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Synthesis of amphiphilic polyethylene-*b*-poly(L-glutamate) block copolymers with vastly different solubilities and their stimuli-responsive polymeric micelles in aqueous solution

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This paper describes the synthesis, characterization, and self-assembly behavior of amphiphilic polyethylene-*block*-poly(L-glutamate) (PE-*b*-PGA) diblock copolymers. PE-*b*-PGA diblock copolymers were obtained by ring-opening polymerization (ROP) of γ-benzyl-L-glutamate-*N*-carboxyanhydride (BLG-NCA) using PE—COOCH(^{i}Pr)NH$_2$ as a macroinitiator and subsequent deprotection of the benzylester groups. The self-assembly behaviors of the PE-*b*-PGA copolymers in water were studied as a function of pH and ionic strength by means of fluorescence spectroscopy, laser light scattering, UV-circular dichroism, and transmission electron microscopy. The size of the polymeric micelles decreases with a decreasing pH value even at high salt concentrations because the solvating PGA units can perform a coil-to-helix transition.

1. Introduction

Polyolefins, especially including polyethylene (PE), are commercially the most important family of polymers, which have reached wide application because of their excellent mechanical, physical, and chemical properties [1]. However, their applications are mainly limited in the field of plastic and resin due to their low polarity and poor reactivity [2]. Indeed, two striking features of polyolefins are perfect hydrophobicity and flexibility. Especially for polyethylene (PE), there are no polar groups and unsaturated bonds on the polymer chain and its glass transition temperature (T_g) is low up to −68 °C. Theoretically, PE can be used as perfect hydrophobic segment to construct amphiphilic copolymer. Although a few of functional PE copolymers (PE-*b*-PS, PE-*b*-PMMA, and PE-*b*-PCL) have been successfully synthesized [3], rare PE based amphiphilic copolymers have been prepared [4]. Particular interests are recently received in amphiphilic block copolymers comprising hydrophilic poly(amino acid) segments because of their exceptionally rich phase behavior, including the formation of stimuli-responsive and hierarchical structures, and their potential applications in the areas of drug delivery and biomaterials [5].

Rare polyolefin-poly(amino acid) copolymers are prepared in the current literature [6–8], and there is no report on synthesis and property of amphiphilic PE-poly(amino acid) copolymers to our knowledge. Two noteworthy examples are polybutadiene-polypeptide [6] and polyisoprene-polypeptide [7] block copolymers which have been synthesized by a tandem synthetic strategy combining anionic living polymerization of diene and controlled ring-opening polymerization (ROP) of *N*-carboxyanhydrides (NCA). Deming has also synthesized ABA triblock polypeptide-*b*-polyoctenamer-*b*-polypeptide copolymers by acyclic diene metathesis (ADMET) polymerization and living polymerization of *N*-carboxyanhydrides (NCAs) [8]. Current advances show that the molecular weights of hydrophobic polyolefin building blocks are very low (M_n < 5 kg/mol) because of restriction of polymerization fashion. Low molecular weight of polyolefin building block limits hydrophobic fraction and property of amphiphilic block copolymer attainable.

Although precise PE building block with high molecular weight can be facilely obtained by living catalytic polymerization of ethylene, poor solubility of PE in reaction media largely limits occurrence of chain-extension reaction. Increasing temperature can slightly improve solubility of polyolefin in media, but this also has the detrimental effect of losing control of the follow-up polymerization and increasing side-reaction. Increasing branching density and changing polymer topology provide another viable access to improving solubility of polyolefin in media [9]. More importantly,

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high branching density endows PE with an amorphous character, which is favorable for facile control of self-assembly by the hydrophobic driving forces without interference of crystallization [4a,b].

Early transition metal (Ti and Zr) catalysts usually afford linear PE with very low branching density. In contrast, transition metal catalyst (Ni and Pd) can polymerize ethylene to produce highly branched PE because of chain walking [9]. PEs with various polymer topologies (linear, hyperbranched, and dendritic PE) can be also obtained by varying ethylene pressure and polymerization temperature [9]. Combination chain walking and living polymerization of late transition catalyst are anticipated to afford the highly branched PE with narrow polydispersity [10]. A type of nickel catalyst bearing amine-imine ligand has been recently developed for living polymerization of ethylene by our groups. Narrowly dispersed PE ($M_w/M_n < 1.10$) with high branching density can be obtained using a bulky amine-imine nickel catalyst [10d]. On the basis of an extension of previous work and new application of amine-imine nickel catalyst [10d,e], we herein synthesized amino-functionalized branched PE as a macroinitiator by living polymerization of ethylene, and prepared new polyethylene-*block*-poly(L-glutamate) (PE-*b*-PGA) amphiphilic copolymers through the subsequent ROP of γ-benzyl-L-glutamate-*N*-carboxyanhydride (BLG-NCA) (Scheme 1). These well-defined amphiphilic block copolymers can self-assemble into micelles in aqueous solution and the conformation of the PGA segment is sensitive to pH value. The novelty in the present case is that the initial PE-*b*-PGA block copolymer with vastly different solubilities opens a way for synthesis of responsive polyolefin materials. Biological interest in this material arises from the possibility of model membrane preparation which is useful in study of protein—lipid bilayer interactions because of structural similarity of polyolefin to lipid and structural similarity of PGA to protein [8].

2. Results and discussion

2.1. Synthesis of PE-b-PGA diblock copolymer

PE-*b*-PGA diblock copolymers were obtained by ring-opening polymerization (ROP) of γ-benzyl-L-glutamate-*N*-carboxyanhydride (BLG-NCA) using PE—COOCH(^{i}Pr)NH_2 as a macroinitiator and subsequent deprotection of the benzylester groups (Scheme 1). On the basis of our previous study [10e], the PE macroinitiator can be firstly prepared by amine-imine nickel-catalyzed ethylene living polymerization and subsequent conversion of the terminated group from hydroxyl to amino group. The structure of amino terminated PE (PE—COOCH(^{i}Pr)NH_2) was characterized to has M_n of 28 kg/mol, M_w/M_n of 1.04, and end functionality of ~91%. Three samples of polyethylene-*b*-poly(γ-benzyl-L-glutamate) (PE-*b*-PBLG) copolymer precursors were synthesized by the ROP of γ-benzyl-L-glutamate-*N*-carboxyanhydride (BLG-NCA) in $CHCl_3$ (Table 1) [10e,11]. Overlapped elution traces with solvent were observed when molecular weights of these PE-*b*-PBLG copolymers were determined by GPC using a good solvent THF as eluant at 40 °C, which could be attributed to the strong interaction between the polypeptide-based copolymers and GPC columns [12]. Amphiphilic PE-*b*-PGA diblock copolymers were obtained after deprotection of the benzylester groups by hydrolysis in the acidic environment (HBr/HAC). Neutralization of the carboxylic functional groups with NaOH yielded the PE-*b*-poly(sodium L-glutamate) copolymers which are readily soluble in water. Therefore, PE-*b*-PGA copolymers were further purified by extraction in water. The pure PE-*b*-PGA copolymers were used to characterize microstructure and study properties in the follow-up experiments.

Table 1
Synthesis of and characterization of PE-*b*-PGA copolymers.

Entry	Copolymer	Copolymer precursor	$n_{NCA/}n_{PE}$[a]	$M_{n\text{-PE}}$[b] (kg/mol)	$M_{n\text{-PGA}}$[c] (kg/mol)	M_n[c] (kg/mol)	DP_{NCA}[d]
1	PE_{1000}-*b*-PGA_{122}	PE_{1000}-*b*-$PBLG_{122}$	150	28.0	15.7	43.7	122
2	PE_{1000}-*b*-PGA_{185}	PE_{1000}-*b*-$PBLG_{185}$	250	28.0	23.9	51.9	185
3	PE_{1000}-*b*-PGA_{284}	PE_{1000}-*b*-$PBLG_{284}$	400	28.0	36.6	64.6	284

Polymerization conditions of ROP: 25 °C, 72 h, chloroform, total volume: 8 mL [10e].

[a] Molar feeding ratio of NCA monomer to macroinitiator PE—COOCH(^{i}Pr)NH_2.

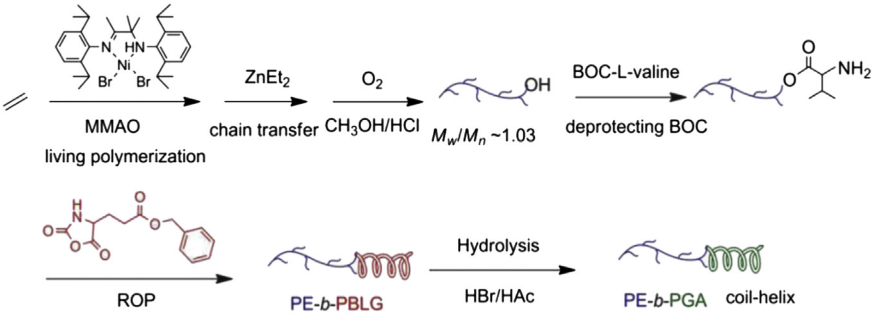
[b] Determined by high temperature gel permeation chromatography (GPC) in 1,2,4-trichlorobenzene at 150 °C using a light scattering (LS) detector.

[c] Determined by ^{1}H NMR.

[d] Deduced by degree of polymerization of NCA.

^{1}H NMR spectrum (Fig. 1) of PE-*b*-PGA copolymer in D_2O shows that the characteristic peaks of the PGA chain are sonly present without the resonances of PE, suggesting the formation of the copolymer aggregates in water. Also, no proton signals of phenyl (e) and methylene (d) on benzylester group are observed at 7.24 and 5.24 ppm, suggesting full deprotection. The methyline signal (c) on the polypeptide main chain is observed to completely shift from 4.58 ppm to 4.15 ppm, further proving full conversion of PBLG to PGA. The more steady support comes from FT-IR spectra of polymer samples (Fig. 2). The characteristic bands of phenyl at ~3065, 751, 698 cm^{-1} completely disappear, and a characteristic band of carboxylate at 1395 cm^{-1} is clearly observed in the FT-IR spectrum of PE-*b*-PGA [6c].

Because of the vastly different solubilities of the two block segments, there is no good solvent for this type of amphiphilic PE-*b*-PGA copolymers. So far, it is impossible to determine the molecular weights distributions of these PE-*b*-PGA block copolymers with GPC due to the high tendency to form aggregates in any kind of organic solvent. However, it is known that the primary anime-initiated polymerization of *N*-carboxyanhydrides usually affords



Scheme 1. Synthesis of PE-b-PGA diblock copolymers.