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Novel temperature-responsive functional polymers based on poly(*N*-(2-hydroxy-*tert*-butyl) acrylamide)

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A type of bifunctional responsive polymer, poly(*N*-(2-hydroxyl-*tert*-butyl) acrylamide) (PHTBAM), having both reactivity and thermosensitivity was synthesized. Such polymer can be considered as a modified poly(*N*-isopropylacrylamide) (PNIPAM) by introducing hydroxymethyl group at α-position, which possesses responsive behavior similar to PNIPAM, and less dependence of external condition. Moreover, thermal phase transition of this polymer is completely reversible without any hysteresis. LCST of PHTBAM occurs around 23 °C, which can be modulated by copolymerization with more hydrophilic comonomer such as *N*-hydroxyethylacrylamide (HEAM). The LCST of the P(HTBAM-*co*-HEAM) copolymer can be adjusted over a wide range by increasing HEAM content up to higher lever, due to the structural similarity between HTBAM and HEAM units without destroying the PNIPAM–type main chain and loss of the response sensibility. In addition, the hydroxyl functional groups at side chain of PHTBAM provide a capability of further chemical modification for a variety of applications in material science and biotechnology.

1. Introduction

Temperature-responsive polymer is one kind of the most important intelligent materials, which displays reverse solubility profile in water, i.e. the polymer precipitates upon heating and dissolves with cooling. The key factor that determines their thermosensitive behaviors is the hydrophilicity–hydrophobicity balance. When the temperature is higher than the lower critical solution temperature (LCST), the polymer chains are dehydrated and the H-bonds between the polymers and water become weaker, leading to rapid increase of the hydrophobicity of the polymer. Concomitantly, the macromolecular conformation changes from a water-soluble random coil to a hydrophobic globule, and then aggregates and precipitates driven by hydrophobic interaction. This unique functional property has attracted a great of interests in many potential applications, such as controlled release of drug, separation technique, sensor, biological engineering and others [1,2]. The most important type of thermosensitive polymers is *N*-alkylacrylamides [3–5], among which the poly(*N*-isopropylacrylamide) (PNIPAM) is a typical example, with an LCST around 32 °C close to the body temperature [6–8]. Nowadays, PNIPAM has been studied extensively, and taken as the golden standard for thermosensitive polymers. However, due to lack of reactive group, this polymer couldn't be modified by chemical modification and deep processing, which hinders its further applications. For example, they could not conjugate with biomacromolecules directly to give them thermosensitivity in biological engineering. They also couldn't be crosslinked, that frequently required for many practical applications. To introduce functional groups onto the polymer structure by copolymerization with a reactive comonomer is the most widely used method, such as copolymer P(NIPAM-*co*-AA) obtained by NIPAM and acrylic acid (AA) monomer [9]. However, their thermal phase transition becomes less sensitive with increasing the content of the comonomer, probably due to destroying the cooperative structure of continuous chain sequences of temperature-sensitive isopropylamide groups after copolymerization [10]. Therefore, an important and meaningful issue is to develop novel kind of thermosensitive functional polymers, which retain simple structure and excellent responsive property like PNIPAM. *N*-Hydroxyalkylacrylamide with a water-soluble hydroxyl group at side chain end is more hydrophilic than *N*-alkylacrylamide, which is possible to introduce alkyl chain with more carbon atoms and to utilize for different chemical modifications. It's also expected to improve the self-coating property for capillary electrophoresis [11]. However, *N*-hydroxyalkylacrylamides with shorter alkyl chain, such as *N*-hydroxymethylacrylamide (HMAM), *N*-hydroxyethylacrylamide

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(HEAM), *N*-hydroxyisopropylacrylamide (HIPAM), have good water solubility, but not LCST behavior. They are usually used as hydrophilic component to increase the LCST of copolymers [12–15].

In accordance with the above views, considering the effect of the length of alkyl chain (C_n) of *N*-hydroxyalkylacrylamide on its water-solubility and thermosensitivity [16], we designed a new water-soluble *N*-hydroxyalkylacrylamide monomer with a proper hydrophilicity–hydrophobicity balance, *N*-(2-hydroxy-*tert*-butyl) acrylamide (HTBAM), also referred as NIPAM substituted by 2-hydroxymethyl group. HTBAM is of interest as to combine of hydroxyl functionality and acrylamide group. The PHTBAM homopolymer is readily prepared using conventional radical polymerization, which displays a clear LCST transition around 23 °C, and reversible without any detectable hysteresis. Moreover, the terminal hydroxyl provides the possibility to further chemical modification. In this work, the thermosensitive behavior and influence factors of PHTBAM were studied by turbidimetry, differential scanning calorimetry (DSC) and dynamic light scattering (DLS). The LCST of its PHTBAM polymer can be tailored over a broad temperature range by copolymerization with HEAM, and P(HTBAM-*co*-HEAM) copolymers with various LCSTs were obtained. The mechanism of the thermosensitive behavior was also preliminarily considered.

2. Experimental section

2.1. Materials

2-Amino-2-methyl-1-propanol (Alfa Aesar), acryloyl chloride (Alfa Aesar), and *N*-hydroxyethylacrylamide (HEAM, Sigma–Aldrich) were used without further purification. 2,2′-Azobis(isobutyronitrile) (AIBN) was recrystallized twice from ethanol and stored in the refrigerator. Triethylamine was purified by distillation over KOH. Other reagents and solvents were commercially available used as received. All the aqueous solutions were prepared using deionized water.

2.2. Synthesis of N-(2-hydroxy-tert-butyl) acrylamide (HTBAM) monomer

2-Amino-2-methyl-1-propanol (9.5 mL, 0.1 mol) and triethylamine (14 mL, 0.1 mol) were dissolved in 200 mL chloroform. The solution was cooled to 0 °C using an ice bath, and added a solution of acryloyl chloride (8.0 mL, 0.1 mol) in 50 mL chloroform. The reaction mixture was then stirred for 4 h while keeping the temperature at 0 °C. Triethylamine hydrochloride was precipitated from the solution, and removed by filtration. The filtrate was concentrated and purified by column chromatography using ethyl acetate/hexane (7/3, v/v) as the eluent. The HTBAM monomer was obtained as a white powder and the yield was 66.0%. ^{1}H NMR ($CDCl_3$, δ, ppm): 1.34 (s, 6H, $C(CH_3)_2CH_2OH$), 3.62 (d, 2H, $C(CH_3)_2CH_2OH$), 5.67, 6.10 (dd, dd, 2H, $CH_2{=}CH$), 6.27 (dd, 1H, $CH_2{=}CH$). ^{13}C NMR ($CDCl_3$, δ, ppm): 24.11 ($C(CH_3)_2CH_2OH$), 55.84 ($C(CH_3)_2CH_2OH$), 70.19 ($C(CH_3)_2CH_2OH$), 126.48 ($CH_2{=}CH$), 130.65 ($CH_2{=}CH$), 165.93 ($C{=}O$). HR-MS (ESI): calcd for $C_7H_{13}NO_2$ $[M + H]^+$: 144.10191, found: 144.10186.

2.3. Preparation of PHTBAM or PHEAM homopolymer, and P(HTBAM-co-HEAM) copolymer

HTBAM or HEAM monomer (0.5 mol L^{-1}) and AIBN (2.5×10^{-3} mol L^{-1}) were dissolved in ethanol. For the P(HTBAM-*co*-HEAM) copolymer, HEAM and HTBAM monomer in different molar ratios were used with the same amount of AIBN. The solution was deoxygenated by purging with nitrogen gas for 20 min. Polymerization was carried out in water bath at 65.0 °C for 24 h. Then unreacted monomers were removed completely by dialysis against water at ambient temperature for one week (water was frequently refreshed). After lyophilization, the homopolymer or copolymer was obtained as a white powder.

2.4. Characterization methods

^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker DPX-400 NMR spectrometer in the deuterated solvents at 25.0 °C, using tetramethylsilane (TMS) as an internal standard.

The high resolution mass spectrometer (HR-MS, ESI) analyses were carried out on a Bruker apex IV FT mass spectrometer.

The molecular weights and molecular weight distributions of polymer were estimated by gel permeation chromatography (GPC) on equipment composed of a Waters 1525 binary HPLC pump, a Waters 2414 refractive index detector, and three Waters Styragel columns. DMF with the presence of LiBr was used as eluent at a flow rate of 1.0 mL min^{-1}; and poly(ethylene glycol) standards was used for calibration.

Differential scanning calorimetry (DSC, Mettler Toledo) was used to estimate the thermoresponsive profile of PHTBAM and P(HTBAM-*co*-HEAM) copolymers. The aqueous solutions of polymers (300 mg mL^{-1}) were placed in pans, which were completely sealed. DSC measurements were conducted at a scanning rate of 1.0 °C min^{-1} in the heating process.

Average hydrodynamic radius and distributions of the aggregates formed in aqueous solutions of the polymers were determined using a DynaPro NanoStar instrument (Wyatt Technology), with a He–Ne laser ($\lambda = 659$ nm) operated at 10 mW. The measurements were made at the scattering angle $\theta = 90°$ at 25.0 °C. Prior to measurement the polymer solutions were clarified by filtering through Millipore membranes with 0.22 μm pore size.

2.5. Phase transition measurements by turbidimetric method

The cloud points of P(HTBAM-*co*-HEAM) aqueous solutions were determined by transmittance measurements using a UV–vis spectrometer. The quartz cell was thermostated using a circular water jacket equipped with a temperature controller. The transmittance of the copolymer solutions was recorded as a function of temperature. The temperature was raised at 1.0 °C min^{-1}, and the wavelength was fixed at 500 nm. The cloud points of the polymer solutions were defined as the temperature when the transmittance was 50%.

3. Results and discussion

3.1. Characterization of PHTBAM and P(HTBAM-co-HEAM)

The synthesis route of HTBAM monomer is shown in Scheme 1. Its chemical structure was confirmed by ^{1}H NMR, ^{13}C NMR spectroscopy and HR-MS (ESI) analysis. Bearing an active polymerizable acrylamide group, the HTBAM monomer was easy to undergo homopolymerization and copolymerization by conventional radical polymerization. The polymerization condition and composition of PHTBAM homopolymer and P(HTBAM-*co*-HEAM) copolymers are shown in Table 1. The feed molar ratios of HTBAM and HEAM were controlled in the range from 10:0 to 5:5. Therefore, these copolymers were denoted as PT_9E_1, PT_8E_2, PT_7E_3, PT_6E_4, PT_5E_5 according to the initial ratios of HTBAM and HEAM monomer. The obtained polymers were soluble in ethanol, methanol, *N,N′*-dimethylformamide, dimethyl sulfoxide, and water. The molecular weights and molecular weight distributions of the polymers