RAFT Polymerization of Acrylamide Derivatives Containing L-Phenylalanine Moiety

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ABSTRACT: We report the controlled synthesis of an amino acid based polymer by reversible addition−fragmentation chain transfer (RAFT) polymerization of *N*-acryloyl-L-phenylalanine (A-Phe-OH), which has a carboxylic acid group. Three chain transfer agents (CTAs), benzyl dithiobenzoate (CTA 1), benzyl 1-pyrrolecarbodithioate (CTA 2), and *O*-ethyl-*S*-(1-phenylethyl) dithiocarbonate (CTA 3), were compared for the direct polymerization of A-Phe-OH without protecting chemistry. With 2,2′-azobis(isobutyronitrile) as an initiator, the dithiocarbamate-type RAFT agent (CTA 2) is efficient for the preparation of poly(A-Phe-OH) with relatively narrow molecular weight distributions. The effects of several parameters, such as solvent, temperature, CTA to initiator molar ratio, etc., were investigated in order to determine the conditions, leading to optimal control of the direct polymerization. Good control of the polymerization in the presence of CTA 2 in methanol was confirmed by the formation of narrow polydispersity products and the linear relationship between the molecular weight and conversion. Depending on the monomer/CTA ratio, the amino acid based polyelectrolytes, poly(A-Phe-OH)s, with number-average molecular weights between 6500 and 54 400 and polydispersities between 1.23 and 1.27 were obtained, as evidenced by size-exclusion chromatography of the methylated samples.

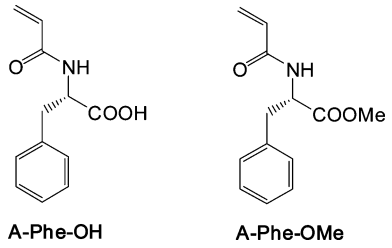
Introduction

In recent years, there has been renewed interest in synthetic polypeptides, because of their potential applications as biodegradable and biomedical polymers,[1−3] as well as their feasibility to create highly ordered hierarchical structures through noncovalent forces, such as hydrogen bonding.[4−6] Incorporation of a high degree of amino acid functionality and chirality in polymer chains can enhance the potential to form secondary structures (α-helix and β-sheet) and higher ordered structures.[4−10] These synthetic polymers can be useful as chiral recognition stationary phases,[11] metal ion absorbents,[12] drug-delivery agents,[13,14] and biocompatible materials.[15] Such characteristic self-assembled structures and the potential applications of polymers derived from amino acids have attracted researchers to develop new synthetic routes to design a variety of amino acid based polymers using various polymerization techniques.[16−24]

Although a variety of amino acid based polymers has been synthesized by conventional free radical polymerization of vinyl monomers carrying amino acid residues,[25] it was difficult to control the molecular weights and their architectures. To utilize these noncovalent bonds between amino acid residues for the self-organization behavior of synthetic polymers and their unique properties and functions, it is desirable to establish precise synthetic methods to control molecular weight, polydispersity, topology, composition, and functions. Recently, we reported controlled radical polymerization of acrylamides having amino acid moieties in the side chains, *N*-acryloyl-L-phenylalanine methyl ester (A-Phe-OMe)[26] and *N*-acryloyl-L-proline methyl ester,[27] via a reversible addition−fragmentation chain transfer (RAFT) process.

In this contribution, we present direct RAFT polymerization of *N*-acryloyl-L-phenylalanine (A-Phe-OH), in which the carboxylic acid moiety is intact without a protecting group, as shown in Scheme 1. Controlled polymerization of amino acid based monomers with carboxylic acid moiety is promising for producing tailored functional polymers for various applications, because the carboxylic acid groups in polymers can be interacted with various metal ions, nonionic proton-accepting polymers, their derivatives, and cationic polyelectrolytes. Polymers containing carboxylic acid groups can be also regarded as weak polyelectrolytes, in which the degree of ionization is governed by the pH and ionic strength of aqueous solution. Their chemical structure and three-dimensional architectures of block and complex polymers containing carboxylic groups may be tuned for a wide range of applications covering different aspects, such as stabilization of colloids, induced micelle formation, components of intelligent materials, and polyelectrolyte complexing toward novel drug carrier systems.[28]

Scheme 1



Recent development in controlled radical polymerization methods has provided methodologies to synthesize well-defined functional polymers by a very facile and simple approach. The systems include atom transfer radical polymerization,[29,30] nitroxide-mediated radical polymerization,[31] and RAFT polymerization.[32,33] Among these controlled radical polymerizations, RAFT is the most versatile with respect to the monomer and the reaction medium, which lead to the development of novel polymeric materials with a variety of functional groups and unique properties. RAFT has been successfully applied for controlled polymerization of acrylamide derivatives, such as

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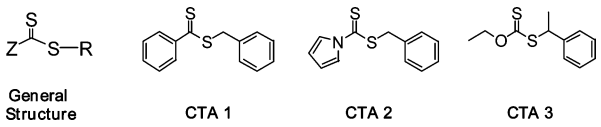
Scheme 2



N,*N*-dimethylacrylamide,[34−36] *N*-isopropylacrylamide,[37−40] and *N*-acryloylmorpholine.[41−43] These results confirm the ability of RAFT to produce well-controlled polymer chains either from monosubstituted or disubstituted acrylamide derivatives with narrow molecular weight distribution. RAFT provided controlled polymerization of carboxylic acid-containing monomers, such as acrylic acid, without protecting chemistry. For example, Rizzardo et al. reported a direct synthesis of poly(acrylic acid) with narrow polydispersity ($M_w/M_n = 1.23$) via RAFT polymerization of acrylic acid with 1-phenylethyl dithiobenzoate as chain transfer agent (CTA) and 2,2′-azobis(isobutyronitrile) (AIBN) as an initiator at 60 °C in *N*,*N*-dimethylformamide (DMF).[32] Controlled polymerization of the acidic monomer, acrylic acid, was also attained using 1-cyanoethyl 2-pyrrolidone-1-carbodithioate as CTA.[44] Polymerization of acrylic acid was reported to be controlled in alcohol and water with phenoxyxanthates or with trithiocarbonates.[45] The polymerization of acrylic acid was also controlled using dibenzyl trithiocarbonate and bis(1-phenylethyl) trithiocarbonate as CTA.[46] Direct synthesis of well-defined poly(acrylic acid) was achieved with a xanthate CTA (so-called macromolecular design via the interchange of xanthates, MADIX, process).[47,48] The polymerization of acrylic acid was also performed under gamma-irradiation in the presence of dibenzyl trithiocarbonate at room temperature, and well-defined poly(acrylic acid) with narrow polydispersity was successfully prepared.[49]

One of the key points for the synthesis of well-defined products via RAFT process is the design of the CTA, as the choice of R and Z groups depends on the monomer.[50,51] The mediating compounds employed in most RAFT polymerizations are dithioesters, Z−C(═S)S−R, with great structural variety with respect to their leaving R-groups and to their stabilizing Z-moieties. Effective RAFT agents include dithiobenzoates, dithioalkanoates, trithiocarbonates, dithiocarbonates (xanthates), and dithiocarbamates.[33] In this study, we selected three different CTAs, namely benzyl dithiobenzoate (CTA 1), benzyl 1-pyrrolecarbodithioate (CTA 2), and *O*-ethyl-*S*-(1-phenylethyl) dithiocarbonate (CTA 3), as shown in Scheme 2. An important monosubstituted acrylamide, *N*-isopropylacrylamide, was polymerized successfully via RAFT using benzyl 1-pyrrolecarbodithioate (CTA 2).[38] We previously demonstrated that controlled radical polymerization of a monosubstituted acrylamide having phenylalanine methyl ester moiety, A-Phe-OMe, was attained by RAFT process using CTA 2.[26] Whereas, benzyl dithiobenzoate (CTA 1) was efficient as the CTA for the preparation of near-monodisperse poly(*N*-acryloyl-L-proline methyl ester)s with controlled molecular weights.[27] CTA 1 was employed as a RAFT agent for well-controlled polymerization of *N*,*N*-dimethylacrylamide[34] and *N*-isopropylacrylamide.[37] The R group in CTA must be a good free radical leaving group and efficient at reinitiating polymerization. CTA 1 and CTA 2 have the same R group, which yields a benzyl radical species upon fragmentation. Indeed, as the Z group influences strongly the stability of the dithioester radical intermediate, strong stabilizing groups will favor the formation of the radical intermediate and, therefore, enhance the reactivity of the S═C bond toward radical addition. However, the stability of the intermediate needs to be finely tuned to favor its fragmentation, which will free the reinitiating group (R). *O*-Ethyl-*S*-(1-phenylethyl) dithiocarbonate (CTA 3), which is a xanthate-type CTA, was employed for controlled polymerization of acrylic acid by so-called MADIX process.[47] We describe the conditions best suited toward the controlled synthesis of poly(A-Phe-OH) without protecting chemistry.

Experimental Section

Materials. 2,2′-Azobis(isobutyronitrile) (Kanto Chemical, 97%) was purified by recrystallization from methanol. 1,4-Dioxane (Kanto Chemical, 99%) was distilled from sodium wire, and toluene (Kanto Chemical, 99.5%) was distilled before use. L-Phenylalanine (Kanto Chemical, 99%), methanol (Wako Pure Chemical, 99.8%), and ethanol (Wako Pure Chemical, 99.5%) were used as received. DMF (Kanto Chemical, 99.5%) was distilled from CaH_2. The methylation agent, trimethylsilyldiazomethane (2 M solution in diethyl ether), was purchased from Aldrich and used as received. Other materials were used without further purification.

***N*-Acryloyl-L-phenylalanine (A-Phe-OH).** The monomer was prepared by the reaction of acryloyl chloride with L-phenylalanine according to a method reported previously with a slight modification.[52,53] Reaction of sodium salt of L-phenylalanine with acryloyl chloride in aqueous solution, followed by acidification of the medium produced the monomer as a white solid, and the product was purified by column chromatography on silica with ethyl acetate as the eluent to give A-Phe-OH. $[M]_D^{25} = 150.2°$, $c = 0.1$ g/dL, THF, m.p. = 125 °C (lit.[52] m.p. = 126 °C). The ^{1}H NMR and FT-IR spectra of the monomer are shown in Figures S1 and S2, respectively (see Supporting Information).

Synthesis of Chain Transfer Agents (CTAs). The syntheses of benzyl dithiobenzoate (CTA 1)[27,51] and benzyl 1-pyrrolecarbodithioate (CTA 2)[50,54] were conducted according to the procedures reported previously. The CTA 2 was finally purified by column chromatography on silica with *n*-hexane as the eluent to afford the corresponding product as yellow oil. CTA 1 was purified by vacuum distillation using a glass tube oven (Shibata GTO-250RS) to give red oil. *O*-Ethyl-*S*-(1-phenylethyl) dithiocarbonate (CTA 3) was synthesized by the reaction of potassium ethyl xanthogenate and (1-bromoethyl)benzene according to a procedure reported in the literature.[45,55] CTA 3 was finally purified by column chromatography on silica with hexane/ethyl acetate, in which the content was gradually changed from 85/15 to 50/50 vol %, as the eluent to give pale yellow oil.

General Polymerization Procedure. All polymerizations were carried out with AIBN as an initiator in a degassed sealed tube. A representative example is as follows: the monomer (0.50 g, 2.3 mmol), CTA 2 (10.7 mg, 0.046 mmol), AIBN (3.8 mg, 0.023 mmol), and methanol (2.0 mL) were placed in a dry glass ampule equipped with a magnetic stirring bar, and then the solution was degassed by three freeze−evacuate−thaw cycles. After the ampule was flame-sealed off under vacuum, it was stirred at 45 °C for the desired time. The characteristic pale yellow color remained during the polymerization. The reaction was stopped by rapid cooling with liquid nitrogen. For the determination of the monomer conversion, the ^{1}H NMR spectrum of the polymerization mixture collected just after the polymerization was measured in DMSO-d_6 at room temperature, and the integration of the monomer C═C−*H* resonance at around 5.6 ppm was compared with the sum of the N−C−*H* peak intensity of the polymer and the monomer at around 4.4−4.7 ppm. Conversion determined by this method was 76%. The polymer obtained was purified by reprecipitation from a tetrahydrofuran (THF) solution into a large excess of ethyl acetate/hexane (7/3 vol-%), and the resulting product was freeze-dried from dioxane: yield 0.32 g, 64%. The resulting poly(A-Phe-OH) was soluble in basic water (pH > 11), methanol, ethanol, dioxane, dimethyl sulfoxide (DMSO), DMF, while insoluble in neutral water (pH ≈ 7), acidic water (pH < 4), ethyl acetate, chloroform, diethyl ether, and hexane. FT-IR (KBr) ν_{max}: 3327 (NH), 2926 (CH), 1727 (carboxylic acid C═O), 1657 (amide C═O), 1530, 1214 cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 0.3−2.4 (3H, CH and CH_2 in the polymer main chain), 2.6−3.7 (2H, CH_2 in the phenylalanine residue), 4.2−4.8 (1H, CH in

the phenylalanine residue) 7.7−8.5 (1H, amide NH), and 6.7−7.7 ppm (5H, aromatic protons).

For size-exclusion chromatography (SEC) measurements, the resulting poly(A-Phe-OH)s were modified by methylation of the carboxylic acid groups using trimethylsilyldiazomethane according to a method reported previously with a slight modification.[56] In this way, 25 mg of each sample was dissolved in a mixture of THF/methanol (2/1 vol %, to get solubilization at room temperature), overall volume 3.0 mL. The yellow solution of trimethylsilyldiazomethane (0.50 mL, 3.38 mmol) was added dropwise at room temperature into the polymer solution. Upon addition, bubbles appeared and the bright yellow solution became instantaneously pale yellow. Addition of the methylation agent was continued until the stopped bubbling. Then, an excess of methylation agent was added and the solution was stirred for 1 h more at room temperature. After the solvents were removed by evaporation and then the resulting solid was freeze-dried from dioxane, the methylated samples were employed without any purification for the SEC measurements. For the confirmation of the degree of the esterification, the methylated mixture was precipitated from THF into hexane/diethyl ether (1/1 vol %), then sample was evaluated by ^{1}H NMR spectroscopy in $CDCl_3$ (see Supporting Information). The degree of esterification was at least 95%, as judged by ^{1}H NMR spectroscopy by comparing the integration of the methyl resonance at around 3.2−3.8 ppm with the intensity of the methine resonance in the phenylalanine residue at 4.4−4.7 ppm peak. The poly(A-Phe-OMe) obtained after the methylation was soluble in most organic solvents, such as dichloromethane, acetone, dioxane, DMF, and DMSO, and insoluble in diethyl ether, hexane, and water. FT-IR (KBr) ν_{max}: 3340 (NH), 2951 (CH), 1737 (ester C═O), 1675 (amide C═O), 1530, 1213 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 0.3−2.4 (3H, CH and CH_2 in the polymer main chain), 2.6−3.2 (2H, CH_2 in the phenylalanine residue), 3.2−3.8 (3H, CH_3), 4.4−4.7 (1H, CH in the phenylalanine residue) 7.6−8.5 (1H, amide NH), and 6.9−7.6 ppm (5H, aromatic protons).

The theoretical number-average molecular weight on conversion is defined as follows:

$$M_n\,(\text{theor}) = \frac{[\text{Monomer}]_0}{[\text{CTA}]_0 + 2f[\text{I}]_0(1 - e^{-k_d t})} \times M_{\text{Monomer}} \times \text{convn} + M_{\text{CTA}} \quad (1)$$

in which M_{CTA} and $M_{Monomer}$ are molecular weights of chain transfer agent and the methylated monomer (A-Phe-OMe), and $[Monomer]_0$ and $[CTA]_0$ are the initial concentrations of the unprotected monomer, A-Phe-OH, and chain transfer agent, respectively. The right-hand side of the denominator accounts for radicals derived from initiator with an initial concentration $[I]_0$ at time t with a decomposition rate, k_d. The initiator efficiency is represented by f. In an ideal RAFT process, polymer directly derived from the initiators is minimal, and thus the second term in the denominator becomes negligible and eq 1 can be simplified to eq 2.

$$M_n\,(\text{theor}) = \frac{[\text{Monomer}]_0}{[\text{CTA}]_0} \times M_{\text{Monomer}} \times \text{convn} + M_{\text{CTA}} \quad (2)$$

For the kinetic study, typically a mixed solution of the A-Phe-OH (2.00 g, 9.1 mmol), CTA 2 (14 mg, 0.061 mmol), AIBN (5.0 mg, 0.030 mmol), and methanol (8.0 mL) were divided into six glass ampules, and then each solution was degassed by three freeze−evacuate−thaw cycles. After the ampule was sealed by flame under vacuum, it was placed in a thermostatic oil bath at 45 °C for the desired time. The reaction was stopped by rapid cooling with liquid nitrogen, and the monomer conversion was determined by the ^{1}H NMR spectrum of the polymerization mixture.

Instrumentation. ^{1}H NMR (270 MHz) spectra were recorded with a JEOL EX-270. Specific rotations ($[\alpha]_D$) were measured on a JASCO DIP-1000 digital polarimeter equipped with a sodium lamp as a light source. Number-average molecular weight (M_n) and molecular weight distribution (M_w/M_n) were estimated by size-exclusion chromatography (SEC) using a Tosoh HPLC HLC-8220 system equipped with refractive index and ultraviolet detectors at 40 °C. The column set was as follows: three consecutive hydrophilic vinyl polymer-based gel columns [TSK-GELs (bead size, exclusion limited molecular weight): SuperAW5000 (7 μm, 4 × 10^6), SuperAW4000 (6 μm, 4 × 10^5), SuperAW3000 (4 μm, 6 × 10^4), 15 cm each] and a guard column [TSK-guardcolumn Super AW−H, 3.5 cm]. The system was operated at a flow rate of 0.6 mL/min, using *N*,*N*-dimethylformamide containing 10 mM LiBr as an eluent. Polystyrene standards were employed for calibration. For detailed SEC evaluation of the polymers obtained by kinetic investigations, the following system was employed; column set: four consecutive vinyl polymer-based gel columns [TSK-GELs (bead size, exclusion limited molecular weight): α-M (13 μm, > 1 × 10^7), α-4000 (10 μm, 4 × 10^5), α-3000 (7 μm, 9 × 10^4), α-2500 (7 μm, 5 × 10^3), 30 cm each] and a guard column [TSK-guardcolumn α, 4.0 cm]; flow rate: 1.0 mL/min.

Table 1. Polymerization of N−Acryloyl-L-phenylalanine (A-Phe-OH) Using Different Chain Transfer Agents (CTAs) in 1,4-Dioxane at 60 °C for 24 h[a]

entry	CTA[b]	conv.[c] %	M_n [d](theory)	M_n [e](SEC)	M_w/M_n [e](SEC)
1		>99		59 000	3.09
2	CTA1	42	5100	3500	1.31
3	CTA2	97	11 500	10 500	1.42
4	CTA3	>99	11 800	6500	1.69

[a] $[AIBN]_0/[CTA]_0/[A\text{-Phe-OH}]_0$ = 1/2/100, monomer concentration = 0.25 g/mL, where AIBN = 2,2′-azobis(isobutyronitrile), A-Phe-OH = *N*-acryloyl-L-phenylalanine. [b] CTA 1 = benzyl dithiobenzoate, CTA 2 = benzyl 1-pyrrolecarbodithioate, CTA 3 = *O*-ethyl-*S*-(1-phenylethyl) dithiocabonate (see Scheme 2). [c] Calculated by ^{1}H NMR in DMSO-d_6. [d] The theoretical molecular weight ($M_{n,theory}$) = (MW of A-Phe-OMe) × $[A\text{-Phe-OH}]_0/[CTA]_0$ × conversion + (MW of CTA), A-Phe-OMe = *N*-acryloyl-L-phenylalanine methyl ester. [e] Methylated samples were measured by size-exclusion chromatography (SEC) using polystyrene standards in *N*,*N*-dimethylformamide (DMF, 10 mM LiBr).

Results and Discussion

Preliminary Comparison of Chain Transfer Agents (CTAs). To provide an effective route for the controlled synthesis of amino acid based polymers derived from L-phenylalanine, we initially investigated the influence of the chain transfer agent (CTA) on the homopolymerization of *N*-acryloyl-L-phenylalanine (A-Phe-OH). The unprotected monomer, A-Phe-OH, was directly polymerized using three different CTAs, and the results are summarized in Table 1. When A-Phe-OH was polymerized using CTA 2 with AIBN as an initiator at $[A\text{-Phe-OH}]_0/[CTA\ 2]_0/[AIBN]_0$ = 100/2/1 in dioxane, almost full conversion (97%, as determined by ^{1}H NMR spectroscopy) was obtained at 60 °C after 24 h. The characteristic pale yellow color remained throughout the polymerization without significant change in the viscosity. For SEC measurement, the resulting poly(A-Phe-OH) was converted into its methyl ester form by treating the carboxylic acid groups using trimethylsilyldiazomethane.[56] As verified by ^{1}H NMR analysis of the polymers, the proportion of methyl ester was almost quantitative in all cases. The methylated polymer, poly(*N*-acryloyl-L-phenylalanine methyl ester) (poly(A-Phe-OMe)), showed symmetrical unimodal SEC peak (see Supporting Information) with relatively narrow molecular weight distribution (M_w/M_n = 1.42). The number-average molecular weight of the poly(A-Phe-OMe), measured by a GPC in DMF with 10 mM LiBr, was M_n = 10 500, which is roughly comparable to the theoretical value (M_n = 11 500) calculated from the monomer/CTA molar ratio and the monomer conversion using eq 2. The polymerization with CTA 3 provided the polymer with broader polydispersity (M_w/M_n = 1.69). In this case, the number-average molecular weight of the methylated polymer (M_n = 6500) is slightly lower than the theoretical

Table 2. Effects of Temperature and Solvent on Polymerization of N−Acryloyl-L-phenylalanine (A-Phe-OH) with AIBN in the Presence of Benzyl 1-Pyrrolecarbodithioate (CTA 2) for 24 h[a]

entry	temp, °C	solvent (vol ratio)	convn,[b] %	M_n[c] (theory)	M_n[d] (SEC)	M_w/M_n[d] (SEC)
1	60	1,4-dioxane	97	11 500	10 500	1.42
2	60	MeOH	94	11 200	12 800	1.30
3	60	MeOH/toluene (1/1)	94	11 200	8800	1.36[e]
4	60	MeOH/toluene (9/1)	91	10 800	7300	1.29
5	45	1,4-dioxane	84	10 000	7100	1.45
6	45	MeOH	76	9100	6500	1.25
7	45	EtOH	63	7600	5000	1.40
8	45	MeOH/toluene (9/1)	73	8700	5700	1.26
9	45	MeOH/1,4-dioxane (1/1)	73	8700	5500	1.30
10	45	DMF	90	10 800	7200	1.35

[a] $[AIBN]_0/[CTA\ 2]_0/[A\text{-Phe-OH}]_0 = 1/2/100$, monomer concentration = 0.25 g/mL, where AIBN = 2,2′-azobis(isobutyronitrile), CTA 2 = benzyl 1-pyrrolecarbodithioate, and A-Phe-OH = *N*-acryloyl-L-phenylalanine. [b] Calculated by ^{1}H NMR in DMSO-d_6. [c] The theoretical molecular weight ($M_{n,theory}$) = (MW of A-Phe-OMe) × $[A\text{-Phe-OH}]_0/[CTA]_0$ × conversion + (MW of CTA), A-Phe-OMe = *N*-acryloyl-L-phenylalanine methyl ester. [d] Methylated samples were measured by size-exclusion chromatography (SEC) using polystyrene standards in *N*,*N*-dimethylformamide (DMF, 10 mM LiBr). [e] Polymer precipitation during the reaction.

value (M_n = 11 800). Here, we cannot exclude the possibility of contributing to the chains derived from the initiators at $[CTA]_0/[AIBN]_0 = 2/1$. If the AIBN-derived chains are taken into account in this system, a rough estimation suggests that $M_{n,theory}$ corresponds to 7800 (calculated form eq 1 with $k_d = 2.5 \times 10^{-5}$ s^{-1},[57] $f = 0.6$, at 60 °C, complete conversion for 24 h reaction), instead of $M_{n,theory}$ = 11 800 (calculated from eq 2 without consideration of AIBN-derived chains).

The polymerization with AIBN in the presence of CTA 1 at 60 °C produced the polymer with a relatively narrow molecular weight distribution ($M_w/M_n = 1.31$, $M_n = 3500$), while achieving only 42% conversion even after 24 h. This is an indication that the polymerization of A-Phe-OH with CTA 1 is much slower than that with CTA 2 in dioxane at 60 °C. Similar phenomenon was observed in our previous work, in which RAFT polymerization of A-Phe-OMe with CTA 1 led to slow polymerization rate, compared to that with CTA 2.[26] In contrast, a conventional radical polymerization of A-Phe-OH under the similar conditions in the absence of CTA afforded a high molecular weight homopolymer with high polydispersity (M_n = 59 000 and M_w/M_n = 3.09, entry 1). The difference in the molecular weights of the polymers obtained in the presence and absence of CTA under the similar conditions supports the effectiveness of the reaction conditions to achieve controlled polymerization.[58] From these preliminary results, we selected CTA 2 for our further investigations toward the precise synthesis of poly(A-Phe-OH)s having low polydispersity and controlled molecular weights.

Optimization of Polymerization Conditions. In the next stage, the effects of the polymerization temperature and solvent were investigated in terms of the molecular weights and the polydispersity of the resulting poly(A-Phe-OH). In a previous publication, we demonstrated that alcohols, such as methanol and toluene/methanol mixture, were effective solvents for the controlled radical polymerization of A-Phe-OMe, and poly(A-Phe-OMe)s with low polydispersity could be obtained by RAFT polymerization at various temperatures (45, 60, and 90 °C, depending on the solvent).[26] The polymerization was carried out in various solvents at $[A\text{-Phe-OH}]_0/[CTA\ 2]_0/[AIBN]_0 = 100/2/1$, and the results are shown in Table 2. In all instances the target molecular weight at quantitative conversion was 11000 g/mol in the carboxylic acid form, poly(A-Phe-OH).

When A-Phe-OH was polymerized using CTA 2 with AIBN in methanol, almost full conversion (94%, as determined by ^{1}H NMR) was obtained at 60 °C after 24 h. Although the polydispersity remains low (M_w/M_n = 1.30, entry 2 in Table 2), the resulting polymer shows SEC peak with a broad shoulder at high molecular weight region, as can be seen in Figure 1. This is frequently observed for RAFT polymer obtained at high monomer conversion, which is most probably attributed to species arising from bimolecular termination reactions of the growing polymer chains. In contrast, the polymerization in methanol at lower temperature (45 °C) was relatively successful in terms of the suppression of the termination reactions and afforded the polymer with low polydispersity (M_w/M_n = 1.25, entry 6 in Table 2) with reduced shoulder peak. The reduced termination may be caused by a significant decrease in radical flux at low temperature. This behavior can be also explained by the assumption that decreasing the temperature leads to a decrease in the radical reactivity, resulting in the increased selectivity of the various radical reactions to minimize unfavorable side reactions. Another possible explanation is that lower polymerization temperature causes a remarkable decrease of the fragmentation rate constant, leading to the decreased number of the active propagating radical. As shown in Table 2, in all cases lower polymerization temperature (from 60 to 45 °C) led to the decrease in the conversion, regardless of the nature of the solvent.

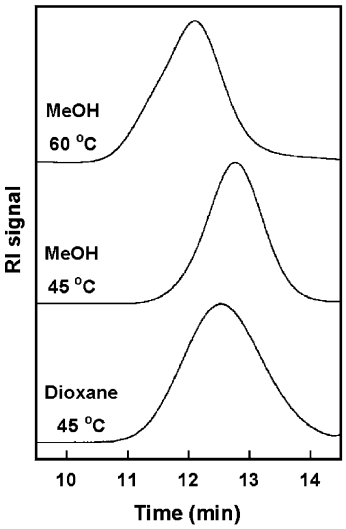


Figure 1. SEC traces of the methylated poly(A-Phe-OH)s obtained by RAFT polymerization of A-Phe-OH at $[A\text{-Phe-OH}]_0/[CTA\ 2]_0/[AIBN]_0 = 100/2/1$ under different conditions, at where AIBN = 2,2′-azobis(isobutyronitrile), A-Phe-OH = *N*-acryloyl-L-phenylalanine. CTA 2 = benzyl 1-pyrrolecarbodithioate. See Table 2 for detailed polymerization conditions.

Narrow polydispersity products (M_w/M_n = 1.26 and 1.29) were obtained by RAFT polymerization in methanol/toluene mixture (9/1 vol %) at 45 and 60 °C, respectively. Whereas, the polymerizations in 1,4-dioxane and ethanol at 45 °C gave the polymers having relatively broad molecular weight distributions (M_w/M_n = 1.40−1.45). When the polymerization was conducted in DMF, which is a strong proton-accepting solvent and is known to act as a complex-breaking (hydrogen bond-breaking) solvent, relatively high conversion (90%, as determined by ^{1}H NMR spectroscopy) was obtained even at 45 °C after 24 h, whereas there was no significant influence on the molecular weight and polydispersity (M_w/M_n = 1.35). These results suggest that the AIBN/CTA 2 system in methanol or methanol/toluene mixture (9/1 vol %) at lower temperature (45 °C) is a suitable system for controlled polymerization of A-Phe-

Table 3. Effect of Chain Transfer Agent/Initiator Molar Ratio on Polymerization of *N*-Acryloyl-L-phenylalanine (A-Phe-OH) Using AIBN and Benzyl 1-Pyrrolecarbodithioate (CTA 2) in MeOH at 45 °C[a]

entry	$[CTA\ 2]_0/[AIBN]_0$	time, h	convn,[b] %	M_n[c] (theory)	M_n[d] (SEC)	M_w/M_n[d] (SEC)
1	1.5	24	81	9700	7300	1.24
2	2	24	76	9100	6500	1.25
3	3	24	69	8300	6300	1.26
4	5	24	67	8100	6100	1.23
5	10	24	49	5900	5200	1.26
6	5	48	72	8600	5800	1.25
7	10	48	62	7500	4400	1.24

[a] $[A\text{-Phe-OH}]_0/[CTA\ 2]_0 = 50$, monomer concentration = 0.25 g/mL, where AIBN = 2,2′-azobis(isobutyronitrile), CTA 2 = benzyl 1-pyrrolecarbodithioate, and A-Phe-OH = *N*-acryloyl-L-phenylalanine. [b] Calculated by ^{1}H NMR in DMSO-d_6. [c] The theoretical molecular weight ($M_{n,theory}$) = (MW of A-Phe-OMe) × $[A\text{-Phe-OH}]_0/[CTA]_0$ × conversion + (MW of CTA), A-Phe-OMe = *N*-acryloyl-L-phenylalanine methyl ester. [d] Methylated samples were measured by size-exclusion chromatography (SEC) using polystyrene standards in *N*,*N*-dimethylformamide (DMF, 10 mM LiBr).

OH, but the increase in the polymerization temperature leads to unfavorable side reactions.

Influence of CTA/I Ratio. The CTA/initiator ratio acts frequently as a critical role in determining the overall success of a RAFT polymerization with respect to control over the molecular weight and molecular weight distribution. To evaluate the effect, we conducted the polymerization of A-Phe-OH in methanol at 45 °C for 24 h at different $[CTA\ 2]_0$:$[AIBN]_0$ ratios between 1.5 and 10, keeping the monomer-to-chain transfer agent ratio at a constant value of $[A\text{-Phe-OH}]_0/[CTA\ 2]_0 = 50/1$. As shown in Table 3, the monomer conversion decreased gradually from 81% to 49% as [CTA]/[AIBN] ratio increased from 1.5 to 10. Interestingly, no significant influence on the molecular weight distribution was observed, and the resulting polymers showed symmetrical unimodal SEC peaks without shoulders and tailing (M_w/M_n = 1.23−1.26, see Supporting Information), regardless of the [CTA]/[AIBN] ratio. In the cases of the polymerizations at [CTA]/[AIBN] = 5 and 10, longer polymerization time led to slight increase in the conversion, while achieving only 72% and 62% conversions even after 48 h, respectively. Since no significant shoulder peaks at high molecular weight regions were observed in GPC charts, the radical coupling reaction at the end of the polymerization is not a main reason for the limited conversions at [CTA]/[AIBN] = 5 and 10. This behavior may be due to that lower concentration of initiator and/or lower fragmentation rate result in lower number of radicals available for the propagation at 45 °C. In all cases, the molecular weights determined by SEC are much smaller than the corresponding calculated ones using eq 2, and the ratios of the calculated molecular weight ($M_{n,theory}$) to the value determined by SEC ($M_{n,SEC}$) are constant ($M_{n,theory}/M_{n,SEC}$ = 1.3−1.4) in the range of the concentration ratio of CTA to initiator, $[CTA\ 2]_0$:$[AIBN]_0$ = 1.5−5 at 24 h. These behaviors may due to the fact that the experimentally determined molecular weights are not absolute values but are apparent ones using polystyrene standards for GPC calibration. In a previous publication,[26] we reported that the absolute molecular weights of poly(A-Phe-OMe)s determined by GPC with a multiangle light scattering detector (GPC-MALS) were comparable to the theoretical values calculated by eq 2, but apparently higher than those determined by conventional GPC. The reported ratios of the molecular weight determined by GPC-MALS to the value determined by SEC ($M_{n,GPC-MALS}/M_{n,SEC}$ = 1.4−1.5) were roughly comparable to the ratio, $M_{n,theory}/M_{n,SEC}$ = 1.3−1.4, observed in this study. Hence, we believe that the discrepancies

Table 4. Effect of Chain Transfer Agent/Initiator Molar Ratio on Polymerization of *N*-Acryloyl-L-phenylalanine (A-Phe-OH) Using AIBN and Benzyl 1-pyrrolecarbodithioate (CTA 2) at 60 °C for 24 h in Different Solvents[a]

entry	solvent	$[CTA\ 2]_0/[AIBN]_0$	convn,[b] %	M_n[c] (theory)	M_n[d] (SEC)	M_w/M_n[d] (SEC)
1		2	97	11 500	10 500	1.42
2	1,4-dioxane	5	94	11 200	10 500	1.41
3		10	92	11 000	10 300	1.42
4		2	94	11 200	12 800	1.30
5	MeOH	5	86	10 300	9600	1.23
6		10	80	9500	8200	1.22
7		2	91	10 800	7300	1.29
8	MeOH/toluene	5	89	10 600	9100	1.24
9	(9/1)	10	86	10 200	8700	1.22

[a] $[A\text{-Phe-OH}]_0/[CTA\ 2]_0 = 50$, monomer concentration = 0.25 g/mL, where AIBN = 2,2′-azobis(isobutyronitrile), CTA 2 = benzyl 1-pyrrolecarbodithioate, A-Phe-OH = *N*-acryloyl-L-phenylalanine. [b] Calculated by ^{1}H NMR in DMSO-d_6. [c] The theoretical molecular weight ($M_{n,theory}$) = (MW of A-Phe-OMe) × $[A\text{-Phe-OH}]_0/[CTA]_0$ × conversion + (MW of CTA), A-Phe-OMe = *N*-acryloyl-L-phenylalanine methyl ester. [d] Methylated samples were measured by size-exclusion chromatography (SEC) using polystyrene standards in *N*,*N*-dimethylformamide (DMF, 10 mM LiBr).

are due to the difference in hydrodynamic volume between poly(A-Phe-OMe) obtained after the methylation and the linear polystyrene standards used for the calibration.

In RAFT polymerization, the total number of chains is determined by the number of CTAs that have successfully fragmented and reinitiated polymerization plus the number of initiator-derived chains. In other words, the molecular weights of resulting polymers should be decreased with decreasing $[CTA]_0/[Initiator]_0$ ratio under the same monomer-to-chain transfer agent ratio and monomer conversion. However, the number of polymer chains directly derived from the initiator molecules should be minimal in an ideal RAFT process, and the initial CTA concentration is large enough compared to the number of the initiator-derived chains.[59,60] In our system at $[A\text{-Phe-OH}]_0/[CTA\ 2]_0 = 50$ in methanol at 45 °C, the molecular weights obtained at $[CTA]_0/[AIBN]_0$ = 1.5−5 can be simply controlled by the monomer conversion and the molecular weight distributions remain narrow, indicating controlled character of the polymerization. Further increase in the $[CTA]_0/[AIBN]_0$ ratio leads to significant retardation of the polymerization rate.

The effect of CTA/initiator ratio was also investigated at 60 °C for 24 h in three different solvents, 1,4-dioxane, methanol, and methanol/toluene mixture (9/1 vol %). The polymerizations were conducted at different $[CTA\ 2]_0$:$[AIBN]_0$ ratios, 2, 5, and 10, keeping the monomer-to-chain transfer agent at a constant value of $[A\text{-Phe-OH}]_0/[CTA\ 2]_0 = 50/1$. The results are summarized in Table 4. The polymerizations in dioxane produced the polymers having relatively broad molecular weight distributions (M_w/M_n = 1.41−1.42), irrespective of the concentration ratio of CTA to initiator. In this case, no significant influence of the CTA/initiator ratio was observed on the monomer conversion, molecular weights, and molecular weight distribution. When the polymerization was carried out in methanol at 60 °C, the monomer conversion decreased gradually from 94% to 80% as the [CTA]/[AIBN] ratio increased from 2 to 10. The molecular weight distributions of the polymers obtained at $[CTA]_0/[AIBN]_0 = 5$ and 10 are narrow (M_w/M_n = 1.23 and 1.22), which are apparently lower than that at $[CTA]_0/[AIBN]_0 = 2/1$ (M_w/M_n = 1.30). Generally, decreasing initiator concentration leads to an improvement of the control of the polymerization, since termination reactions will be disfavored. The narrow molecular weight distribution is apparently due to rapid establishment of the "preequilibrium", which involves the

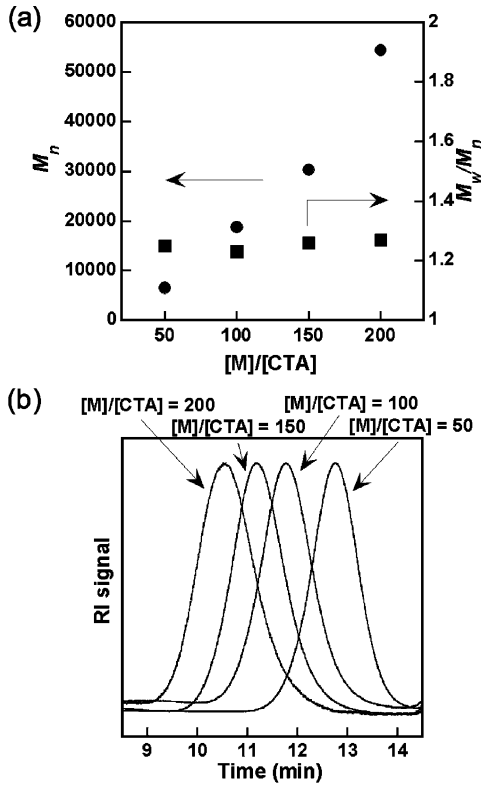


Figure 2. (a) Dependence of number-average molecular weight and molecular weight distribution on $[M]_0$:$[CTA]_0$ ratio for the polymerization of *N*-acryloyl-L-phenylalanine (A-Phe-OH) with 2,2′-azobis(isobutyronitrile) (AIBN) in the presence of benzyl 1-pyrrolecarbodithioate (CTA 2, see Scheme 2) in methanol at 45 °C. Monomer concentration = 0.25 g/mL. $[CTA\ 2]_0/[AIBN]_0$ = 2/1. Monomer conversion = 76−85%. (b) SEC traces of the corresponding poly(A-Phe-OMe)s obtained after the methylation.

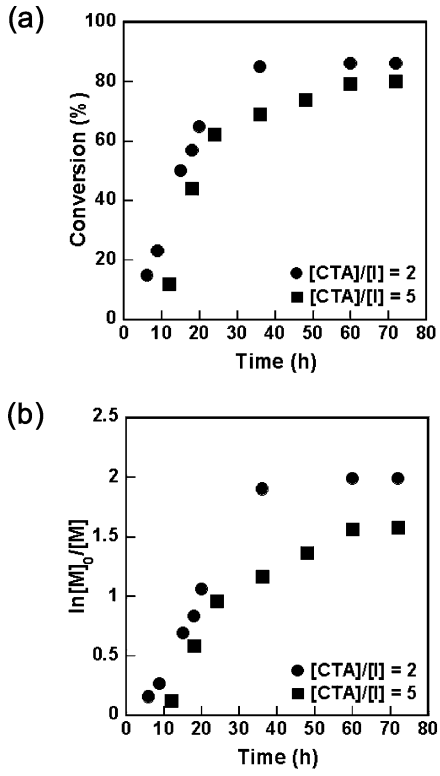


Figure 3. (a) Time−conversion and (b) first-order kinetic plots for the polymerization of *N*-acryloyl-L-phenylalanine (A-Phe-OH) with 2,2′-azobis(isobutyronitrile) (AIBN) in the presence of benzyl 1-pyrrolecarbodithioate (CTA 2, see Scheme 2) in methanol at 45 °C. Monomer concentration = 0.25 g/mL. $[A\text{-Phe-OH}]_0/[CTA\ 2]_0$ = 150. $[CTA\ 2]_0/[AIBN]_0$ = 2 (circles) and 5 (squares).

consumption of CTA and reversible fragmentation of intermediate to produce reinitiating R• fragment, efficient reinitiation from the R• fragment, and attainment of the so-called "main-equilibrium" in which the population of dormant chains and/or intermediate radicals is much higher than the total number of propagating chains.[61] The polymerization in methanol/toluene mixture (9/1 vol %) afforded the polymers with relatively low polydispersities (M_w/M_n = 1.22−1.24) and reasonable molecular weights at $[CTA]_0/[AIBN]_0$ = 5 and 10.

Control of Molecular Weights. Aiming to control the molecular weights, we further examined the polymerization of A-Phe-OH in methanol at 45 °C for 24 h at different $[M]_0$:$[CTA]_0$ ratios between 50 and 200, keeping the chain transfer agent-to-initiator ratio at a constant value of $[CTA\ 2]_0/[AIBN]_0$ = 2/1. Under the conditions, the conversion determined by ^{1}H NMR was 76−85% in all cases. Figure 2a shows the relation of the molecular weight and polydispersity of the methylated samples, poly(A-Phe-OMe)s, with $[M]_0$:$[CTA]_0$ ratio for the polymerization. A linear increase of the number-average molecular weight with the ratio without significant change of the polydispersity (M_w/M_n = 1.23−1.27) indicates a feasibility to control the molecular weights by the ratio. Note that the straight line could be obtained only when the monomer conversions are substantially the same in all cases. When high molecular weight product (M_n = 54 400, M_w/M_n = 1.27 in the methylated sample, which corresponds to M_n = 51 100 in the original carboxylic acid form) was produced, apparent viscosity increase was detected during the polymerization. Nevertheless, in all cases the SEC traces are unimodal with no evidence of high molecular weight species, as can be seen in Figure 2b. In the SEC experiments of representative samples, the RI detector and the UV detector monitoring the absorption due to the phenyl groups in the polymer at 280 nm gave similar curves within the same elution time range (Figure S6, see Supporting Information). These results suggest good control of the polymerization, leading to that the molecular weights of the amino acid based polyelectrolytes, poly(A-Phe-OH)s, can be easily adjusted by the monomer-to-CTA ratio.

Polymerization Kinetics. The polymerization kinetics of A-Phe-OH in the presence of CTA 2 in methanol at 45 °C was investigated at different chain transfer agent-to-initiator ratios, $[CTA\ 2]_0$:$[AIBN]_0$ = 2 and 5, keeping the monomer-to-chain transfer agent ratio at a constant value of $[A\text{-Phe-OH}]_0/[CTA\ 2]_0$ = 150. The time−conversion and the pseudo-first-order kinetic plots are shown in Figure 3. When A-Phe-OH was polymerized using CTA 2 with AIBN at $[A\text{-Phe-OH}]_0/[CTA\ 2]_0/[AIBN]_0$ = 300/2/1 in methanol (0.25 g/mL), which corresponds to [M] = 1.14 mol/L, [CTA] = 0.0076 mol/L, [AIBN] = 0.0038 mol/L, relatively high conversion (85%, as determined by ^{1}H NMR spectroscopy) was reached after 36 h. Actually, the reaction times are 6, 9, 15, 18, 20, 36, 60, and 72 h, corresponding to monomer conversions of 15, 23, 50, 57, 65, 85, 86, and 86%, respectively, suggesting that the polymerization is relatively slow and the conversion reaches a plateau value under the mild conditions used in this study. The polymerization was relatively slower for the ratio of 5 than for the ratio of 2, which is due to lower number of propagating radicals. Indeed, 74% conversion was reached after 48 h, and then the conversion "plateau" was observed in the case of the polymerization at $[CTA\ 2]_0$:$[AIBN]_0$ = 5. In both cases, the initial polymerization rate was relatively high, in which more than 60% conversion was reached after 20−24 h, and then the polymerization

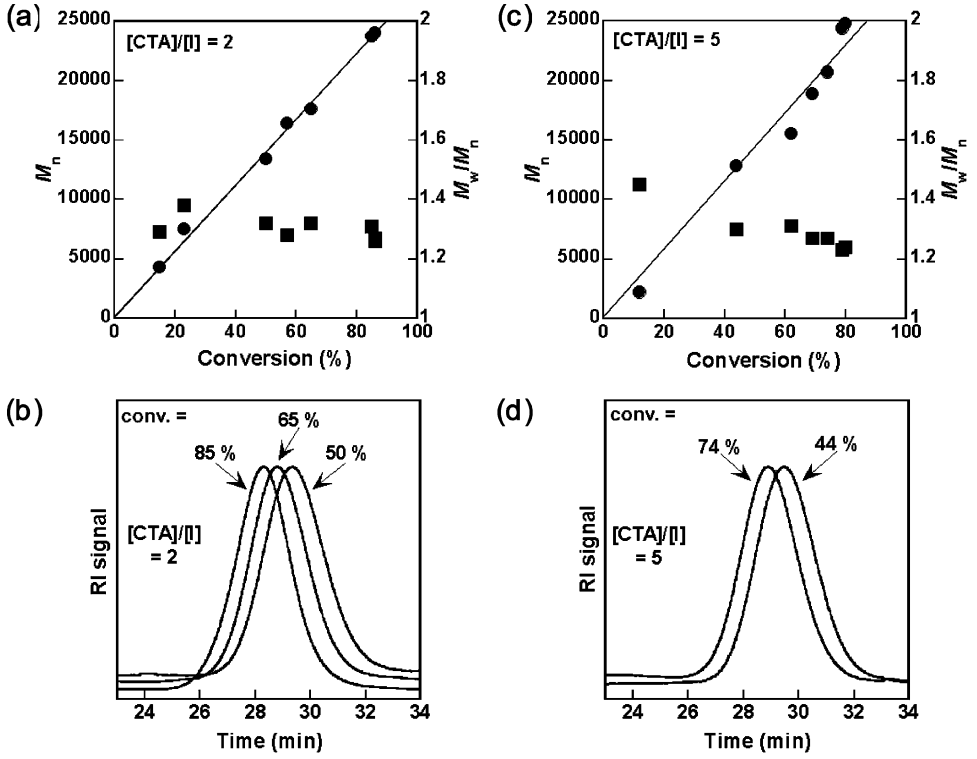


Figure 4. (a, c) Number-average molecular weight (circles) and polydispersity (squares) as a function of conversion, and (b, d) evolution of SEC traces with conversion for the polymerization of A-Phe-OH with AIBN in the presence of CTA 2 in methanol at 45 °C. $[CTA\ 2]_0/[AIBN]_0 = 2$ (a, b) and 5 (c, d). See Figure 3 for detailed polymerization conditions.

apparently slowed. Such curved semilogarithmic plots indicate complex kinetics. Similar conversion "plateau" was also reported on RAFT polymerization of bulky monosubstituted acrylamide, such as *N*-*tert*-butylacrylamide and *N*-octadecylacrylamide.[62] The first-order kinetic plot is considered to be linear only if the kinetics is first-order with respect to the monomer and the concentration of active species remains constant. Since there is no reason to suspect a higher order dependence of the polymerization rate on monomer conversion, the concentration of radicals are not constant under the conditions. Note that the viscosity is low enough to ensure an efficient stirring up to relatively high conversion under the conditions, which is due to relatively low molecular weighs of the resulting products (M_n of poly(A-Phe-OH) < 25000) and good solubility in methanol.

In both cases, induction periods are seen in the pseudo-first-order kinetic plots at 45 °C, as shown in Figure 3. The induction period roughly estimated simply by extrapolating the linear part of each curve to the time axis is about 10 h at $[CTA\ 2]_0:[AIBN]_0 = 5$, while it apparently decreases to less than 5 h at $[CTA\ 2]_0:[AIBN]_0 = 2$ (Figure S7, see Supporting Information). This is an indication that both the induction period and the polymerization rate, namely inhibition and retardation, are apparently affected by the ratio. The consumption of CTA and reversible fragmentation of intermediate to produce reinitiating R• fragment are referred to as the "preequilibrium", which is correlated closely with the induction period. An induction period is often observed in RAFT polymerization of various monosubstituted and disubstituted acrylamides.[26,36,38,40,41] However, the reasons for the induction periods with some CTAs are not clearly understood.[63−67] The rate retardation effect is attributed to the main equilibrium after all initial CTA have been transformed into macro-CTA (the so-called macro-RAFT agent), and may therefore be ascribed to different stabilities of the intermediate radicals in the main equilibrium. There is an ongoing debate on the mechanism that causes the inhibition and retardation.[58,68−71]

Figure 4 shows the evolutions of M_n and M_w/M_n with conversion for A-Phe-OH during the polymerizations at $[CTA\ 2]_0:[AIBN]_0 = 2$ and 5, respectively. In both cases the number-average molecular weights, M_n, increase linearly with conversion. The molecular weight vs monomer conversion plots go through the origin, while the experimental molecular weights are slightly lower than the calculated ones. The SEC traces of the methylated samples of poly(A-Phe-OH)s obtained at different polymerization times clearly illustrate the increase in molar mass with time (Figure 4b,d) having symmetrical unimodal SEC peaks without shoulders and tailings. These results suggest that the polymerization proceeds in a controlled fashion without nondegenerative chain transfer. For the polymerizations at $[CTA\ 2]_0:[AIBN]_0 = 2$, the polydispersity indices (M_w/M_n) for all samples range between 1.26 and 1.38, regardless of the monomer conversion. In the case of the polymerization at $[CTA\ 2]_0:[AIBN]_0 = 5$, the polydispersity obtained a maximum value of $M_w/M_n = 1.45$ at 12% conversion, which then decreased with conversion, reaching a final value of 1.24 at 80%.

The polymerization of A-Phe-OH in the presence of CTA 2 was also investigated in methanol at 60 °C at a constant monomer/chain transfer agent/initiator molar ratio, $[A\text{-Phe-OH}]_0/[CTA\ 2]_0/[AIBN]_0 = 750/5/1$. The time−conversion and the pseudo-first-order kinetic plots are shown in Figure 5a. More than 80% conversion was reached within 15 h and an induction period less than 5 h is seen in the pseudo-first-order kinetic plot. The induction period roughly estimated simply by extrapolating the linear part of the curve to the time axis is about 3 h (Figure S7, see Supporting Information). It means that the induction period significantly decreases with increasing the polymerization temperature from 45 to 60 °C at $[CTA\ 2]_0:[AIBN]_0 = 5$. A similar tendency was also observed in our previous paper,[26] in which the induction was about 50 min at 60 °C, while it decreased to less than 10 min at 90 °C in RAFT polymerization of A-Phe-OMe. In general, increasing the

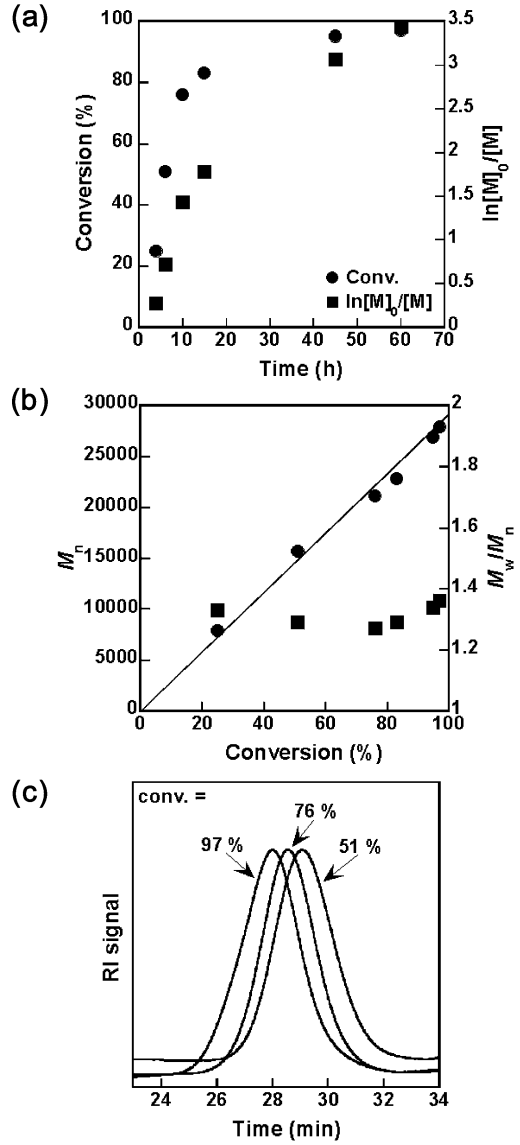


Figure 5. (a) Time−conversion (circles) and first-order kinetic (squares) plots for the polymerization of *N*-acryloyl-L-phenylalanine (A-Phe-OH) with 2,2′-azobis(isobutyronitrile) (AIBN) in the presence of benzyl 1-pyrrolecarbodithioate (CTA 2, see Scheme 2) in methanol at 60 °C. Monomer concentration = 0.25 g/mL. $[\text{A-Phe-OH}]_0/[\text{CTA 2}]_0 = 150$. $[\text{CTA 2}]_0/[\text{AIBN}]_0 = 5$. (b) Number-average molecular weight (circles) and polydispersity (squares) as a function of conversion. (c) Evolution of SEC traces with conversion.

temperature favors the increase in the AIBN decomposition rates and the fragmentation of the intermediate radical, leading to an increased polymerization rate. In the present system, higher polymerization temperature may also lead to the increase in the fragmentation of the intermediate radical in the preequilibrium to produce the reinitiating R• fragment efficiently, resulting in a shorter induction period. Note that higher temperature conditions also have a potential drawback for achieving controlled radical polymerizations, such as accelerated side reactions and the gradual decomposition of CTA. Nevertheless, the linear relationship between the M_n and the conversion, maintaining low polydispersity, was observed at 60 °C in methanol at $[\text{CTA 2}]_0:[\text{AIBN}]_0 = 5$, as shown in Figure 5b. Symmetrical unimodal SEC peaks without shoulders and tailings were observed for the polymers obtained even at higher conversion (> 80%, Figure 5c), and the polydispersity indices (M_w/M_n) for all samples ranged between 1.27 and 1.36. These results suggest that the polymerization of A-Phe-OH mediated by CTA 2 shows a good control in methanol at both temperatures, 45 and 60 °C under the conditions used in this study, even if the kinetic behavior is affected by the polymerization temperature.

Comparison of A-Phe-OH and A-Phe-OMe. To clarify the effect of the carboxylic acid group on the control of the polymerization of the amino acid-containing monomer, we compared RAFT polymerizations of the unprotected monomer, A-Phe-OH, and the protected monomer, A-Phe-OMe, under the same conditions. In all cases, the polymerization was carried out with AIBN in the presence of CTA 2 at $[\text{M}]_0/[\text{CTA 2}]_0/[\text{AIBN}]_0 = 200/2/1$, and the results are summarized in Table 5. When the polymerization was conducted in dioxane (monomer concentration = 0.5 g/mL) at 60 °C, almost full conversion was obtained after 24 h, regardless of the monomer. The polydispersity index ($M_w/M_n = 1.49$) of the product prepared by direct polymerization of A-Phe-OH, followed by methylation was broader than that ($M_w/M_n = 1.27$) obtained from A-Phe-OMe. The behavior should be attributed to the difference in the solubility of poly(A-Phe-OH) and poly(A-Phe-OMe) formed during the polymerization. Actually, the polymer precipitation occurred when A-Phe-OH was polymerized in dioxane. Although the homogeneous system could be achieved with maintaining characteristic pale yellow color in a diluted dioxane solution (0.25 g/mL), the solution became viscous at the end of the polymerization, leading to the production of poly(A-Phe-OH) having relatively broad polydispersity (entry 1, Table 2). In general, dilution favors intramolecular reactions, like fragmentation, against intermolecular reactions, like termination. In our cases, the dilution had no remarkable effect on the RAFT polymerization of A-Phe-OH in methanol at lower temperature (45 °C). Narrow polydispersities products with reasonable monomer conversions were obtained, regardless of the monomer concentration (0.25−0.50 g/mL). Under the conditions, the monomer conversion, molecular weights, and polydispersity of the product obtained by RAFT polymerization of A-Phe-OH are almost the same to those of A-Phe-OMe. In both cases, the resulting polymers exhibited symmetrical unimodal SEC peaks with low polydispersity (M_w/M_n = 1.20−1.30). This is an indication that the existence of the carboxylic acid group has no significant influence on the control of the polymerization under the suitable conditions.

Table 5. Comparison of RAFT Polymerizations of A-Phe-OH and A-Phe-OMe Using AIBN and Benzyl 1-Pyrrolecarbodithioate (CTA 2) for 24 h[a]

conditions		A-Phe-OH				A-Phe-OMe			
solvent	temp, °C	convn,[b] %	M_n[c] (theor)	M_n[d] (SEC)	M_w/M_n[d] (SEC)	convn,[b] %	M_n[c] (theor)	M_n[d] (SEC)	M_w/M_n[d] (SEC)
dioxane	60	95[e]	22 400	20 500[f]	1.49[f]	96	22 600	17 000	1.27
MeOH	45	80	18 900	15 400[f]	1.30[f]	81	19 000	19 000	1.20

[a] $[\text{AIBN}]_0/[\text{CTA 2}]_0/[\text{M}]_0 = 1/2/200$, where AIBN = 2,2′-azobis(isobutyronitrile), CTA 2 = benzyl 1-pyrrolecarbodithioate, A-Phe-OH = *N*-acryloyl-L-phenylalanine, A-Phe-OMe = *N*-acryloyl-L-phenylalanine methyl ester, and monomer concentration = 0.50 g/mL. [b] Calculated by ^{1}H NMR in DMSO-d_6. [c] The theoretical molecular weight ($M_{n,\text{theory}}$) = (MW of A-Phe-OMe) × $[\text{M}]_0/[\text{CTA}]_0$ × conversion + (MW of CTA). [d] Measured by size-exclusion chromatography (SEC) using polystyrene standards in *N*,*N*-dimethylformamide (DMF, 10 mM LiBr). [e] Heterogeneous system. [f] Samples modified by methylation.

Conclusion

We have demonstrated the first successful controlled radical polymerization of *N*-acryloyl-L-phenylalanine (A-Phe-OH), in which the carboxylic acid moiety is intact without protecting group, via RAFT process. Near-monodisperse poly(A-Phe-OH)s with controlled molecular weights were obtained by the polymerization of the monosubstituted acrylamide having L-phenylalanine as an amino acid residue using benzyl 1-pyrrolecarbodithioate (CTA 2). The controlled character of the polymerization in the presence of CTA 2 in methanol was confirmed by the formation of narrow polydispersity products, the molecular weight controlled by the monomer/CTA molar ratio, the linear relationship between the molecular weight and conversion. To conclude, RAFT polymerization proves to be an effective technique for the direct synthesis of a well-defined amino acid based polymer without protective group chemistry.

This procedure may extend to the synthesis of well-defined polymers having various amino acid moieties in the side chains and controlled architectures, such as graft, star, and block copolymers. Since poly(A-Phe-OH) is a weak polyelectrolyte, in which the degree of ionization is governed by the pH and ionic strength of aqueous solution, the charge, the concentration of free counterion, and the degree of swelling can be tuned via adjustment of pH value. Such a tuning capability is of great interest as a component of intelligent materials. Further, phenylalanine is most hydrophobic amino acids according to the hydrophilicity values, which may favor hydrophobic interaction. Poly(A-Phe-OH) segments in the complex macromolecules can show specific interactions, such as hydrogen-bonding, acid−base interactions, and oppositely charged ionic interactions, which can help to prepare novel self-organized materials. Multiscale ordering of such functional nanomaterials is a powerful technique for the creation of tailored amino acid based materials with unique properties for various applications, such as controlled release, biochemical sensing, biocompatible materials, and optical resolution. We are currently extending our studies toward such directions.

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Supporting Information Available: Figures showing ^{1}H and FT-IR spectra of the monomer and polymers, SEC traces of methylated poly(A-Phe-OH)s obtained with different CTAs and at different $[CTA\ 2]_0/[AIBN]_0$ ratios, comparison of UV (280 nm) and RI detector responses of the SEC traces, and first-order kinetic plots used for the determination of the induction periods and tables summarizing the date for effect of $[A\text{-}Phe\text{-}OH]_0/[CTA\ 2]_0$ and all kinetic investigations. This material is available free of charge via the Internet at http://pubs.acs.org.

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