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Synthesis of novel hyperbranched poly(ester-amide)s based on acidic and basic amino acids via "AD + CBB′" couple-monomer approach

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ABSTRACT

A series of novel hydroxyl- or methyl ester- terminated hyperbranched poly(ester-amide)s (HBPEAs) based on acidic (L-glumatic acid and L-aspartic acid) and basic amino acids (L-lysine) have been synthesized via the "AD + CBB′" couple-monomer approach. The ABB′ intermediates were stoichiometrically formed through thio-ene reaction benefited from reactivity differences between functional groups. Without any purification, *in situ* self-polycondensations of the intermediates at elevated temperature in the presence of $Ti(OBu)_4$, as a catalyst, afforded HBPEAs with high molecular weights. More rapid polymerization rate and much higher molecular weight as well as broader polydispersity were observed for the polymerization process of intermediates based on acidic amino acids than basic amino acids which is related to the catalytic mechanism and structure difference of intermediates. Moreover, polymerization of intermediate derived from L-aspartic acid was carried out faster by comparison with that from L-glumatic acid. The DB values were approximately estimated to be 47%–49% for the polymers derived from L-aspartic acid and L-glutamic acid. The resultant HBPEAs possessed glass transition temperature (T_g) in the range of −3 to 11 °C, among which those derived from L-lysine shows the highest T_g, and decomposition temperatures at 10% weight loss under air and nitrogen are in close regions of 261–271 °C and 264–268 °C, respectively.

1. Introduction

The interest in biodegradable polymers has increased significantly in recent years due to their wide range of applications, particularly in biomedical fields such as drug delivery, gene transfer, tissue engineering, and regenerative medicine [1,2]. In the past decades, functionalized biodegradable polymers, in particular α-amino acids containing degradable polymers have attracted much attention [3–5]. It has been shown that incorporation of α-amino acids in biodegradable polymers produce a wealth of novel materials combining features of traditional synthetic degradable polymers and natural polypeptides. Most of the resultant polymers possess linear [6–12], grafted [13–16], branched or star-shaped architecture [17–20]. In recent years, significant efforts have focused on the synthesis and application of a new class of modern polymer called dendrimer as they exhibit many special merits [21,22], such as a regular and highly branched three-dimensional globular architecture, low viscosity, high solubility, abundance of functional end groups and internal cavities in the molecule [23,24], which gained them great interest in biomedical applications. From a synthetic point of view, hyperbranched polymers (HBP) obtained in a one-step procedure from AB_x monomers, represent an interesting alternative for perfect dendrimers [25], which can only be prepared via tedious, time-consuming multistep protocols. Hyperbranched polymers inherits most of the virtues from dendrimers in spite of their neither perfectly monodisperse nor free of structural defects. To date, numerous examples of hyperbranched polymers have been reported [23,26–28], including various hyperbranched polyamides [29].

The first examples of hyperbranched polypeptides already date back to the 1950s, where a number of authors investigated the thermal polymerization of amino acids, including AB_2 type monomers, such as L-aspartic acid, L-glutamic acid, and L-lysine [30–37]. Rohlfing and Bugna polymerized the free base of L-lysine at 195 °C resulting in polymers with molecular weight of 100 kg/mol, which were subsequently proved to be composed of N^{ε} – linked linear

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units, dendritic lysine units, $N^{\alpha}-$ linked linear units and terminal lysine units in a ratio of 4:3:1:1 [32]. Fox and Suzuki demonstrated that the ratio between $N^{\varepsilon}-$ and $N^{\alpha}-$ linked linear lysine units could be changed by copolymerization of L-lysine with other amino acids, for example, from 1:2.5 (Lys, Asp) to 1:0.8 (Lys, Glu) [34]. These authors also reported that L-lysine monohydrochloride does not homopolymerize, but can copolymerize with glutamic acid and other amino acids in the presence of orthophosphoric acid [34]. The interest in L-lysine hyperbranched polymers has steadily increased. Menz and Chapman explored the synthesis of hyperbranched polylysine using the *N*-hydroxysuccinimide ester of L-lysine dihydrochloride as the AB_2 building block. The DBs of these polymers ranged from 32% to 64% [38]. Scholl and coworkers reinvestigated the thermal polymerization of L-lysine hydrochloride with regards to its feasibility for the synthesis of hyperbranched polypeptides. The degree of branching and the average number of branches varied between 35%–45% and 15%–25%, respectively [39]. A series of novel hyperbranched poly(ester-amide)s (HBPEAs) from neutral amino acid and gallic acid were reported by our group [40]. The hydrolytic and enzymatic degradation studies indicated that the HBPEAs were degradable hydrolytically as well as enzymatically, and the rate of hydrolytic degradation increases with the pH value of the solution [40].

Very recently, we have reported the successful synthesis of another series of novel hyperbanched poly(ester-amide)s (HBPEAs) based on neutral α-amino acids via of "AD + CBB′" couple-monomer approach [41]. The ABB′ intermediates were stoichiometrically formed through thio-ene reaction owing to reactivity difference between different functional groups, followed by *in situ* self-polycondensations at elevated temperature without any purification affording HBPEAs with numerous hydroxyl end groups. Polymers with moderate molecular weight and degree of branching were obtained resulting from the reactivity difference between the secondary and primary hydroxyls in the intermediates. $Ti(OBu)_4$ turned out to be the most effective catalyst among the four common catalysts investigated for this series of polymerization, leading to polymers with the highest molecular weight and degree of branching values. The polymers will be attractive due to potential degradability and biocompatibility resulting from the amino acid moieties in the scaffold.

Acidic and basic amino acids are the other two kinds of amino acids essential to human body. In this article, we intended to extend the strategy mentioned above to the synthesis of a type of hyperbranched poly(ester-amide)s (HBPEAs) based on acidic (Asp, Glu) and basic (Lys) amino acids. The 2-mercaptoethanol was used as the Michael donor instead of 1-thioglycerol in the thio-ene reaction to stoichiometrically produce the ABB′ intermediates. Subsequent self-polymerization gave HBPEAs with high molecular weight and numerous hydroxyl or ester as peripheral functional groups depending on the amino acids. The structures of the resultant polymers were characterized by FTIR in combination with ^{1}H NMR, ^{13}C NMR, and the molecule weight was measured by size exclusion chromatography (SEC) analyses. The mechanism of the polymerization catalyzed by $Ti(OBu)_4$ was roughly discussed by comparing the polymerization process of intermediates with different structures.

2. Experimental section

2.1. Materials

L-Glutamic acid (L-Glu), L-Aspartic acid (L-Asp) and L-Lysine (L-Lys) were purchased from ACROS and used as received. 2-Mercaptoethanol (90 wt % aqueous solution) was purchased from Aladdin and distilled under reduced pressure before use. Acryloyl chloride was used as received. CH_2Cl_2 was purified by a solvent purification system (MBraun, Germany). Triethylamine (Et_3N) was distilled over CaH_2 after refluxing for 12 h. Other organic reagents and solvents were analytically pure and used without purification.

2.2. Measurements

^{1}H NMR spectra were recorded on a Bruker AV 300 MHz spectrometer, ^{13}C NMR spectra were recorded using a Varian Unity 400 spectrometer operating at 100.0 MHz with DMSO-d_6 as the solvent, the residual 1H solvent peak as reference and the solvent carbon signal as the standard, respectively. The specific parameters used to collect the quantitative ^{13}C NMR data (inverse gated decoupling) were as follows: INSTRUM: av600, Solvent: DMSO, NS: 7662, SWH: 33333.332 Hz, D1: 8.00000000 s, P1: 7.50 usec. FTIR spectra were recorded on a Bio-Rad FTS-135 spectrophotometer at room temperature using the KBr pellet technique.

Glass transition temperature (T_g) were measured by differential scanning calorimetry (DSC) (Perkin–Elmer Pyris 1) under nitrogen atmosphere with the heating rate of 10 °C/min from −50 to 100 °C, respectively. The specimens were crimp sealed in aluminum crucibles. The T_g was taken as the midpoint of the inflection tangent, upon the second heating scan. Thermogravimetric analysis (TGA) was conducted on a Perkin–Elmer Pyris 1 thermogravimetric analyzer. The sample was heated from 40 to 900 °C with a heating rate of 10 °C/min under nitrogen and air, respectively.

ESI-MS was measured by LCQ ion trap instrument (Finnigan MAT, San Jose, CA) with an electrospray source in positive or negative ion mode. Electrospray voltage was 5.0 kV and capillary temperature was set as 260 °C.

Size exclusion chromatography (SEC) was performed with a Waters 1525 fitted with two columns (Styragel HT3 and HT4 THF 7.8 × 300 mm column) connected in series and 2414 Refractive Index Detector with TEDIA dimethylformamide (DMF) containing 0.05 M LiBr as the mobile phase. The SEC measurements were calibrated against narrow-dispersity polystyrene standards.

2.3. Synthesis

2.3.1. Vinyl monomers containing amino acid residues (**2a**–**c**)

Firstly, various amino acids were transformed to their hydrochloride salts of amino acid methyl esters (**1a**–**c**) by reacting with 15 equiv. methanol and 2 equiv. thionyl chloride at room temperature according to the literature procedure [42]. Subsequently, the acylation processes of compounds **1a**–**c** were accomplished by treating with acryloyl chloride in the presence of excess Et_3N to give the vinyl monomers (**2a**–**c**) according to the reference [43].

2.3.2. ABB′ intermediates (**3a**–**c**)

In a flask were placed compound **2a** (2.29 g, 10 mmol), 2 mL of CH_2Cl_2 and 0.14 mL of Et_3N (10 mol% with respect to compound **2a**) under nitrogen atmosphere. The mixture was stirred for a few minutes until compound **2a** was dissolved. Then 2-mercaptoethanol (0.7 mL, 10 mmol) was added slowly into the flask immersed in ice-water bath, and then the solution was kept at room temperature for 4 h. Under reduced pressure, CH_2Cl_2 and Et_3N were removed from the reaction system to yield green-yellow viscous liquid. Intermediates **3b** and **3c** were prepared analogously. (When the intermediate **3c** was prepared, dry CH_3OH was used as the solvent instead of CH_2Cl_2 due to limited solubility of **2c** in CH_2Cl_2).

3a. ^{1}H NMR (DMSO-d_6): δ (ppm) 1.71–1.83 (m, −NHCHC*H*H, 1H), 1.89–2.00 (m, −NHCHCH*H*−, 1H), 2.33–2.66 (m, −C*H*$_2$SCH$_2$CH$_2$CO−, −CH$_2$SC*H*$_2$CH$_2$CO−, −CH$_2$SCH$_2$C*H*$_2$CO−, CH$_3$OC(O)C*H*$_2$CH$_2$−, 8H), 3.44–3.50 (q, HOC*H*$_2$−, 2H), 3.55 (s, C*H*$_3$OC(O)CH$_2$−, 3H), 3.58