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Multi-responsive polymethacrylamide homopolymers derived from tertiary amine-modified L-alanine

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ABSTRACT

Four poly(*N*-methacryloyl-L-alanine) homopolymers containing different tertiary amine moieties, dimethylaminoethyl, dimethylaminopropyl, diethylaminoethyl, and diethylaminopropyl, were prepared by reversible addition-fragmentation chain transfer (RAFT) polymerization in an effort to use natural amino acids as building blocks to design stimuli-responsive polymers that display pH-tunable lower critical solution temperature (LCST) transitions in the basic pH range. Monomer structure was found to be critical for the corresponding polymer to exhibit desired stimuli-responsive properties in water. While all four polymethacrylamides showed thermosensitive property in water, only poly(*N*-methacryloyl-L-alanine 2-(diethylamino)ethylamide) (PMAEE) exhibited LCST behavior in a wide pH range, from 9.0 to 13.0. Other polymers' thermoresponsive properties were found either at very high pH values (e.g., ≥13.0) or in a rather narrow pH range. The effects of pH, polymer molecular weight, polymer concentration, presence of NaCl, and end groups on cloud point of PMAEE in water were investigated; the cloud point decreased with the increase of solution pH and polymer concentration, the addition of NaCl, and the introduction of a more hydrophobic end group but varied little with polymer molecular weight. The incorporation of tertiary amine moieties endowed the polymers with a CO_2-responsive property; we demonstrated that the thermosensitive property of PMAEE can be reversibly tuned by bubbling its solution alternately with CO_2 and N_2 gases.

1. Introduction

Stimuli-responsive polymers can undergo reversible or irreversible changes in polymer conformations, chemical structures, or physical properties in response to external stimuli such as temperature, pH, light, or specific molecular species. These smart materials have potential applications ranging from drug delivery to tissue engineering, catalysis, and nanotechnology [1–5]. Among them, thermosensitive water-soluble polymers that exhibit a lower critical solution temperature (LCST) in water have been intensively studied both fundamentally and practically; examples of such polymers include poly(*N*-isopropylacrylamide) (PNIPAM) [4], poly(oligo(ethylene oxide) (meth)acrylate)s [6], pyrrolidone-based polymers [7–9], and polypeptides [10–13]. Of particular interest are thermo- and pH-sensitive polymers [2,3,14,15], these dually responsive polymers can provide greater flexibility in the design of polymeric systems for, e.g., drug delivery, and can be employed to mimic biological processes, which are often triggered by multiple external stimuli instead of a single one. Thermo- and pH-responsive polymers typically bear weak acid (e.g., -COOH) or base (e.g., tertiary amines) moieties, and their LCSTs depend on the degree of ionization of the weak acid or base moiety. They are usually prepared by random copolymerization of different monomers that have distinct functions in the polymers. However, the monomers may have very different reactivity ratios, and the distribution of different monomer units along the random copolymer chain may affect the thermoresponsive property. An alternative approach is to combine different groups into one monomer, which can be polymerized to produce a homopolymer and thus avoids the

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problem in the copolymerization of multiple monomers.

Using natural materials such as amino acids or polypeptides as building blocks to design and prepare responsive and functional polymeric materials have many advantages including biocompatibilities, higher-ordered structures, and optical activity [16–27]. In particular, vinyl monomers bearing α-amino acids and their derivatives have gained considerable interest in recent years, owing to the prospect of using "living"/controlled radical polymerization to synthesize well-defined polymers. For example, Endo et al. developed thermoresponsive (co)polymers containing *N*-acryloyl-L-proline methyl ester, poly(A-Pro-OMe) [16,18]. McCormick and coworkers synthesized and studied the self-assembly behavior of poly(*N*-acryloyl-alanine) and poly(*N*-acryloyl-valine) block copolymers [20,21]. O'Reilly group prepared amino acid-derived diblock copolymers by reversible addition-fragmentation chain transfer (RAFT) polymerization and investigated their self-assembly behaviors; they found that the diblock copolymers could form spherical micelles with relatively narrow dispersities [22,23]. We previously reported dual thermo- and pH-sensitive homopolymers made from aspartic acid- and alanine-containing methacrylamides with the *N*-terminal capped with amide or ester moieties [25–27]. Interestingly, we observed that the cloud points of poly(*N*-methacryloyl-L-alanine isopropyl amide) and poly(*N*-methacryloyl-L-alanine methyl ester) at similar degrees of polymerization (DPs) were almost the same, suggesting that the methyl ester group had similar hydrophilicity contribution as the isopropyl amide group [26]. Besides individual amino acids, oligopeptides, usually a VPGVP pentapeptide sequence, have also been employed to construct thermoresponsive polymers [28,29]. We note here that thus far the reported thermo- and pH-sensitive amino acid-derived homopolymers display pH-tunable LCSTs only in acidic water due to the nature of the carboxyl acid. Considering the widespread use of thermosensitive water-soluble polymers, it is relevant and of significance to expand the thermoresponsive behavior to the basic pH range.

Much like carboxylic acid-containing thermosensitive water-soluble polymers displaying a pH-tunable LCST in acidic water, tertiary amine-based homopolymers could exhibit pH-dependent LCST behavior in water in the basic pH range if an appropriate hydrophilic/hydrophobic balance is achieved among backbone, side chain, and tertiary amine moieties [30–38]. For example, poly(*N,N*-dimethylaminoethyl methacrylate) (PDMAEMA) has a cloud point of around 50 °C at pH = 8 and the cloud point decreases with increasing pH [30,32]. Lee et al. introduced primary and tertiary amines into the side chain of poly(2-hydroxyethyl methacrylate); the resultant polymers showed thermosensitivity in a very narrow pH range [33]. More recently, Huang et al. reported thermo- and pH-responsive homopolymer bearing oligo(ethylene glycol) unit and *N,N*-diethylamino ethyl group [35]. We also note here that one advantage of incorporating tertiary amine moieties into the thermosensitive water-soluble polymers is that CO_2 gas can also be used as a pH stimulus to adjust the cloud point of the polymer [39]. Despite the progress, the reported multi-sensitive homopolymers are rather limited, and none of them contains amino acids and derivatives, for most of the tertiary amine-based polymers are only pH-sensitive [3,31,40].

Herein we reported a series of novel homopolymers derived from L-alanine and tertiary amines (Scheme 1) that exhibited pH-tunable cloud points in water in the basic pH range. L-Alanine was used as a chiral center and its *N*-terminal was bonded to the polymerizable methaycryloyl group through an amide linkage. The carboxylic acid terminal of L-alanine was capped also via an amide linkage with various tertiary amine groups: 2-dimethylaminoethyl, 3-dimethylaminopropyl, 2-diethylaminoethyl, and 3-diethylaminopropyl. These L-alanine-derived homopolymers were prepared by RAFT polymerization, and their stimuli-responsive properties in water were studied by visual inspection, dynamic light scattering, and variable temperature ^{1}H NMR spectroscopy. We found that their thermosensitive properties in water were dependent on their chemical structures and slight variations of monomer structures can dramatically change their stimuli-responsive properties. In addition, the introduction of tertiary amine moieties endows the polymers with a CO_2-responsive property. As an example, we demonstrated that the thermoresponsive property of poly(*N*-methacryloyl-L-alanine 2-(diethylamino)ethylamide) (PMAEE, Scheme 1) can be reversibly tuned by bubbling alternately with CO_2 and N_2. The design principle reported here will also take advantage of natural amino acids, which can provide additional functionality, optical activity, and tunable side groups. These additional features might offer more potential applications for these amino acid derived thermoresponsive polymers.

2. Experimental section

2.1. Materials

L-Alanine (L-Ala), methacryloyl chloride (98%), 2-(dimethylamino)ethylamine, 3-(dimethylamino)-1-propylamine, 2-(diethylamino)ethylamine, 3-(diethylamino)-1-propylamine, dicyclohexylcarbodiimide (DCC), *N*-hydroxysuccinimide (NHS), and Na_2CO_3 were purchased from Fisher Scientific and used as received. 2,2′-Azobis(isobutyronitrile) (AIBN) was purified by recrystallization from methanol. Tetrahydrofuran (THF) was dried with and distilled from sodium and benzophenone and used immediately. Three RAFT chain transfer agents, 4-cyano-4-(dodecylsulfanylthiocarbonyl)sulfanylpentanoic acid (CDPA), 4-cyano-4-(butylsulfanylthiocarbonyl)sulfanylpentanoic acid (CBPA), and 2-cyanoprop-2-yl butyl trithiocarbonate (CBTB) shown in Scheme 1 and Scheme S1 were synthesized following the procedures reported in the literature [41], and their molecular structures were confirmed by ^{1}H NMR spectroscopy analysis. *N*-Methacryloyl-L-alanine (Ma-Ala-OH) was prepared by reacting equal molar methacryloyl chloride with L-alanine in basic water in the presence of Na_2CO_3, and the molecular structure was verified by ^{1}H NMR spectroscopy analysis [26]. All other chemical reagents were purchased from either Fisher or Sigma and used without further purification.

2.2. General characterization

^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 300 NMR spectrometer, and the residual solvent proton signal was used as the internal reference. Variable temperature ^{1}H NMR spectroscopy analysis was conducted on a Varian VNMRS 500 MHz spectrometer. High resolution mass spectroscopy (HRMS) experiments were performed using a JEOL Model JMS-T100LC (AccuTOF) orthogonal time-of-flight (TOF) mass spectrometer (Peabody, MA) with an IonSense (Danvers, MA) DART source. Circular dichroism (CD) spectroscopy was conducted on an Aviv 202 CD spectrophotometer at room temperature. Size exclusion chromatography (SEC) was carried out at ambient temperature using PL-GPC 50 Plus, an integrated GPC/SEC system from Polymer Laboratories, Inc., composed of a Waters 510 pump, a Knauer Smartline 2300 RI detector, one PLgel 10 μm guard column (50 × 7.5 mm, Agilent Technologies), and three PLgel 10 μm mixed-B columns in series (each 7.5 × 300 mm, Agilent Technologies, Inc.). HPLC grade *N,N*-dimethylformamide (DMF) with 50 mM LiBr was used as the mobile phase with a flow rate of 1.0 mL min^{-1}. The system was calibrated with polystyrene standards, and the data were processed using Cirrus GPC/SEC software. The pH values of polymer aqueous