The First Report on the Atom Transfer Radical Polymerization of an Optically Active Acidic Monomer Based on L-Phenylalanine

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ABSTRACT: For the first time, acidic monomer chiral N-acryloyl-L-phenylalanine was polymerized directly by atom transfer radical polymerization under mild conditions. Controlled polymerization was carried out in pure water, methanol/water mixture, or pure methanol using water-soluble initiators, such as 2-hydroxyethyl-2′-methyl-2′-bromopropionate and sodium-4-(bromomethyl)benzoate at room temperature. The corresponding optically active biocompatible amino acid-based homopolymers were obtained in good yields with narrow molecular weight distributions. © 2011 Wiley Periodicals, Inc. J Appl Polym Sci 124: 4512–4516, 2012

Key words: atom transfer radical polymerization; N-acryloyl-L-phenylalanine; controlled polymerization; water-soluble initiators; optically active

INTRODUCTION

Optically active polymers received much attention due to their distinctive chiral structures (e.g., helix) that resemble those of naturally occurring materials such as proteins, nucleic acids, and amino acids. An important application of these macromolecules is chiral recognition. This ability of chiral polymers has been utilized in various forms of catalytic and separation chemistry.[1–7] Amino acid-based synthetic polymers are expected to show a diversity of chemical and biochemical functions such as biocompatibility and biodegradability similar to those of polypeptides and form secondary structures such as helices.[8,9]

There is great interest in the atom transfer radical polymerization (ATRP), first discovered by Matyjaszewski[10] and Sawamoto[11]. It is among the most extensively used controlled/living radical polymerization methods that lead to the preparation of polymers with well-defined molecular weights and narrow polydispersities. ATRP consists of an alkyl halide (R—X) or pseudo-halide as an initiator and a transition metal complex (e.g., Cu,[12] Ru,[13] Os,[14] Mo,[15] or Fe[16]) as a catalyst. ATRP involves homolytic cleavage of an R—X bond by a transition metal complex, such as $Cu^{I}X/L$ (with a rate constant k_a), followed by propagation (with a rate constant k_p) and reversible deactivation of the propagating chain radical (R.; with a rate constant k_{da}) by the higher oxidation state catalyst complex, $Cu^{II}X_2/L$. The reaction progresses by repetitive transfer of halogen or pseudo-halogen atoms to and from the transition metal complex.[17–19]

Synthesis and properties of poly[(meth)acrylamide]s having amino acid moieties have been developed[8] due to their distinctive characteristic and numerous potential applications, such as biologically active materials, stimuli-responsive materials, optically active adsorbents, polyelectrolytes, controlled release systems, and photochromic materials. Patten and Matyjaszewski[20] reported that ATRP is commonly not able to polymerize acidic monomers due to a side reaction of the monomer with the metal complex and quaternization of the nitrogen ligands. However, Armes and coworkers[21] polymerized sodium methacrylate by aqueous media, and the resulting copolymers were obtained in good yields and narrow molecular weight distributions. Recently, Mays and coworkers[22] have also reported successful ATRP of acryloyl β-alanine in aqueous
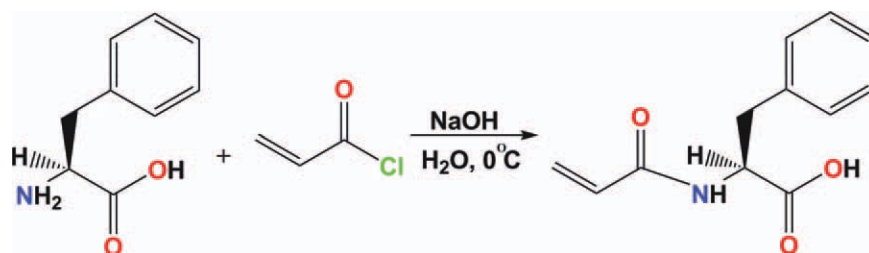
Scheme 1 Synthesis of APA. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

media at ambient temperature. Mori et al.[23] recently published the polymerization of N-acryloyl-L-phenylalanine (APA) methyl ester via reversible addition–fragmentation chain transfer (RAFT). They were reported that the combination of RAFT and Lewis acid complexation allows the synthesis of well-defined amino acid-based polymers with predetermined molecular weight, narrow molecular weight distribution, and improved tacticity. In this article, for the first time we wish to report the successful ATRP of optically active APA in pure water, 50 : 50 methanol/water mixture or pure methanol at room temperature.

EXPERIMENTAL

Materials

All chemicals were purchased from Fluka Chemical (Buchs, Switzerland), Aldrich Chemical (Milwaukee, WI), Riedel-deHaen AG (Seelze, Germany), and Merck Chemical (Darmstadt, Germany).

Techniques

Molecular weight distributions were measured by size exclusion chromatography (SEC), the elution rate was 1 mL/min, and standard polystyrene was used for calibration. End group titration was also applied for measuring molecular weight of one of the polymers. Briefly, 0.1 g of polymer was dissolved in 4 mL of N-methylformamide. This solution was titrated with a sodium methoxide solution ($0.005M$) in the same solvent, with phenolphthalein as an indicator. Proton nuclear magnetic resonance (^{1}H-NMR, 500 MHz) spectra were recorded in Dimethyl sulfoxide DMSO-d_6 solution using a Bruker (Germany) Avance 500 instrument. Specific rotations were measured by a Jasco Polarimeter (Japan).

Synthesis of initiator

2-Hydroxyethyl-2′-methyl-2′-bromopropionate (HMB) was synthesized as described previously.[24,25]

Synthesis of monomer

The vinyl monomer APA was synthesized by the general techniques previously reported.[26] As shown

in Scheme 1, the acylation reaction of L-phenylalanine with acryloyl chloride was performed in the presence of alkali at 0°C. Treatment with concentrated hydrochloric acid provided a white solid. Recrystallization from ethanol gave white crystals with good yield and purity. The chemical structure and purity of the optically active monomer were proven with Fourier transform infrared (FT-IR), ^{1}H-NMR, and ^{13}C-NMR spectroscopic techniques. $[\alpha]_D^{25} = + 18.32$ (0.05 g in 10 mL of Ethanol), mp 127°C (Ref. 26: mp 126°C).

ATRP of APA

General procedure

Mixture of HMB (0.012 g, 0.057 mmol) and APA monomer (1.00 g; 4.56 mmol) were dissolved in 2 mL of a 50 : 50 v/v methanol/doubly distilled water mixture, and then 5% NaOH was added to achieve pH = 8. This solution was degassed by passing dry nitrogen gas, and then 2,2′-bipyridine (bpy) ligand (0.023 g; 0.15 mmol) and Cu^{I}Br catalyst (0.008 g; 0.056 mmol) were added rapidly. On addition to these reagents, a dark brown solution was created. An exothermic polymerization reaction started immediately leading to an increase in viscosity of the mixture, and it was observed by sensing the vessel of reaction. After certain period of reaction time (Table I), the mixture was exposed to air. The dark brown reaction solution turned blue, indicating aerial oxidation of Cu(I) to Cu(II). The polymer solution was diluted with 5 mL of water, was mixed with about 1 g of silica gel, and was stirred for 1 h. Then, it was filtered off and was acidified with a solution of concentrated HCl (12 N) to provide white solid polymers. The resulting polymers were washed with cold Tetrahydrofuran (THF) to remove traces of residual APA monomer and/or unreacted initiator, affording APA homopolymer in high yield.

RESULTS AND DISCUSSION

In this investigation, for the first time, we describe an efficient direct synthesis of well-defined poly (APA) via ATRP using CuBr/bpy catalyst system and HMB or sodium-4-(bromomethyl)benzoate (SBB)

TABLE I
Summary of Conversion, Molecular Weight, and Polydispersity Data for Homopolymerization of APA Using Two
Initiators in Various Ratios of Water and Methanol at Room Temperature[a]

| Initiator | Solvent H$_2$O : MeOH | Time (h) | Conversion (%) | Molecular weight | | | | $[\alpha]^{25}_{Na,589}$ [c] | $[\alpha]^{25}_{Hg}$ [c] |
				M_n[b] (theory)	M_n (SEC)	M_n (titration)	M_w/M_n		
SBB	50 : 50	1	81.2	–	–	–	–	+17.46	+45.08
SBB	50 : 50	2	98.6	17,500	18,700	18,200	1.1	+20.22	+45.21
SBB	50 : 50	4	98.6	–	–	–	–	+20.28	+45.22
SBB	50 : 50	6	98.7	–	–	–	–	+20.44	+45.68
SBB	50 : 50	8	99.3	–	–	–	–	+20.72	+46.62
SBB	50 : 50	10	99.4	–	–	–	–	+21.16	+46.34
SBB	50 : 50	12	100.0	17,800	23,100	–	1.3	+21.96	+48.34
SBB	100 : 0	2	99.1	17,600	23,100	–	1.1	+18.43	+37.11
SBB	0 : 100	2	81.5	14,400	12,400	–	1.2	+18.69	+36.27
HMB	50 : 50	1	81.5	–	–	–	–	+21.43	+37.44
HMB	50 : 50	2	83.4	14,500	16,200	–	1.2	+21.94	+37.63
HMB	50 : 50	4	83.6	–	–	–	–	+21.69	+37.48
HMB	50 : 50	6	84.8	–	–	–	–	+22.53	+37.26
HMB	50 : 50	8	86.9	–	–	–	–	+25.68	+37.68
HMB	50 : 50	10	87.3	–	–	–	–	+25.94	+38.42
HMB	50 : 50	12	89	–	–	–	–	+24.47	+37.87

[a] $[APA]_o = 2.28M$ and the molar ratio of initiator : CuBr : bpy was 2 : 2 : 5.
[b] M_n (theory) $= 219.2([APA]_o/[\text{initiator}]) \times \%\text{Conversion}/100 + M_w$ (initiator).
[c] Measured at a concentration of 0.5 g/dL in DMF at 25°C.

as initiators in pH = 8 at room temperature. Bpy was chosen as ligand, because it is commercially available and readily forms a water-soluble complex with Cu^I.[21] The route of the synthesis of poly(APA) by ATRP is outlined in Scheme 2.

The water-soluble initiator, HMB, was synthesized from the reaction of 2-bromoisobutyryl bromide with ethylene glycol. The ^{1}H-NMR spectrum of poly(APA) is shown in Figure 1.

The ^{1}H-NMR spectrum of this polymer shows the characteristic resonance of acidic and amidic protons at 12.71 and 8.43 ppm, C—H chiral center at 4.41 ppm, two diastereotopic hydrogens of methylene group at 2.96 and 3.43 ppm, backbone methine proton at 2.05 ppm, and backbone methylene protons at

1.30 ppm. The disappearance of vinyl peaks at 5.58 and 6.28 ppm confirmed complete conversion of monomer to poly(APA), after 2-h reaction time. In the first step, we examined the homopolymerization of APA in doubly distilled, deionized water at room temperature under a nitrogen atmosphere. Exceptional rate acceleration in polymerization was observed, so high conversions were obtained in short period of time. The same experiments were also conducted in the presence of 50 : 50 methanol/water mixture or pure methanol as a solvent (Figs. 2 and 3). Rates of polymerization were noticeably slower in methanol compared with 50 : 50 methanol/water, probably owing to the more active nature of the Cu(I) catalyst in the presence of water.[27] The
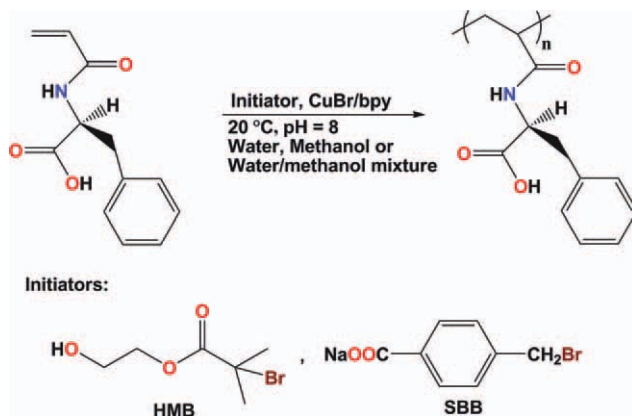
Scheme 2 Synthesis of poly(APA) via ATRP using two initiators. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]
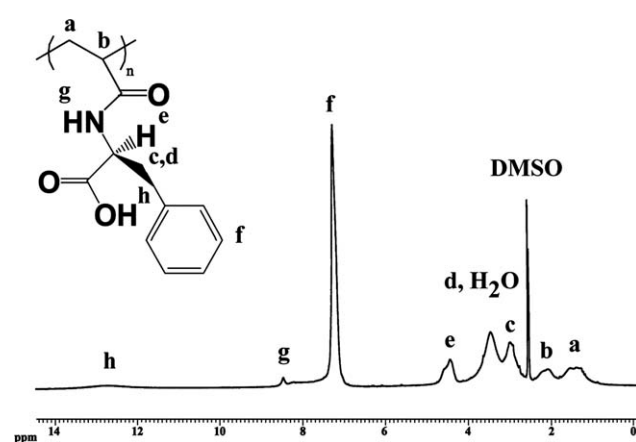

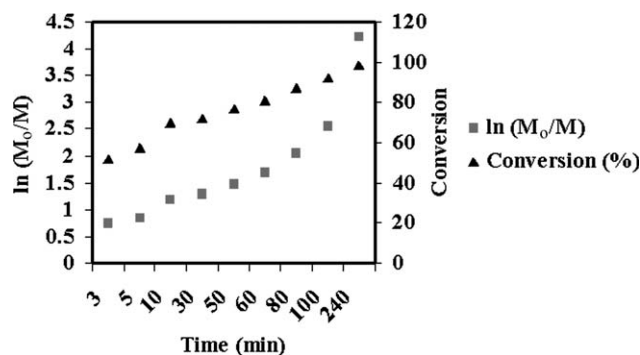Figure 1 ^{1}H-NMR (500 MHz) spectrum of poly(APA) using SBB as an initiator.

Figure 2 Kinetic plot of ATRP of APA in 50/50 methanol/water mixture as a solvent.

results of a particular set of experiments are summarized in Table I.

As predictable for a living polymerization, the molecular weights of the homopolymers enhanced with conversion. Figure 2 represents typical kinetic data for the homopolymerization of APA in 50 : 50 methanol/water mixture at room temperature. Conversions of more than 92% are attained within 100 min, and the plot of $\ln([M]_o/[M])$ versus time was linear up to 86.9% conversion, but after this time a deviation from first-order kinetics is observed. Armes and coworkers[28] reported that the kinetics for ATRP of acidic monomers is complex.

Figure 3 depicts kinetic data for the homopolymerization of APA in pure methanol. Under these conditions, the polymerization is rather slower than in the presence of water and 50 : 50 methanol/water mixture, so conversions of more than 92% are achieved within 12 h. In this case, the polymerization is first order with respect to APA monomer up to around 65% of conversion.

SEC of a homopolymer with number average molecular weight 18,700 g mol^{-1} using SBB initiator as typical polymers is shown in Figure 4.

Chiral poly(APA)s with $M_n = 18,700$ ($M_w/M_n = 1.1$), $M_n = 23,100$ ($M_w/M_n = 1.1$), $M_n = 12,400$ ($M_w/M_n = 1.2$), $M_n = 16,200$ ($M_w/M_n = 1.2$) and $M_n =$
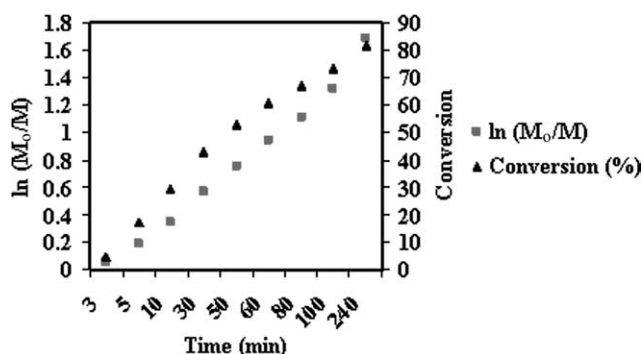

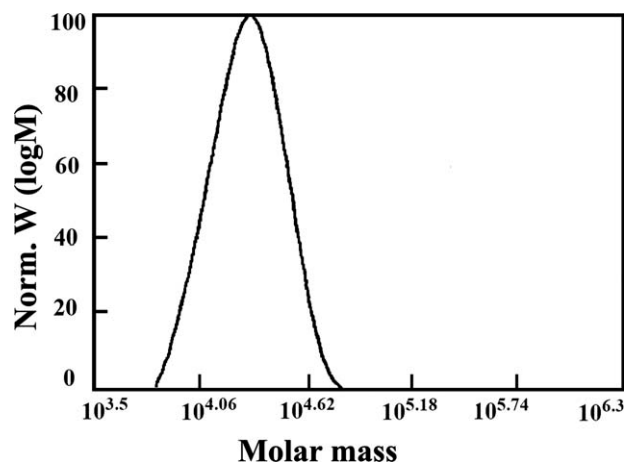**Figure 3** Kinetic plot of ATRP of APA in methanol as a solvent.

Figure 4 A representative SEC curve of poly(APA).

23,100 g mol^{-1} ($M_w/M_n = 1.3$) were obtained, so molecular weight distribution value remained low ($M_w/M_n = 1.3$) even for a homopolymer with higher molecular weight. Molecular weight of a sample of poly(APA) at 98.6% conversion was also determined by titration, and the measured value was 18,200 g mol^{-1}, which is close to one was determined by SEC (Table I). It is very interesting to mention that comparing the data obtained from this work with the study performed previously,[22] higher M_n with similar M_w/M_n was obtained at shorter reaction time. On the other hand, comparing with other investigation,[23] higher M_n with lower M_w/M_n was obtained at lower reaction temperature. However, it is important to note that; based on biocompatibility considerations, HMB initiator was preferred than SBB initiator.[22]

CONCLUSIONS

The ATRP of APA was successfully performed in pure water, 50/50 methanol/water mixture or pure methanol using HMB or SBB as water-soluble initiators and CuCl/bPy as catalyst. Well-defined poly(-APA) contain amino acid, L-phenylalanine in the side chain was obtained directly, without requiring protection chemistry for the carboxylic acid residues, with narrow weight distributions ($M_w/M_n < 1.3$) and high conversions (100%).

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