasing volume of water in solvent. Clear and obvious trend can be concluded that larger ratio of water leads to higher reaction rate, which may resulting from the increased polarity of solvent (Lligadas, Rosen, Monteiro, & Percec, 2008; Percec et al., 2002). With water addition, it is possible to achieve controllable polymerization. Then system with less volume of water (H_2O/THF = 1/2, v/v) was chosen as a model and its kinetics data is listed in Fig. 3b. Linear conversion growing with reaction time can be observed and the first-order kinetics proves the “living” feature of the polymerization. The results also indicate that the reaction rate of the SET-LRP can be simply adjusted by changing the H_2O/THF ratio of the solvent.

The success of the synthesis of the graft copolymers can be confirmed by FT-IR and ^{1}H NMR. On the FT-IR spectrum of HPC-*g*-PNIPAm, the peaks at 1550 and 1650 cm^{-1} come from the stretching absorption of the carbonyl groups (C=O) and the N-H groups on the PNIPAm side chains (Fig. 1c). The peaks at δ = 1.60 (***e***′), 2.9 (***e***), 4.0 ppm (***g***), around 6 ppm on the ^{1}H NMR spectrum of the HPC-g-PNIPAm correspond to the protons on the PNIPAm side chains (Fig. 2c). Moreover, the peak at δ = 1.10 ppm (***a*** and ***f***) is much stronger than that of HPC and HPC-Br, which is partially attributed by the methyl groups of PNIPAm side chains. Both IR and ^{1}H NMR results confirm the success of the synthesis of HPC-g-PNIPAm copolymers.

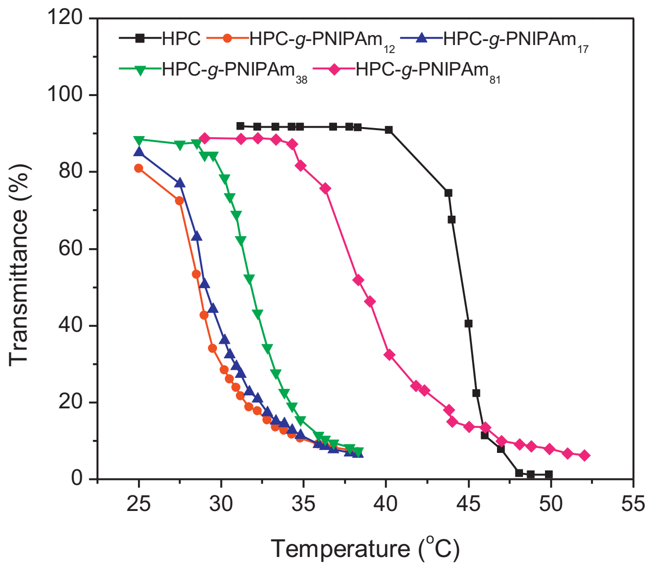


Fig. 4. Transmittance of the aqueous solution of HPC and HPC-*g*-PINIPAm copolymers as a function of termperature.

3.2. Lower critical solution temperature (LCST)

The transmittance of HPC and HPC-*g*-PNIAPm copolymers as a function of temperature is shown in Fig. 4. The temperature at which the transmittance changed for 50% was taken as the LCST or cloud point of the graft copolymers. The results indicate that the LCST of HPC-*g*-PNIAPm copolymers decreases with the decrease in the length of PNIPAm side chains. DSC measurements result the similar phenomenon (Fig. 5). The HPC used in this work has a LCST around 44 °C, which is similar to that in literature (Gao, Haidar, Lu, & Hu, 2001). For HPC itself, the good solubility in water at room temperature is due to the abundant hydrophilic hydroxyl groups on HPC chains, which can form hydrogen bond with water at room temperature. When the HPC solutions are heated to a higher temperature, hydrogen bonds between water and HPC molecular chains will be broken and the HPC molecules become more hydrophobic simultaneously. The loss of hydrogen bonds between HPC chains and the water molecules leads to the collapse and hereafter the aggregation of HPC chains, which results a LCST at around 44 °C (Gao et al., 2001). For the purpose to clarify the mechanism of the effects of the short PNIAPm side chains on the thermal sensitivity of the HPC-*g*-PNIAPm copolymers in aqueous media, ^{1}H NMR spectra of HPC-*g*-PNIAPm copolymer at different temperature were recorded at different temperatures in D_2O (Fig. 6). Clearly, the characteristic peaks of both HPC and PNIPAm can be observed on the ^{1}H NMR spectrum of HPC-*g*-PNIPAm copolymer solution at low temperature (22 °C) (Fig. 6a). Heating the copolymer solution to a temperature near the LCST of PNIPAm (32 °C), no obvious change of the characteristic peaks of PNIPAm can be observed on the ^{1}H NMR spectrum of HPC-*g*-PNIPAm aqueous solution, whereas the characteristic peaks of HPC backbones at δ = 2.8–4.2 ppm become weak (Fig. 6b). Further heating the copolymer aqueous solution to

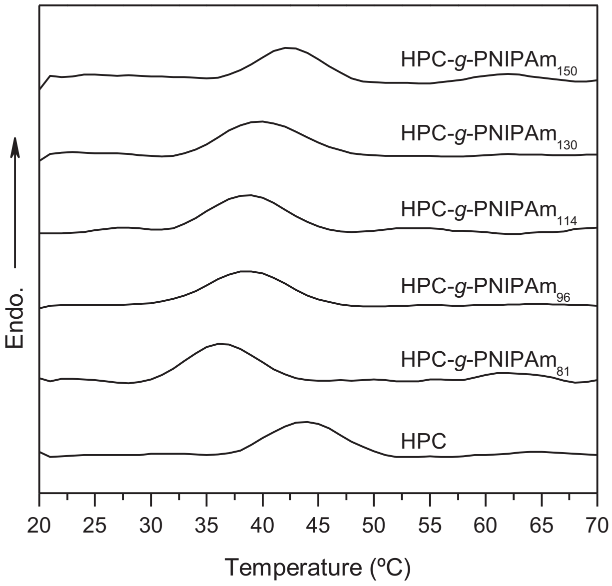


Fig. 5. DSC traces of HPC and HPC-*g*-PNIPAm at a heating rate of 2 °C/min in the temperature range from 20 to 70 °C.

42 °C, the characteristic peaks of HPC backbones at δ = 2.8–4.2 ppm almost disappeared, which indicates that the HPC de-solubilized and collapsed. It has been reported that PNIPAm with low molecular weight do not have LCST as that of high molecular weight PNIPAm (Zhu, Yan, Winnik, & Leckband, 2006). The lengths of PNIPAm side chains in this work are controlled to remain short, with ranging from 10 to 150 monomer units. Considered with the low density grafting (DS = 0.1), the PNIPAm side chains could act only as the hydrophilic chains at all temperature scale (Plunkett, Zhu, Moore, & Leckband, 2006). Based on this assumption, the dependence of the LCST of HPC-g-PNIPAm copolymers with relatively short PNIPAm side chains might block the hydrogen bond forming on HPC backbone. It could result in a lower Gibbs energy needed to destroy the balance between hydrophilic and hydrophobic interaction, presenting as lowered LCST for all graft-copolymers (Nabzar, Duracher, Elaïssari, Chauveteau, & Pichot, 1998). Among the samples, HPC-g-$PNIPAm_{12}$, which has the shortest side chains, acts with lowest LCST of 28 °C. The structure with short side chain with low density could attribute to that the side chains cannot interact with each other and thus remain random-coil around the backbones. When the chains grow longer, they tend to form intra-molecular entanglement and form strong hydrogen bond among amide groups rather than with water. The entanglement of long side chains also acts cooperatively as a hydration shell around the backbones. The shell could limit water within the shell from escaping, causing an increase in hydrogen bond rupturing potency (Scheme 2). Therefore, higher LCSTs can be observed in Figs. 4 and 5 for graft-copolymer with long side chains. It is worth to mention that HPC-g-$PNIPAm_{81}$ has a LCST at 38 °C, which is quite close to body temperature. That indicates that grafting PNIPAm onto HPC backbone is a very effective strategy to regulate and obtain polymers with body temperature LCST.

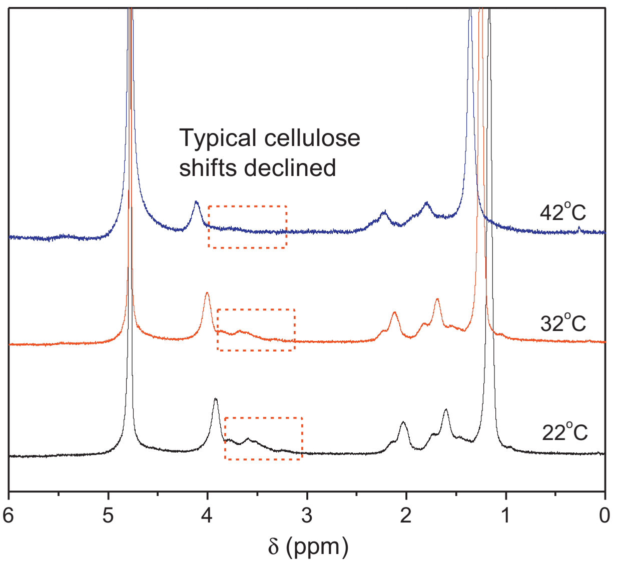
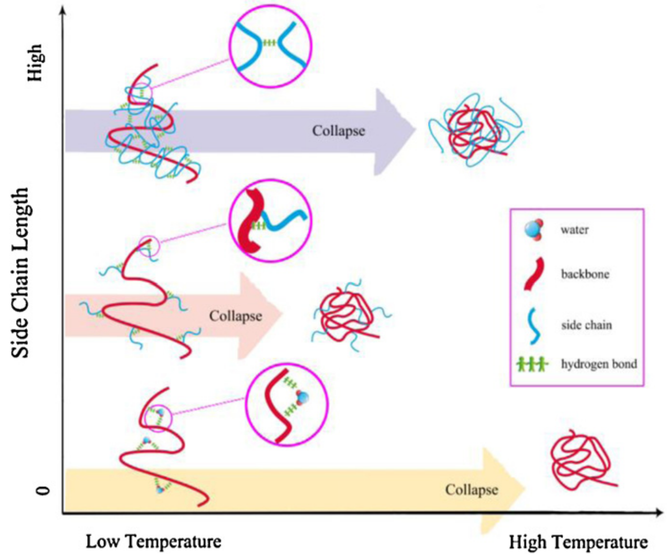


Fig. 6. ^{1}H NMR of HPC-*g*-$PNIPAm_{81}$ in D_2O at 22, 32 and 42 °C.



Scheme 2. Mechanism for regulating LCST of HPC-g-PNIPAm by the side chain length.

4. Conclusion

HPC-g-PNIPAm copolymers with well-defined architecture have been successively synthesized by SET-LRP through "grafting from" approach in H_2O/THF mixture solvent. The SET-LRP has a relatively lower polymerization rate in the mixture solvents with low water content. The thermal sensitivity of the HPC-g-PNIPAm copolymers were investigated ant it was found that the shorter side PNIPAm chains correlate to a relatively lower LCST of the copolymers in aqueous solution. The LCST of the HPC-g-PNIPAm copolymers can be regulated to a LCST close to body temperature by controlling the PNIPAm side chains to a proper length.

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