Controlled Radical Polymerization of an Acrylamide Containing L-Phenylalanine Moiety via RAFT

Hideharu Mori,* Kazuhiko Sutoh, and Takeshi Endo*

Department of Polymer Science and Engineering, Faculty of Engineering, Yamagata University, 4-3-16, Jonan, Yonezawa 992-8510, Japan

Received May 7, 2005; Revised Manuscript Received August 9, 2005

ABSTRACT: Homopolymers of a monosubstituted acrylamide having an amino acid moiety in the side chain, *N*-acryloyl-L-phenylalanine methyl ester (A-Phe-OMe), have been synthesized by reversible addition−fragmentation chain transfer (RAFT) polymerization. Two dithioesters were used as chain transfer agents: benzyl 1-pyrrolecarbodithioate (CTA 1) and benzyl dithiobenzoate (CTA 2). The controlled character of the polymerization in the presence of CTA 1 in dioxane at 60 °C 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, and the ability to increase the molecular weight by a second addition of monomer. Poly(A-Phe-OMe) with controlled molecular weight, low polydispersity, and enhanced isotacticity was also prepared by RAFT polymerization in the presence of catalytic amounts of Lewis acid, $Y(OTf)_3$. The RAFT polymerizations of A-Phe-OMe in methanol at 45 °C and in methanol−toluene mixture at 60 °C were also found to afford the polymers with narrow molecular weight distributions.

Introduction

Amino acids are the constitutional components of peptides and proteins, which are able to produce highly ordered hierarchical structures scaling from a few nanometers to several microns. Their secondary structures (α-helix and β-sheet) and higher-order (tertiary and quaternary) structures are assembled through intra- and interchain associations by noncovalent forces, such as hydrogen bonding, hydrophobic stacking, electrostatic, and dipolar interactions. The primary structures of the biomacromolecules are constructed via covalent linkage of the building blocks, and the molecular information such as amino acid sequence, chain chirality, and amphiphilicity encoded in the primary structures determines their highly ordered structures. Incorporation of amino acid residues into synthetic polymers is of interest because these combinations may create new nonbiological macromolecules with biomimetic structures and properties.

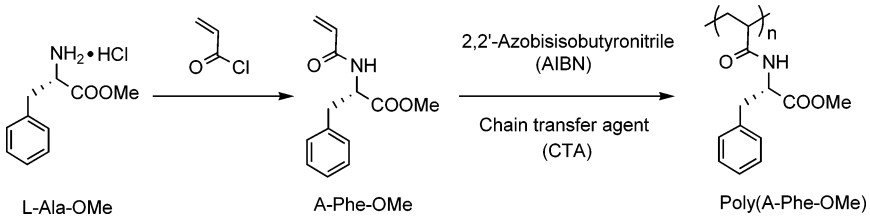
In recent years, much interest has been devoted to preparing mimics of these natural macromolecules and artificial polypeptides for various biorelated applications. An attractive approach is the self-organization of block copolymers containing amino acids segments,[1−3] which can form a variety of hierarchical structures, depending upon the structure and property of each segment, composition, chain length, and secondary structures of poly(amino acid) segments. Recent developments in novel polymerization methods, such as ring-opening polymerization[4−6] and polycondensation,[7] can produce amino acid-based polymers with novel structures and architectures. Another direction is to produce peptide−polymer hybrids by combining solid-phase synthesis and controlled radical polymerization.[8,9] However, there is still a large gap between the performance and architectures of most synthetic polymers and biologically produced polymers. The desirable requirement is to develop synthetic methods to control the sequence and composition of amino acids, chain chirality, conformation, amphiphilicity, and chain length. It is also important to produce polymers with narrow chain length distributions, which can assemble linear macromolecules into precisely defined nanostructures. Here, we report the synthesis of a polyacrylamide with amino acid moieties in the side chains, poly(*N*-acryloyl-L-phenylalanine methyl ester) (poly(A-Phe-OMe)), with narrow molecular weight distributions, controlled molecular weights, and tacticity (Scheme 1). A variety of poly[(meth)acrylamide]s with amino acid moieties have been developed to study their characteristic polymerization behavior, structures, and properties mainly based on the functional amino acid moieties.[10] Because of their unique properties, these polymers not only are of fundamental interest but also have many potential applications, such as polyelectrolytes,[11] optically active adsorbents,[12] photochromic materials,[13] controlled release systems,[14,15] biologically active materials,[16] and stimuli-responsive materials.[17−19] The ease of monomer synthesis, in which various amino acid-containing monomers can be easily prepared by the reaction of (meth)acryloyl chloride with amino acids, is promising for producing functional polymers for various applications. However, the preparation of these polymers is based almost entirely on conventional free radical polymerizations, which yield poorly defined polymers.

Recent developments in controlled radical polymerizations enable the synthesis of functional polymers with controlled molar mass, narrow molecular weight distribution, and well-defined architectures and functionalities. The systems include atom transfer radical polymerization,[20,21] nitroxide-mediated radical polymerization,[22] and reversible addition−fragmentation chain transfer (RAFT) polymerization.[23,24] Among these controlled radical polymerizations, RAFT has been successfully applied for controlled polymerization of acrylamide derivatives, such as *N,N*-dimethylacrylamide,[25−27]

* To whom correspondence should be addressed: e-mail h.mori@yz.yamagata-u.ac.jp or tendo@yz.yamagata-u.ac.jp; Ph +81-238-26-3765; Fax +81-238-26-3092.

10.1021/ma0509558 CCC: $30.25
Published on Web 09/28/2005

Scheme 1



N-isopropylacrylamide,[28−31] and *N*-acryloylmorpholine.[32−34] These results confirm the ability of RAFT to produce well-controlled polymer chains from either monosubstituted or disubstituted acrylamide derivatives with narrow molecular weight distribution. Furthermore, stereocontrol over radical polymerizations by the addition of Lewis acid has recently been demonstrated for RAFT polymerization of acrylamides[26,30,31] and methacrylamides.[35]

In this study, we investigated radical polymerization of a monosubstituted acrylamide with an amino acid moiety, *N*-acryloyl-L-phenylalanine methyl ester (A-Phe-OMe), in the presence of a chain transfer agent (CTA) under various conditions. First, the effects of the nature of CTA, CTA/initiator molar ratio, and polymerization temperature were studied to optimize the polymerization conditions. The RAFT polymerization of A-Phe-OMe using a suitable CTA was then evaluated by performing polymerizations at different monomer/CTA molar ratios, kinetic measurements, and a chain extension experiment. Control of the structures of the amino acid-based polymers was attempted in terms of the molecular weight, polydispersity, and tacticity, which are crucial for manipulating the properties and in further practical applications.

Experimental Section

Materials. L-Phenylalanine methyl ester hydrochloride (Kanto Chemical, 98%) was used as received. 2,2′-Azobis(isobutyronitrile) (AIBN, Kanto Chemical, 97%) was purified by recrystallization from methanol. Triethylamine (Kanto Chemical, 98%) and pyrolle (Kanto Chemical, 99%) were distilled from CaH_2 before use. 1,4-Dioxane (Kanto Chemical, 99%) was distilled from sodium wire, and toluene (Kanto Chemical, 99.5%) was distilled before use. Yttrium trifluoromethanesulfonate (triflate; $Y(OTf)_3$, Aldrich, 98%), yitterbium trifluoromethanesulfonate (triflate; $Yb(OTf)_3$, Aldrich, 99.99%), and scandium trifluoromethanesulfonate (triflate; $Sc(OTf)_3$, Aldrich, 99%) were dried under vacuum before use. 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP, Wako Pure Chemical, 99%) and methanol (Wako Pure Chemical, 99.8%) were used as received. Other materials were used without further purification.

Synthesis of Chain Transfer Agent. Benzyl 1-pyrrolecarbodithioate (CTA 1)[36] and benzyl dithiobenzoate (CTA 2)[37] were synthesized by literature procedures. CTA 1 was purified by column chromatography on silica with *n*-hexane as the eluent to afford a yellow oil. CTA 2 was purified by sublimation to give red oil.

***N*-Acryloyl-L-phenylalanine Methyl Ester (A-Phe-OMe).** The monomer was prepared by the reaction of acryloyl chloride with L-phenylalanine methyl ester hydrochloride according to a method reported previously.[38] $[M]_D^{25} = 102.2°$, $c = 0.1$ g/dL, tetrahydrofuran (THF) (lit.[38] $[M]_D^{27} = 141.7°$, $c = 1.0$, $CHCl_3$). The ^1H and ^{13}C NMR spectra of the monomer are shown in Figures S1 and S2, respectively (see Supporting Information).

Polymerization. A representative example is as follows. The monomer (0.50 g, 2.1 mmol), CTA 1 (9.9 mg, 0.042 mmol), AIBN (3.5 mg, 0.021 mmol), and dioxane (1.0 mL) were placed in a dry glass ampule equipped with a magnetic stir bar, and then the solution was degassed by three freeze−evacuate−thaw cycles. After the ampule was flame-sealed under vacuum, it was held at 60 °C for 24 h. The characteristic pale yellow color kept constant during the polymerization. The reaction was stopped by rapid cooling with liquid nitrogen. The reaction mixture was precipitated in a large excess of diethyl ether and isolated by filtration. The resulting product was freeze-dried from dioxane and finally dried under vacuum at room temperature to yield poly(A-Phe-OMe) as a white or pale yellow powder. The polymer had $M_n = 7800$ and $M_w/M_n = 1.23$ according to GPC using polystyrene calibration. The structure of the resulting polymer was confirmed by ^1H and ^{13}C NMR measurements (Figures S1 and S2 in Supporting Information).

The monomer conversion was determined by ^1H NMR spectroscopy of the polymerization mixture in $CDCl_3$ at room temperature by integration of the monomer C═C−*H* peak at around 5.7 ppm, compared with the sum of N−C−*H* peak intensity of the polymer and the monomer at around 4.2−5.0 ppm. Conversion determined by this method was 93%. Additionally, the polymer yield was gravimetrically determined from the ether-insoluble polymer sample (yield = 87%, 0.43 g). The resulting polymer was soluble in most organic solvents, such as dichloromethane, acetone, dioxane, DMF, and DMSO, and insoluble in diethyl ether, hexane, and water. For the polymerization in the presence of a Lewis acid, the resulting polymer was precipitated in water and then in diethyl ether. The theoretical number-average molecular weight on conversion is defined as follows:

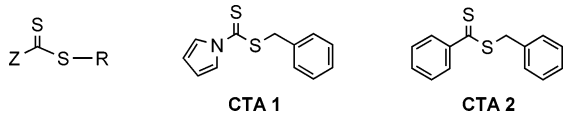
$$M_n(\text{theor}) = \frac{[\text{monomer}]_0}{[\text{CTA}]_0 + 2f\,[\text{I}]_0(1 - e^{-k_d t})} \times M_{\text{monomer}} \times \text{conv} + M_{\text{CTA}} \quad (1)$$

in which M_{CTA} and $M_{monomer}$ are molecular weights of chain transfer agent and monomer and $[monomer]_0$ and $[CTA]_0$ are the initial concentrations of monomer 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.

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

Chain Extension Using Poly(A-Phe-OMe) as Macro-CTA. For the chain extension experiments, low molecular weight poly(A-Phe-OMe) was prepared according to the below procedure. A-Phe-OMe (0.497 g, 2.13 mmol), CTA 1 (9.9 mg, 0.042 mmol), AIBN (3.5 mg, 0.021 mmol), and dioxane (1.0 mL) were placed in an ampule, and then the solution was degassed by three freeze−evacuate−thaw cycles. The polymerization was conducted at 60 °C for 3 h. Conversion of the double bonds, as detected by ^1H NMR spectroscopy, was 64%. The resulting poly(A-Phe-OMe) had an M_n (as determined by SEC) of 6400 and a polydispersity index of 1.29. The product was purified by precipitation into diethyl ether and then isolated by filtration. Finally, the resulting poly(A-Phe-OMe) was freeze-dried from dioxane and dried under vacuum at room temperature.

Scheme 2



A representative example of chain extension experiment is as follows. The dithiocarbamate-terminated poly(A-Phe-OMe) (0.133 g, 0.018 mmol; $M_n = 6400$, $M_w/M_n = 1.29$), A-Phe-OMe (0.485 g, 2.1 mmol), AIBN (1.7 mg, 0.010 mmol), and dioxane (4.0 mL) were placed in a dry ampule, and then the solution was degassed by three freeze−evacuate−thaw cycles. The ampule was subsequently immersed in an oil bath preheated to 60 °C, and it was held for 24 h before being quenched by rapid cooling with liquid nitrogen. Conversion of the double bonds, as detected by ^{1}H NMR spectroscopy, was 97%. The resulting poly(A-Phe-OMe) had an M_n (as determined by SEC) of 23 000 and a polydispersity index of 1.38.

Instrumentation. ^{1}H (270 and 500 MHz) and ^{13}C NMR (67.5 and 125 MHz) spectra were recorded with a JEOL EX-270 and a Varian INOAVA-500. The dyad tacticity of poly(A-Phe-OMe) was determined from the methylene proton peaks of the polymer recorded in DMSO-d_6 at 170 °C. Specific rotations ($[\alpha]_D$) were measured on a JASCO DIP-1000 digital polarimeter equipped with a sodium lamp as a light source. Circular dichroism (CD) spectra were measured on a JASCO J-720 spectropolarimeter. 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 (DMF) containing 10 mM LiBr as an eluent. Polystyrene standards were employed for calibration. GPC with a multiangle light scattering detector (GPC-MALS) was also performed to determine the true molecular weights of the resulting polymer. The measurement was conducted using a Shodex GPC system 21 with two consecutive columns (Shodex KD-806M × 2, exclusion limited molecular weight = 2×10^7, 30 cm each) and DAWN DSP-F (Wyatt Technology Co.) detector equipped with He−Ne laser (632.8 nm). DMF containing 10 mM LiBr was used as an eluent at a flow rate of 1.0 mL/min. Excess refractive index increment (d*n*/d*c*) was measured using a differential refractometer DRM1021 at 25 °C.

Thermogravimetric analysis (TGA) was performed on a SEIKO SSC/5200 at a heating rate of 10 °C/min under N_2. For differential scanning calorimetry (DSC) measurements, a SEIKO DSC/6200 apparatus was used (heating rate: 10 °C/min; cooling rate: 10 °C/min). Samples were heated from 50 to 250 °C at a rate of 10 °C/min, kept for 5 min, and cooled at a rate of 10 °C/min. The data collection was carried out on the second heating process, and the glass transition temperature (T_g) was taken to be the midpoint—the temperature corresponding to half of the endothermic shift. The calorimeter was calibrated with an indium standard.

Results and Discussion

Preliminary Comparison of CTA 1 and CTA 2. One of the key points for the synthesis of well-defined products via RAFT process is the design of the chain transfer agent (CTA), as the choice of R and Z groups depends on the monomer.[36,37] In this study, we selected two different chain transfer agents, namely benzyl 1-pyrrolecarbodithioate (CTA 1) and benzyl dithiobenzoate (CTA 2), as shown in Scheme 2. An important monosubstituted acrylamide, *N*-isopropylacrylamide, has been polymerized successfully via RAFT using benzyl 1-pyrrolecarbodithioate (CTA 1).[29] Benzyl dithiobenzoate (CTA 2) is a RAFT agent that has been employed for well-controlled polymerization of *N*,*N*-dimethylacrylamide[25] and *N*-isopropylacrylamide.[28] 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. As the Z group influences strongly the stability of the dithioester intermediate radical, strong stabilizing groups will favor the formation of the intermediate radical 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 the fragmentation, which will release the reinitiating group (R).

Table 1. Reversible Addition−Fragmentation Chain Transfer (RAFT) Polymerization of *N*-Acryloyl-L-phenylalanine Methyl Ester (A-Phe-OMe) in Dioxane for 24 h[a]

entry	CTA[b]	temp (°C)	conv[c] (%)	M_n[d] (theory)	M_n[e] (SEC)	M_w/M_n[f] (SEC)
1		60	100		89000	3.36
2	CTA1	60	93	11000	7800	1.23
3	CTA1	90	97	11600	9200	1.29
4	CTA2	60	45	5400	4000	1.20
5	CTA2	90	97	11600	9900	1.48

[a] $[M]_0/[CTA]_0 = 50$, $[CTA]_0/[AIBN]_0 = 2$, monomer concentration = 0.5 g/mL ([M] = 1.38 mol/L), where M = acryloyl-L-phenylalanine methyl ester (A-Phe-OMe), AIBN = 2,2′-azobis(isobutyronitrile). [b] CTA 1 = benzyl 1-pyrrolecarbodithioate, CTA 2 = benzyl dithiobenzoate (see Scheme 2). [c] Calculated by ^{1}H NMR in $CDCl_3$. [d] The theoretical molecular weight ($M_{n,theory}$) = (MW of M) × conv × $[M]_0/[CTA]_0$ + (MW of CTA). [e] Number-average molecular weight (M_n) was measured by size-exclusion chromatography (SEC) using polystyrene standards in *N*,*N*-dimethylformamide (DMF, 10 mM LiBr). [f] Molecular weight distribution (M_w/M_n) was measured by SEC in DMF (10 mM LiBr).

To find suitable systems for the synthesis of well-defined polyacrylamides containing amino acid moieties in the side chains, we initially investigated the influence of the nature of CTA on the radical polymerization of *N*-acryloyl-L-phenylalanine methyl ester (A-Phe-OMe). A-Phe-OMe was polymerized using CTA 1 or CTA 2 under various conditions, and the results are summarized in Table 1. When A-Phe-OMe was polymerized using CTA 1 with AIBN as an initiator at $[A\text{-Phe-OMe}]_0/[CTA\ 1]_0/[AIBN]_0 = 100/2/1$ in dioxane (0.5 g/mL), which corresponds to [M] = 1.38 mol/L, [CTA] = 0.0276 mol/L, and [I] = 0.0138 mol/L, almost full conversion (93%, 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. The resulting polymer showed sharp symmetrical unimodal SEC peak ($M_w/M_n = 1.23$) without shoulders and tailings. The number-average molecular weight of the poly(A-Phe-OMe), measured by a GPC in DMF with 10 mM LiBr, was $M_n = 7800$, which is roughly comparable to the theoretical value ($M_n = 11\ 000$) calculated from the monomer/CTA molar ratio and the monomer conversion using eq 2. However, a conventional radical polymerization of A-Phe-OMe under the similar condition in the absence of CTA afforded a high molecular weight homopolymer with high polydispersity ($M_n = 89\ 000$ and $M_w/M_n = 3.36$, 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 con-

trolled polymerization.[39] Note that the significant increase in the viscosity could not be observed visually even at almost full conversion during the RAFT polymerization, which was due to relatively low molecular weights of the resulting product (M_n = 7800, M_w/M_n = 1.23). Whereas, apparent viscosity increase was detected in the case of the conventional radical polymerization in the absence of CTA, in which high molecular weight product (M_n = 89 000, M_w/M_n = 3.36) was produced.

The polymerization of A-Phe-OMe was also conducted using benzyl dithiobenzoate (CTA 2) to compare the effect of different Z groups, phenyl and pyrrole, on the polymerization behavior. As shown in Table 1 (entry 4), the polymerization with AIBN in the presence of CTA 2 at 60 °C produced a polymer with a relatively narrow molecular weight distribution (M_w/M_n = 1.20), while achieving only 45% conversion even after 24 h. This is an indication that the polymerization with CTA 2 is much slower than that with CTA 1 at 60 °C. At 90 °C, the polymerization with CTA 2 led to increase of the reaction rate but afforded the polymer with broad molecular weight distribution (M_w/M_n = 1.48). The retardation of the polymerization rate, depending on the structure of CTA, has been intensively discussed in the literature.[39−42] The rate retardation effect is attributed to the main equilibrium after all initial CTA have been transformed into macro-CTA (so-called macro-RAFT agent) and may therefore be ascribed to different stabilities of the intermediate radicals in the main equilibrium. It has frequently been observed that dithiobenzoates show pronounced retardation phenomena due to the significant stabilization effect of phenyl group. The transfer constant is another important parameter in the RAFT process. The transfer constants of a series of benzyl thiocarbonylthio compounds of general structures, Z−C(=S)−CH_2Ph, in styrene polymerization have been reported, and it was demonstrated that the transfer constant with CTA 2 (Z = Ph, C_{tr} = 26) is apparently larger than that with CTA 1 (*Z* = pyrrole, C_{tr} = 9).[39] Note that the chain transfer constant (C_{tr}) is given by the ratio of the rate constant for chain transfer to that for propagation (k_{tr}/k_p) in the case of conventional radical polymerization, while k_{tr} is composed of two factors: the rate constant for addition to the thiocarbonyl group and the partitioning of the intermediate radical between starting materials and products in the RAFT process. Since the leaving group (benzyl radical) of CTA 2 is the same to that of CTA 1, the retardation with CTA 2 should be related to the slower fragmentation rate from the phenyl-substituted intermediate radical than that from pyrrole one and/or fast addition rate of expelled radical to the thiocarbonyl group. The high transfer constant for CTA 2 is reflecting the stability of the intermediate radicals because the value directly leads to increased addition rates. This process, however, may mainly apply for the initial stage (preequilibrium), which is related closely to the induction period discussed in the next section. From these preliminary results, we selected CTA 1 for our further investigations toward the precise synthesis of poly(A-Phe-OMe)s having low polydispersity, controlled molecular weights, and tacticity. In the next stage, the effects of the polymerization temperature and the ratio of CTA 1 to initiator were investigated in terms of the molecular weights and the polydispersity of the resulting poly(A-Phe-OMe). The polymerization of A-Phe-OMe was conducted in dioxane at 60 °C for 24 h at different

Table 2. Effect of Chain Transfer Agent/Initiator Molar Ratio on Reversible Addition−Fragmentation Chain Transfer (RAFT) Polymerization of *N*-Acryloyl-L-phenylalanine Methyl Ester (A-Phe-OMe) in the Presence of CTA 1 in Dioxane for 24 h[a]

entry	temp (°C)	$[CTA\ 1]_0/[AIBN]_0$	conv[b] (%)	M_n[c] (theory)	M_n[d] (SEC)	M_w/M_n[e] (SEC)
1	60	1.5	90	10 700	17000	1.35
2	60	2	93	11 100	7800	1.23
3	60	3	91	10 800	9400	1.25
4	60	5	94	11 200	9500	1.27
5	60	10	92	11 000	8800	1.23
6	90	2	97	11 500	9200	1.29
7	90	5	92	11 000	9200	1.23
8	90	10	91	10 800	8500	1.24

[a] $[M]_0/[CTA\ 1]_0$ = 50, monomer concentration = 0.5 g/mL ([M] = 1.38 mol/L), where M = acryloyl-L-phenylalanine methyl ester (A-Phe-OMe), AIBN = 2,2′-azobis(isobutyronitrile), and CTA 1 = benzyl 1-pyrrolecarbodithioate (see Scheme 2). [b] Calculated by ^{1}H NMR in $CDCl_3$. [c] The theoretical molecular weight ($M_{n,theory}$) = (MW of M) × conv × $[M]_0/[CTA]_0$ + (MW of CTA). [d] Number-average molecular weight (M_n) was measured by size-exclusion chromatography (SEC) using polystyrene standards in *N*,*N*-dimethylformamide (DMF, 10 mM LiBr). [e] Molecular weight distribution (M_w/M_n) was measured by SEC in DMF (10 mM LiBr).

$[CTA\ 1]_0$:$[AIBN]_0$ ratios between 1.5 and 10, keeping the monomer-to-chain transfer agent at a constant value of $[A\text{-}Phe\text{-}OMe]_0/[CTA\ 1]_0$ = 50/1. As shown in Table 2, the molecular weight obtained at $[CTA]_0/[AIBN]_0$ = 2/1 is slightly lower than that at $[CTA]_0/[AIBN]_0$ = 10/1, and the molecular weight distribution remains narrow (M_w/M_n = 1.23−1.27). However, low initiator concentration ([CTA 1]/[I] = 1.5, entry 1 in Table 2) led to remarkable increase in the molecular weights with broader polydispersity, suggesting the loss of the controlled character. 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 $[CTA]_0/[I]_0$ ratio under the same monomer-to-chain transfer agent ratio and monomer conversion. In an ideal RAFT process, however, the number of polymer chains directly derived from the initiator molecules should be minimal, and the initial CTA concentration is large enough compared to the number of the initiator-derived chains.[43,44] Further, the reactivity of the CTAs is usually substantially higher than that of monomer, favoring initiation by R• fragments. The consumption of CTA and reversible fragmentation of intermediate to produce reinitiating R• fragment are often referred to as the "preequilibrium". The narrow molecular weight distribution is apparently due to rapid establishment of the preequilibrium, 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.[45] In our system, the molecular weight obtained at $[CTA]_0/[AIBN]_0$ = 10/1 is comparable to that at $[CTA]_0/[AIBN]_0$ = 2/1, with keeping low polydispersity. A similar tendency was also reported in another RAFT system,[44] in which no deterioration in the control of the polymerization was observed as $[CTA]_0/[I]_0$ decreased from 8 to 1.5.

The polymerization at 90 °C under the same conditions ($[A\text{-}Phe\text{-}OMe]_0/[CTA\ 1]_0/[AIBN]_0$ = 100/2/1, 24 h) afforded the polymer with low polydispersity (M_w/M_n = 1.29) and reasonable molecular weights. Note that the

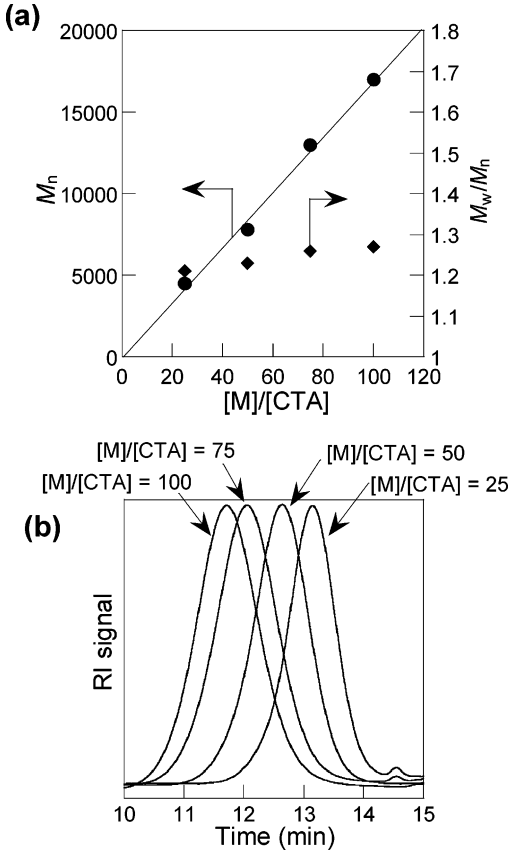


Figure 1. (a) Dependence of number-average molecular weight and molecular weight distribution on $[M]_0$:$[CTA\ 1]_0$ ratio for the polymerization of *N*-acryloyl-L-phenylalanine methyl ester (A-Phe-OMe) with 2,2′-azobis(isobutyronitrile) (AIBN) in the presence of benzyl 1-pyrrolecarbodithioate (CTA 1, see Scheme 2) in dioxane at 60 °C. Monomer concentration = 0.5 g/1.0 mL ([M] = 1.38 mol/L). $[CTA\ 1]_0/[AIBN]_0$ = 2/1. Monomer conversion = 93−95%. (b) Size-exclusion chromatography (SEC) traces of the corresponding poly(A-Phe-OMe)s obtained at different $[M]_0$:$[CTA\ 1]_0$.

half-life time of AIBN at 90 °C is only 17 min; that is, after 170 min = 2.9 h of reaction time the initiator has decomposed quantitatively. No significant influence on the conversion, molecular weight, and polydispersity was observed, as the concentration ratio of CTA to initiator increased up to $[CTA\ 1]_0/[AIBN]_0$ = 10/1 (entries 6−8, Table 2), suggesting that the difference in the initiator concentration had minor effect on the total number of the polymer chains. Nevertheless, it is hard to evaluate the number of the initiator-derived chain existed in this system. Further investigations, such as MALDI-TOF MS investigation, may be required to clarify this point, which will be reported elsewhere.

Polymerization in the Presence of CTA 1. The polymerization of A-Phe-OMe was investigated with AIBN in the presence of CTA 1 in dioxane at 60 °C for 24 h at different $[A\text{-Phe-OMe}]_0$:$[CTA\ 1]_0$ ratios between 25 and 100, while the AIBN:CTA 1 molar ratio was held constant at 1:2. Under the conditions, the conversions were quantitative (>90%, as determined by ^1H NMR) in all cases. Figure 1a shows the relation of the molecular weight and polydispersity with the $[M]_0$:$[CTA\ 1]_0$ ratio. A linear increase of the number-average molecular weight with the ratio is observed clearly, and the molecular weight distributions remain narrow (M_w/M_n = 1.21−1.26), indicating a feasibility to control the molecular weights. Note that the straight line could be obtained only when the monomer conversions are substantially the same in all cases. Nevertheless, the result suggests that the molecular weights of the poly(A-Phe-OMe)s can be easily adjusted by the monomer-to-CTA ratio. In all cases, the SEC traces are unimodal with no evidence of high molecular weight species, as can be seen in Figure 1b. The phenomenon, namely the linearity of the M_n vs $[A\text{-Phe-OMe}]_0$:$[CTA\ 1]_0$ ratio with keeping low polydispersity, was also observed for the polymerization under nitrogen at 90 °C (Figure S3, see Supporting Information). These results suggest that uncontrolled polymerization and/or termination by coupling of propagating polymer radicals can be negligible under the condition used in this study. A possibility to form a three-arm star chain reported in the RAFT polymerization of styrene by Kwak et al.[41] can be also excluded, as judged from the SEC charts of the poly(A-Phe-OMe)s obtained under various conditions.

In all cases, the experimental molecular weights were slightly lower than calculated ones, as shown in Tables 1 and 2. These discrepancies may result from the difference in hydrodynamic volume between poly(A-Phe-OMe) and the linear polystyrene standards used for GPC calibration. Another possible explanation is that the number of living polymer chains is larger than that of CTA due to an initiator-derived chain. To clarify the point, GPC with a multiangle light scattering detector (GPC-MALS) was applied for the determination of the absolute molecular weights of representative samples (Figure S4, see Supporting Information). The polymers obtained at $[A\text{-Phe-OMe}]_0$:$[CTA]_0$ ratios = 75 and 100 had M_w = 23 400 and M_w/M_n = 1.20 ($M_{n,GPC-MALS}$ = 19 400, as determined by GPC-MALS), compared to $M_{n,calcd}$ = 16 000 and $M_{n,GPC}$ = 13 000 (M_w/M_n = 1.26), and M_w = 30 000 and M_w/M_n = 1.19 ($M_{n,GPC-MALS}$ = 25 200, as determined by GPC-MALS), compared to $M_{n,calcd}$ = 20 000 and $M_{n,GPC}$ = 17 000 (M_w/M_n = 1.25), respectively. There was no significant difference between $M_{n,GPC-MALS}$ and $M_{n,calcd}$, suggesting that the number of living polymer chains is comparable to that of CTA. In the SEC experiments of the two 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 S5, see Supporting Information).

The polymerizations of A-Phe-OMe in the presence of CTA 1 in dioxane at 60 and 90 °C were investigated at a constant monomer/chain transfer agent/initiator molar ratio, $[A\text{-Phe-OMe}]_0/[CTA\ 1]_0/[AIBN]_0$ = 200/2/1. The time−conversion and the pseudo-first-order kinetic plots are shown in Figure 2. The polymerization at 90 °C was very fast, in which more than 90% conversion was reached within 0.5 h. Whereas, less than 10% conversion could be reached in the same time period when the polymerization was conducted at 60 °C. Indeed, an induction period of less than 2 h is seen in the pseudo-first-order kinetic plot at 60 °C. The induction period roughly estimated simply by extrapolating the linear part of each curve to the time axis is about 50 min at 60 °C, while it decreased to less than 10 min at 90 °C. An induction period is often observed in RAFT polymerization of various monosubstituted and disubstituted acrylamides.[27,29,31,32] The reasons for the induction periods with some CTAs are not clearly understood, but a number of possible explanations have been suggested,[46−50] including slow fragmentation of the initiating leaving group radical, slow reinitiation by the expelled radical, increased stability of the intermediate

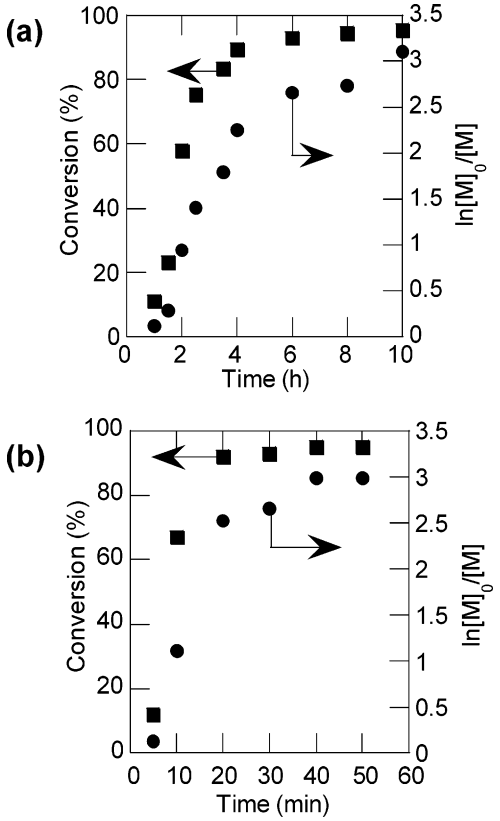


Figure 2. Conversion−time (squares) and the first-order kinetic plots (circles) for the polymerization of *N*-acryloyl-L-phenylalanine methyl ester (A-Phe-OMe) with 2,2′-azobis(isobutyronitrile) (AIBN) in the presence of benzyl 1-pyrrolecarbodithioate (CTA 1, see Scheme 2) in dioxane at 60 °C (a) and 90 °C (b). Monomer concentration = 0.5 g/1.0 mL ([M] = 1.38 mol/L). $[\text{A-Phe-OMe}]_0/[\text{CTA 1}]_0/[\text{AIBN}]_0 = 200/2/1$.

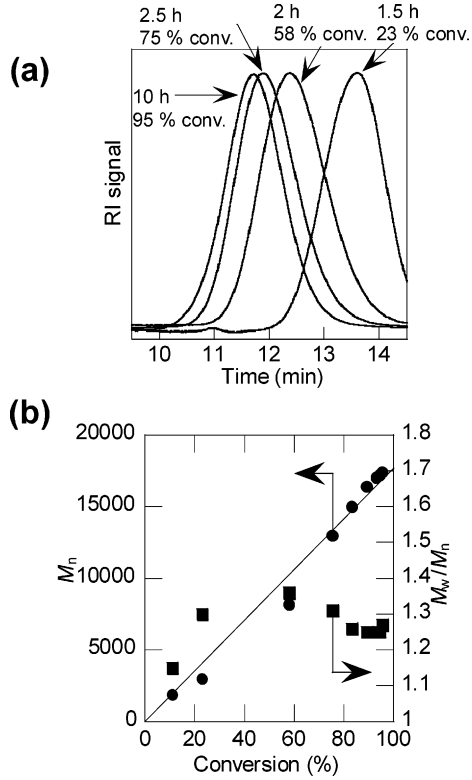


Figure 3. (a) Evolution of size-exclusion chromatography (SEC) traces with conversion and (b) number-average molecular weight (circles) and polydispersity (squares) as a function of conversion at 60 °C. See Figure 2 for detailed polymerization conditions.

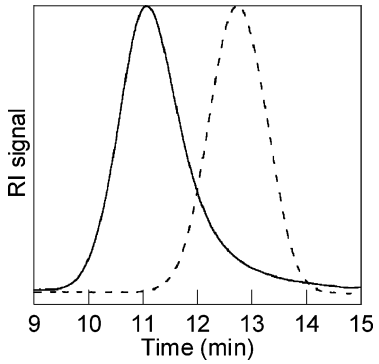


Figure 4. Size-exclusion chromatography (SEC) traces of the parent poly(A-Phe-OMe) macro-CTA (dotted trace, $M_n = 6400$, $M_w/M_n = 1.29$) and the chain extended polymer (solid trace, $M_n = 23\,000$, $M_w/M_n = 1.38$) obtained after the polymerization with A-Phe-OMe.

radical (with and without intermediate radical termination), tendency of the expelled radical to add to the CTA rather than to monomer, and impurities in the CTA. The SEC traces of poly(A-Phe-OMe) obtained at 60 °C at different polymerization times clearly illustrate the increase in molar mass with time (Figure 3a). Symmetrical unimodal SEC peaks without shoulders and tailings are observed for the polymers obtained even at higher conversion (>90%). The polydispersity indices (M_w/M_n) for all samples ranged between 1.15 and 1.36, regardless of the polymerization temperature. Figure 3b shows the evolution of M_n and M_w/M_n with conversion during the polymerization of A-Phe-OMe. The linearity of the M_n vs conversion plot was observed at 60 °C, indicating that the polymerization proceeded in a controlled fashion without nondegenerative chain transfer. The linear relationship between the M_n and the conversion with maintaining low polydispersity was also observed at 90 °C (Figure S6, see Supporting Information). These results suggest that the polymerization of A-Phe-OMe mediated by CTA 1 shows a good control at both temperatures, 60 and 90 °C.

To get further insights into to the controlled/living character of the polymerization, the poly(A-Phe-OMe) obtained from the polymerization in the presence of CTA 1 was isolated and then used as a macro-CTA for further reaction. The chain extension was conducted using the poly(A-Phe-OMe) ($M_n = 6400$, $M_w/M_n = 1.29$) as the macro-CTA, A-Phe-OMe as the monomer, and AIBN as the initiator in dioxane at 60 °C. When the polymerization was conducted at $[\text{A-Phe-OMe}]_0/[\text{macro-CTA}]_0/[\text{AIBN}]_0 = 200/2/1$, almost full conversion was reached after 24 h. SEC traces of the starting poly(A-Phe-OMe) macro-CTA and the second-growth polymer are shown in Figure 4. A shift of the SEC trace toward a higher molecular weight region clearly shows that the extension was successful. Tiny tailing can be seen, suggesting that a small amount of residual low molecular weight dead chains remains in the final product. Nevertheless, the polydispersity remained below 1.4, even at almost full conversion. These results suggest that most of the chain ends of poly(A-Phe-OMe) are functionalized with the dithiocarbamate end groups, which can be used as a macro-CTA for further chain extension reactions. Experiments aiming to synthesize well-defined block copolymers containing poly(A-Phe-OMe) segment by

Table 3. Reversible Addition−Fragmentation Chain Transfer (RAFT) Polymerization of *N*-Acryloyl-L-phenylalanine Methyl Ester (A-Phe-OMe) in the Presence of Lewis Acid in Dioxane at 60 °C for 6 h[a]

entry	Lewis acid	[Lewis acid]/[M]	conv[b] (%)	M_n[c] (theory)	M_n[d] (SEC)	M_w/M_n[e] (SEC)	tacticity *m*/*r*[f]
1			93	22 000	17 000	1.25	49/51
2	$Y(OTf)_3$	0.05	93	22 000	14 000	1.35	62/38
3	$Y(OTf)_3$	0.1	98	23 500	18 500	1.53	67/33
4	$Y(OTf)_3$	0.2	98	23 500	18 000	1.55	68/32
5	$Y(OTf)_3$	0.5	47	11 000	16 900	1.80	69/31
6[g]	$Y(OTf)_3$	0.2	23	5 600			
7	$Yb(OTf)_3$	0.05	95	23 000	21 000	1.63	65/35
8	$Yb(OTf)_3$	0.2	99	23 500	18 000	1.59	66/34
9	$Sc(OTf)_3$	0.05	84	20 000	17 000	1.55	61/39
10	$Sc(OTf)_3$	0.2	21	5 100			

[a] $[CTA\ 1]_0/[AIBN]_0 = 2$, $[M]_0/[CTA\ 1]_0 = 100$, monomer concentration = 0.5 g/mL ([M] = 1.38 mol/L), where M = acryloyl-L-phenylalanine methyl ester (A-Phe-OMe), AIBN = 2,2′-azobis(isobutyronitrile), and CTA 1 = benzyl 1-pyrrolecarbodithioate (see Scheme 2). [b] Calculated by ^{1}H NMR in $CDCl_3$. [c] The theoretical molecular weight ($M_{n,theory}$) = (MW of M) × conv × $[M]_0/[CTA]_0$ + (MW of CTA). [d] Number-average molecular weight (M_n) was measured by size-exclusion chromatography (SEC) using polystyrene standards in *N*,*N*-dimethylformamide (DMF, 10 mM LiBr). [e] Molecular weight distribution (M_w/M_n) was measured by SEC in DMF (10 mM LiBr). [f] Determined by ^{1}H NMR in dimethyl-d_6 sulfoxide (DMSO-d_6) at 170 °C. [g] Polymerization was conducted at 45 °C for 24 h.

using this method are now in progress, which will be reported elsewhere.

RAFT Polymerization in the Presence of Lewis Acids. Recently, Lewis acids, such as rare earth metal trifluoromethanesulfonates (triflates), $Yb(OTf)_3$, $Y(OTf)_3$, and $Sc(OTf)_3$, have been successfully applied to attain stereocontrol over conventional radical polymerization of acrylamides,[51] methacrylamides,[52,53] α-alkoxymethyl acrylates,[54] and methacrylates.[55] The effect of Lewis acid on the stereocontrol was also reported on conventional radical polymerization of an optically active methacrylamide containing amino acid moiety, *N*-[(*R*)-α-methoxycarbonylbenzyl]methacrylamide.[56] The mechanism controlling tacticity is believed to involve coordination of the Lewis acid with the last two segments of a growing polymer chain, which forces them into the meso configuration during the monomer addition and leads to isotactic polymers. A suitable choice of the nature of Lewis acid as well as Lewis acid/monomer ratio is crucial to attain tacticity control without harming the narrow polydispersity and controlled molecular weights of resulting polymers.[26,30,31,35] For example, Okamoto et al. reported that a ratio of Lewis acid/monomer equal to 0.1 is sufficient to achieve successful stereocontrol of the polymerization of various acrylamide derivatives.[51] However, Matyjaszewski et al. demonstrated that a RAFT polymerization of *N*,*N*-dimethylacrylamide exhibited uncontrolled molecular weight and a relatively broad molecular weight distribution at a ratio of Lewis acid/monomer equal to 0.1, and the RAFT polymerization was therefore conducted in the presence of a lower amount of Lewis acid (Lewis acid/monomer = 0.05).[26] The stereocontrol over radical polymerization strongly depends on the monomer structure, involving the nature of the α-substituted group and of the coordination functions, such as ester or amide group. In the cases of free radical polymerization without Lewis acid, the effect of α-substituted group is important. For acrylate and acrylamide monomers, the probability of meso and racemo addition is nearly equal,[35] resulting in atactic polymers. In the presence of Lewis acid, the coordination functions are predominant parameter for the stereocontrol. We, therefore, examined the effect of Lewis acid on RAFT polymerization of A-Phe-OMe in dioxane using AIBN and CTA 1. The monomer/chain transfer agent/initiator molar ratio was maintained at $[A\text{-Phe-OMe}]_0/[CTA\ 1]_0/[AIBN]_0 = 200/2/1$. The results are summarized in Table 3. The microstructure of poly(A-Phe-OMe)s obtained under different conditions was investigated by

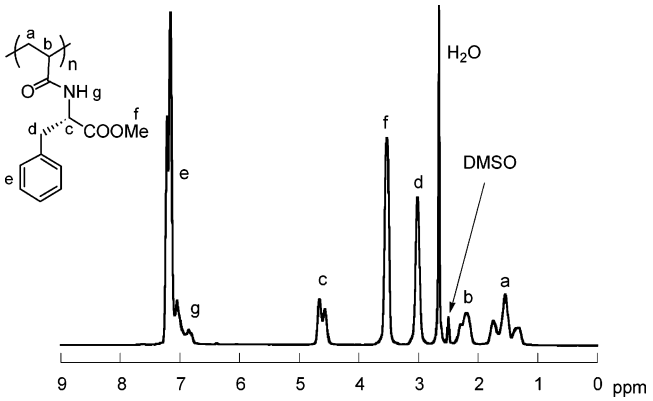


Figure 5. ^{1}H NMR (500 MHz, DMSO-d_6, 170 °C) spectrum of poly(A-Phe-OMe) prepared in the absence of Lewis acid.

^{1}H NMR in DMSO-d_6 at 170 °C. Figure 5 shows the representative ^{1}H NMR spectrum of poly(A-Phe-OMe) obtained by the RAFT polymerization in the absence of Lewis acid. The characteristic peaks at 7.4−6.8 (aromatic protons and amide methine proton), 4.8−4.5 (methine proton attached to chiral carbon atom), 3.4−3.6 (methyl protons), 3.2−2.8 (methylene protons), 2.6−2.0 (backbone methine proton), and 1.9−1.2 ppm (backbone methylene protons) are clearly seen. As reported in poly(*N*,*N*-dimethylacrylamide)[26] and poly(*N*-isopropylacrylamide),[30,31] the proportion of meso and racemic dyads and the degree of isotacticity in the polymer can be estimated from the backbone methylene region of the ^{1}H NMR spectra. In the signal from the meso dyads, the two methylene protons are not equivalent and lead to two broad peaks of almost equal intensity, as can be seen in Figure 6. For poly(A-Phe-OMe) prepared in this study, these meso dyads peaks are observed at around 1.75 and 1.35 ppm. However, the methylene protons of racemo dyads are equivalent and the racemo peak is seen at 1.55 ppm.

In the absence of Lewis acid, the polymerization of A-Phe-OMe with CTA 1 at 60 °C yielded the polymer with a similar proportion of meso and racemic dyads (m = 49%, entry 1 in Table 3, Figure 6a), namely an atactic polymer. The polymerization in the presence of $Y(OTf)_3$ (0.05 equiv of $Y(OTf)_3$ as compared to monomer) produced the polymer with higher isotacticity (m = 62%, entry 2 in Table 3, Figure 6b). The polymer yield was almost quantitative after 6 h, and the control over molecular weight and molecular weight distribution remained as good as in the absence of Lewis acid. Thus,

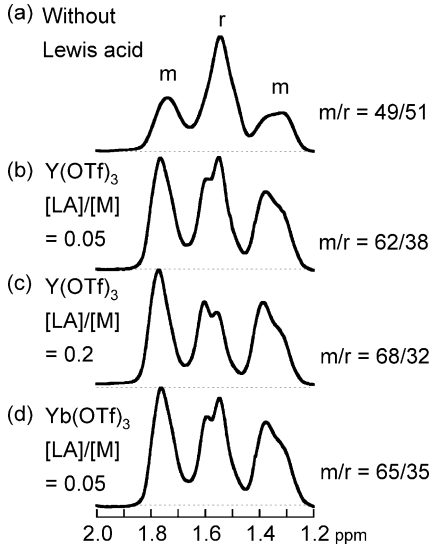


Figure 6. ^{1}H NMR (500 MHz, DMSO-d_6, 170 °C) spectra of poly(A-Phe-OMe)s prepared in the absence (a) and presence (b−d) of Lewis acids.

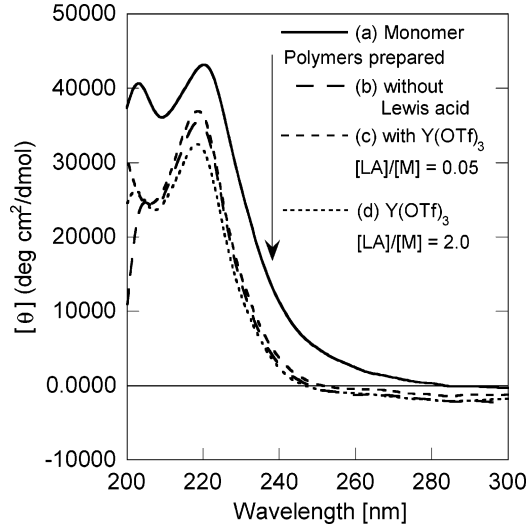


Figure 7. Circular dichroism (CD) spectra (c = 0.1 g/dL, THF) of A-Phe-OMe and poly(A-Phe-OMe)s prepared by RAFT polymerization in the absence and presence of Lewis acid.

the combination of RAFT and the Lewis acid complexation technique allows the synthesis of well-defined poly(A-Phe-OMe) with enhanced isotacticity. Increasing the concentration of $Y(OTf)_3$ to 0.1 and 0.2 equiv led to further increase in the tacticity (m = 67−68%), whereas the molecular weight distributions of the resulting polymers were relatively broad (M_w/M_n = 1.53−1.55). Further increase of the $Y(OTf)_3$ concentration (Lewis acid/monomer = 0.5) led to the retardation of the polymerization, in which the monomer conversion was ca. 47% even after 6 h. In this case, the color of the reaction mixture turned form a typical pale yellow into brown during the polymerization, resulting in the polymer (m = 69%) with broad polydispersity (M_w/M_n = 1.80).

Similar observations were also reported in the literature, in which RAFT polymerization of acryamides in the presence of Lewis acid led to the higher polydispersity.[26,31] Several assumptions have been reported to explain the observed higher polydispersity in the presence of Lewis acid, which involve the increase of the polymerization rate owing to the complexation of the Lewis acid with the monomer and propagating radical and the decrease of the exchange rate within the dormant intermediate radical complexed with Lewis acid and the active propagating radical. Both behaviors should be responsible for the rate enhancement of RAFT polymerization. In our case, actually, the presence of Lewis acid (Lewis acid/monomer = 0.1 or 0.2) in the RAFT polymerization of A-Phe-OMe in dioxane led to the increase in the monomer conversion, as shown in Table 3. Drastic decrease in the polymerization rate was also observed in the RAFT polymerization of A-Phe-OMe with higher $Y(OTf)_3$ concentration (Lewis acid/monomer = 0.5), suggesting the existence of some unknown side reactions assisted by Lewis acid. To achieve a better control over the stereoregularity, we attempted to slow the growth of the polymer chains by decreasing the temperature to 45 °C. However, the conversion was low (<30%) even at moderate $Y(OTf)_3$ concentration (Lewis acid/monomer = 0.2) after 24 h (entry 6 in Table 3).

To obtain information on the complexation of the Lewis acid with the monomer as well as a possible interaction between the Lewis acid and CTA, we conducted preliminary experiments by ^{13}C NMR analyses in $CDCl_3$ at room temperature. In the ^{13}C NMR measurements of the monomer (A-Phe-OMe), apparent chemical shifts were observed for N−*C*=O and *C*=O carbons with the addition of $Y(OTf)_3$ (Table S1, see Supporting Information), suggesting that the Lewis acid interacts with ester and amide groups of the monomer. The changes in the chemical shifts of the CTA with the addition of $Y(OTf)_3$ were found to be smaller than those of the monomer (Table S2, see Supporting Information) under the same conditions. Nevertheless, further parameters, such as interaction of the growing polymer chains with Lewis acid, concentration and molar ratio of the reagents, and effects of the temperature and solvent, have to take into account for the detailed investigations of the complexations in real polymerization system, which will be reported in our forthcoming paper.

The effects of three triflates were compared at Lewis acid/monomer = 0.05. Compared with $Y(OTf)_3$, $Yb(OTf)_3$ and $Sc(OTf)_3$ exhibited a similar isotacticity enhancing effect (m = 65 and 61%) but led higher polydispersity (M_w/M_n = 1.63 and 1.55). In these runs, the conversions were nearly quantitative (>84%, as determined by ^{1}H NMR). When the polymerization was conducted with $Yb(OTf)_3$, the Lewis acid/monomer ratio had no significant influence on the tacticity, conversion, molecular weight, and polydispersity. However, the significant retardation was observed at Lewis acid/monomer = 0.2 in the case of the polymerization with $Sc(OTf)_3$. These results suggest that moderate isotacticity enhancing effect (m = 61−69%) can be achieved by all Lewis acids used in this study, but the nature of Lewis acid has remarkable influence on the polymerization rate and polydispersity of the resulting poly(A-Phe-OMe)s. Figure 7 illustrates CD spectra of A-Phe-OMe and poly(A-Phe-OMe)s measured in THF solutions (c = 0.1 g/dL). The monomer showed positive Cotton effects at 205 and 220 nm, and the molecular ellipticity at the maximum is 43 186 deg·cm^2/dmol. All polymers possessed positive Cotton effects at 218−219 nm, and the values of the ellipticity were lower than that of the monomer. Among the polymers, poly(A-Phe-OMe) obtained by RAFT polymerization in the absence of Lewis acid ($[M]_D^{25}$ = 37.0, m = 49%) exhibited a higher ellipticity (36 944 deg·cm^2/

Table 4. Reversible Addition−Fragmentation Chain Transfer (RAFT) Polymerization of *N*-Acryloyl-L-phenylalanine Methyl Ester (A-Phe-OMe) in Alcohols[a]

entry	solvent	temp (°C)	time (h)	$[Y(OTf)_3]/[M]$	conv[b] (%)	M_n[c] (theory)	M_n[d] (SEC)	M_w/M_n[e] (SEC)	tacticity *m*/*r*[f]
1	MeOH	60	24		96	23000	15000	1.28	46/54
2	MeOH	60	6	0.05	41	9500	5700	1.35	54/46
3	MeOH	60	6	0.2	39	9300	4100	2.34	62/38
4	MeOH	45	24		81	19000	19000	1.20	47/53
5	MeOH/toluene (1/1)	60	24		96	23000	28000	1.28	48/52
6	HFIP[g]	45	24		38	9100	6100	1.85	46/54
7	HFIP[g]	60	24		52	12000	7200	1.71	48/52

[a] $[CTA1]_0/[AIBN]_0 = 2$, $[M]_0/[CTA1]_0 = 100$, monomer concentration = 0.5 g/mL ([M] = 1.38 mol/L), where M = acryloyl-L-phenylalanine methyl ester (A-Phe-OMe), AIBN = 2,2′-azobis(isobutyronitrile), and CTA 1 = benzyl 1-pyrrolecarbodithioate (see Scheme 2). [b] Calculated by ^{1}H NMR in $CDCl_3$. [c] The theoretical molecular weight ($M_{n,theory}$) = (MW of M) × conv × $[M]_0/[CTA]_0$ + (MW of CTA). [d] Number-average molecular weight (M_n) was measured by size-exclusion chromatography (SEC) using polystyrene standards in *N*,*N*-dimethylformamide (DMF, 10 mM LiBr). [e] Molecular weight distribution (M_w/M_n) was measured by SEC in DMF (10 mM LiBr). [f] Determined by ^{1}H NMR in dimethyl-d_6 sulfoxide (DMSO-d_6) at 170 °C. [g] 1,1,1,3,3,3-Hexafluoro-2-propanol.

dmol). The value decreases slightly with increasing the *m* content in the polymers (35 542 deg·cm^2/dmol at *m* = 62% and 32 507 deg·cm^2/dmol at *m* = 68%). The tendency may be attributed to small conformation difference based on the tacticity. The polymers obtained by the RAFT polymerization in the absence and presence of $Y(OTf)_3$ (Lewis acid/monomer = 0.05) showed the specific rotations of $[\alpha]^{25}_D = 37.0$ and $[\alpha]^{25}_D = 13.0$, respectively. The significant decrease of the specific rotations was observed in the transformation of the monomer ($[\alpha]^{25}_D = 102.2$) to the polymers. The thermal properties of the resulting polymers were also evaluated by differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) measurements. The glass transition temperature (T_g) of poly(A-Phe-OMe) prepared in the presence of Lewis acid (*m* content = 62%, sample; entry 2 in Table 3) was found to be 87.2 °C, which is slightly higher than that in the absence of Lewis acid (T_g = 82.1 °C, sample; entry 1 in Table 3). The temperatures for 10% weight loss of poly(A-Phe-OMe)s under nitrogen atmosphere were in the range 338−340 °C.

RAFT Polymerization in Alcohols. In the next stage, we investigated the effect of polar solvent, in particular alcohols, on the control over stereoregularity and molecular weights of poly(A-Phe-OMe)s obtained by RAFT polymerization. Alcohols, such as methanol and butanol, are effective solvents for the stereocontrol of poly(meth)acrylamides with Lewis acid.[26,30,31,35] Higher levels of the stereocontrol in radical polymerizations required not only a complexing Lewis acid but also the presence of relatively polar solvents. Recently, Okamoto et al. demonstrated another effective approach to achieve control of stereoregularity by radical polymerization. They reported that fluoro alcohols, such as 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), were effective solvents for producing highly syndiotactic poly(methyl methacrylate) by conventional radical polymerization[57,58] and atom transfer radical polymerization.[59] The control of the tacticity is considered to be due to the hydrogen-bond interaction between the alcohol and monomers or growing species. We therefore attempted to extend this methodology to the synthesis of well-defined poly(A-Phe-OMe)s by RAFT polymerization. The polymerization was carried out in methanol, methanol/toluene, and HFIP at $[A\text{-Phe-OMe}]_0/[CTA\ 1]_0/[AIBN]_0 = 200/2/1$, and the results are shown in Table 4. When A-Phe-OMe was polymerized using CTA 1 with AIBN in methanol, almost full conversion (96%, as determined by ^{1}H NMR) was obtained at 60 °C after 24 h. Although the polydispersity remains low (M_w/M_n = 1.28), the resulting polymer shows SEC peak with a shoulder at high molecular weight region, as can be seen in Figure 8. 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 = 1.20) with reduced shoulder peak, as shown in Figure 8. The SEC traces with UV detector also showed the same tendency (Figure S7, see Supporting Information). This behavior may be due to that decreasing the temperature leads to a decrease in the radical reactivity, resulting in the increased selectivity of the various radical 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. In the case of the polymerization in methanol at 45 °C, the monomer conversion was 81% after 24 h, and the tacticity of the resulting poly(A-Phe-OMe) was *m* = 47%. In the RAFT polymerization of A-Phe-OMe in methanol at 60 °C, the Lewis acid, $Y(OTf)_3$, exhibited a less isotacticity enhancing effect (*m* = 54% at $Y(OTf)_3$/monomer = 0.05), as compared in dioxane (*m* = 62%). In both cases, the Lewis acid enhanced isotacticity moderately, but higher Lewis acid concentration resulted in the polymers having higher polydispersity. Interestingly, the significant retardation of the polymerization rate was observed

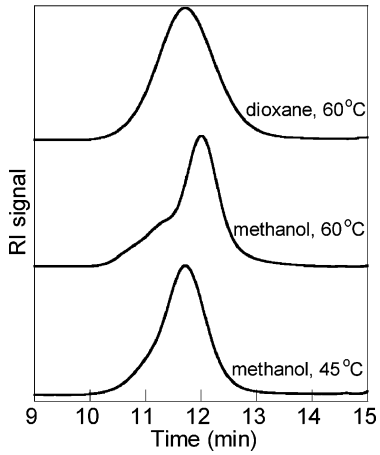


Figure 8. Size-exclusion chromatography (SEC) traces of poly(A-Phe-OMe)s obtained by RAFT polymerization in different solvents.

by the addition of the Lewis acid in methanol, which is the opposite tendency observed in the case of polymerization in dioxane. Higher polarity of methanol compared to that of dioxane may disturb the interaction of Lewis acid with the monomer, resulting in the depression of the isotacticity enhancing effect and polymerization rate. Narrow polydispersity product (M_w/M_n = 1.28) was obtained by the RAFT polymerization in methanol−toluene mixture at 60 °C. Under the similar experimental conditions, the polymerizations in HFIP, which can be regarded as the highly polar solvent, led to insufficient monomer conversions and broad molecular weight distributions (M_w/M_n > 1.7). Different from the cases in methanol, the polymerizations in HFIP at low temperature (45 °C) was relatively unsuccessful and produced the polymer with broader polydispersity and lower conversion.

From the polymerization results mentioned above, it was demonstrated that the synthesis of the well-defined poly(A-Phe-OMe)s with predetermined molecular weight and narrow molecular weight distribution was possible by RAFT polymerization using CTA 1, even in the presence of Lewis acid, in dioxane or alcohols. This indicates the feasibility to achieve simultaneous control of the molecular weight and stereochemistry, but further improvement is needed for the preparation of the amino acid-based polymer with higher stereoregularity. It seems reasonable to expect that the bulky phenylalanine side chain in A-Phe-OMe has negative influence on the stereocontrol because the coordination of the Lewis acid with monomers or growing polymer chains is crucial to attain the stereocontrol by Lewis acid, and the hydrogen-bond interaction is key factor to produce syndiotactic polymers in fluoro alcohols. The bulky phenylalanine side chain in A-Phe-OMe may disturb the coordination and the hydrogen-bond interaction, resulting in insufficient control of the tacticity. In other words, RAFT polymerization of a monosubstituted acrylamide having a smaller amino acid moiety, such as alanine and glycine, in the side chain may help to achieve simultaneous control of the molecular weight and stereochemistry. Further studies for such directions are now in progress, which will be reported separately.

Conclusion

We have demonstrated the first successful controlled radical polymerization of a monosubstituted acrylamide having an amino acid moiety, *N*-acryloyl-L-phenylalanine methyl ester (A-Phe-OMe), via the RAFT process. Benzyl 1-pyrrolecarbodithioate (CTA 1) is efficient as the chain transfer agent for the preparation of near-monodisperse poly(A-Phe-OMe)s with controlled molecular weights. Good control of the polymerization in dioxane at 60 °C was confirmed by the linear relationship between the molecular weight and the monomer/CTA molar ratio, the linear increase in the molecular weight with the conversion, and successful chain extension. The poly(A-Phe-OMe)s with low polydispersity could be obtained also under various conditions (solvent = dioxane, methanol, and methanol/toluene; temperature = 45, 60, and 90 °C). This work presents the feasibility 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. 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 specific intra- and intermolecular interactions via hydrogen bonding may be manipulated by the nature of the amino acid moiety, the self-organization of the well-defined polymers can provide a viable route to the production of tailored amino acid-based materials with unique properties for various applications, such as controlled release, biochemical sensing, biocompatible materials, and optical resolution.

Acknowledgment. This work has been partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology, Japan (17550112). The authors acknowledge Associate Professor Seigou Kawaguchi for GPC-MALS measurement.

Supporting Information Available: Figures showing ^1H and ^{13}C NMR spectra of the monomer and polymer, experimental conditions and results of the polymerizations at different $[M]_0$:$[CTA\ 1]_0$ ratios under nitrogen at 90 °C, and kinetic results of the polymerization with CTA 1 at 90 °C, comparison of UV (280 nm) and RI detector responses of the SEC traces, comparison of light scattering (90°) and RI detector responses of the SEC traces, and changes in the ^{13}C NMR chemical shifts of the monomer (A-Phe-OMe) and CTA 1 with the addition of $Y(OTf)_3$. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Klok, H.-A.; Langenwalter, J. F.; Lecommandoux, S. *Macromolecules* **2000**, *33*, 7819−7826.
(2) Schlaad, H.; Kukula, H.; Smarsly, B.; Antonietti, M.; Pakula, T. *Polymer* **2002**, *43*, 5321−5328.
(3) Floudas, G.; Papadopoulos, P.; Klok, H.-A.; Vandermeulen, G. W. M.; Rodriguez-Hernandez, J. *Macromolecues* **2003**, *36*, 3673−3683.
(4) Deming, T. J. *Nature (London)* **1997**, *390*, 386−389.
(5) Deming, T. J. *J. Polym. Sci., Part A: Polym. Chem.* **2000**, *38*, 3011−3018.
(6) Nagai, A.; Sato, D.; Ishikawa, J.; Ochiai, B.; Kudo, H.; Endo, T. *Macromolecules* **2004**, *37*, 2332−2334.
(7) Naka, K.; Nemoto, T.; Chujo, Y. *J. Polym. Sci., Part A: Polym. Chem.* **2003**, *41*, 1504−1510.
(8) Mei, Y.; Beers, K. L.; Byrd, H. C. M.; VanderHart, D. L.; Washburn, N. R. *J. Am. Chem. Soc.* **2004**, *126*, 3472−3476.
(9) Becker, M. L.; Liu, J. Q.; Wooley, K. L. *Chem. Commun. (Cambridge)* **2003**, 180−181.
(10) Sanda, F.; Endo, T. *Macromol. Chem. Phys.* **1999**, *200*, 2651−2661.
(11) Methenitis, C.; Morcellet, J.; Pneumatikakis, G.; Morcellet, M. *Macromolecues* **1994**, *27*, 1455−1460.
(12) Blaschke, G. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 13−23.
(13) Angiolini, L.; Caretti, D.; Carlini, C.; Salatelli, E. *Macromol. Chem. Phys.* **1995**, *196*, 2737−2750.
(14) Barbucci, R.; Casolaro, M.; Magnani, A. *J. Controlled Release* **1991**, *17*, 79−88.
(15) Casolaro, M.; Barbucci, R. *Int. J. Artif. Organs* **1991**, *14*, 732−738.
(16) Bentolila, A.; Vlodavsky, I.; Ishai-Michaeli, R.; Kovalchuk, O.; Haloun, C.; Domb, A. J. *J. Med. Chem.* **2000**, *43*, 2591−2600.
(17) Bignotti, F.; Penco, M.; Sartore, L.; Peroni, I.; Mendichi, R.; Casolaro, M.; D'Amore, A. *Polymer* **2000**, *41*, 8247−8256.
(18) Casolaro, M. *Macromolecues* **1995**, *28*, 2351−2358.
(19) Yoshida, M.; Safranj, A.; Omichi, H.; Katakai, R. *Macromolecules* **1996**, *29*, 2321−2323.
(20) Matyjaszewski, K.; Xia, J. *Chem. Rev.* **2001**, *101*, 2921−2990.
(21) Kamigaito, M.; Ando, T.; Sawamoto, M. *Chem. Rev.* **2001,** *101*, 3689−3745.
(22) Hawker, C. J.; Bosman, A. W.; Harth, E. *Chem. Rev.* **2001**, *101*, 3661−3688.
(23) Chiefari, J.; Chong, Y. K.; Ercole, F.; Krstina, J.; Jeffery, J.; Le, T. P. T.; Mayadunne, R. T. A.; Meijs, G. F.; Moad, C. L.; Moad, G.; Rizzardo, E.; Thang, S. H. *Macromolecues* **1998**, *31*, 5559−5562.

(24) Rizzardo, E.; Chiefari, J.; Mayadunne, R.; Moad, G.; Thang, S. *Macromol. Symp.* **2001,** *174* (Polymerization Processes and Polymer Materials I), 209−212.
(25) Chong, Y. K.; Le, T. P. T.; Moad, G.; Rizzardo, E.; Thang, S. H. *Macromolecules* **1999**, *32*, 2071−2074.
(26) Lutz, J.-F.; Neugebauer, D.; Matyjaszewski, K. *J. Am. Chem. Soc.* **2003,** *125*, 6986−6993.
(27) Donovan, S. M.; Lowe, B. A.; Sumerlin, S. B.; McCormick, L. C. *Macromolecues* **2002**, *35*, 4123−4132.
(28) Ganachaud, F.; Monteiro, M. J.; Gilbert, R. G.; Dourges, M.-A.; Thang, S. H.; Rizzardo, E. *Macromolecules* **2000**, *33*, 6738−6745.
(29) Schilli, C.; Lanzendörfer, M. G.; Müller, A. H. E. *Macromolecules* **2002**, *35*, 6819−6827.
(30) Ray, B.; Isobe, Y.; Morioka, K.; Habaue, S.; Okamoto, Y.; Kamigaito, M.; Sawamoto, M. *Macromolecules* **2003**, *36*, 543−545.
(31) Ray, B.; Isobe, Y.; Matsumoto, K.; Habaue, S.; Okamoto, Y.; Kamigaito, M.; Sawamoto, M. *Macromolecues* **2004**, *37*, 1702−1710.
(32) Favier, A.; Charreyre, M. T.; Chaumont, P.; Pichot, C. *Macromolecules* **2002**, *35*, 8271−8280.
(33) D'Agosto, F.; Hughes, R.; Charreyre, M.; Pichot, C.; Gilbert, R. G. *Macromolecules* **2003**, *36*, 621−629.
(34) Favier, A.; Ladaviere, C.; Charreyre, M. T.; Pichot, C. *Macromolecules* **2004**, *37*, 2026−2034.
(35) Lutz, J. F.; Jakubowski, W.; Matyjaszewski, K. *Macromol. Rapid Commun.* **2004**, *25*, 486-492.
(36) Chiefari, J.; Mayadunne, R. T. A.; Moad, C. L.; Moad, G.; Rizzardo, E.; Postma, A.; Skidmore, M. A.; Thang, S. H. *Macromolecules* **2003**, *36*, 2273−2283.
(37) Chong, Y. K.; Krstina, J.; Le, T. P. T.; Moad, G.; Postma, A.; Rizzardo, E.; Thang, S. H. *Macromolecules* **2003**, *36*, 2256−2272.
(38) Sanda, F.; Abe, T.; Endo, T. *J. Polym. Sci., Part A: Polym. Chem.* **1997,** *35*, 2619−2629.
(39) Moad, G.; Chiefari, J.; Chong, Y. K.; Krstina, J.; Mayadunne, R. T. A.; Postma, A.; Rizzardo, E.; Thang, S. H. *Polym. Int.* **2000**, *49*, 993−1001.
(40) Monteiro, M. J.; de Brouwer, H. *Macromolecules* **2001**, *34*, 349−352.
(41) Kwak, Y.; Goto, A.; Tsujii, Y.; Murata, Y.; Komatsu, K.; Fukuda, T. *Macromolecules* **2002**, *35*, 3026−3029.
(42) Barner-Kowollik, C.; Quinn, J. F.; Morsley, D. R.; Davis, T. P. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 1353−1365.
(43) Thomas, D. B.; Convertine, A. J.; Myrick, L. J.; Scales, C. W.; Smith, A. E.; Lowe, A. B.; Vasilieva, Y. A.; Ayres, N.; McCormick, C. L. *Macromolecules* **2004**, *37*, 8941−8950.
(44) Vasilieva, Y. A.; Thomas, D. B.; Scales, C. W.; McCormick, C. L. *Macromolecules* **2004**, *37*, 2728−2737.
(45) McCormick, C. L.; Lowe, A. B. *Acc. Chem. Res.* **2004**, *37*, 312−325.
(46) Vana, P.; Davis, T. P.; Barner-Kowollik, C. *Macromol. Theory Simul.* **2002**, *11*, 823−835.
(47) Perrier, S.; Barner-Kowollik, C.; Quinn, J. F.; Vana, P.; Davis, T. P. *Macromolecules* **2002**, *35*, 8300−8306.
(48) Plummer, R.; Goh, Y.-K.; Whittaker, A. K.; Monteiro, M. J. *Macromolecules* **2005**, *38*, 5352−5355.
(49) Coote, M. L. *Macromolecules* **2004**, *37*, 5023−5031.
(50) McLeary, J. B.; Calitz, F. M.; McKenzie, J. M.; Tonge, M. P.; Sanderson, R. D.; Klumperman, B. *Macromolecules* **2005**, *38*, 3151−3161.
(51) Isobe, Y.; Fujioka, D.; Habaue, S.; Okamoto, Y. *J. Am. Chem. Soc.* **2001,** *123*, 7180−7181.
(52) Isobe, Y.; Suito, Y.; Habaue, S.; Okamoto, Y. *J. Polym. Sci., Part A: Polym. Chem.* **2003**, *41*, 1027−1033.
(53) Suito, Y.; Isobe, Y.; Habaue, S.; Okamoto, Y. *J. Polym. Sci., Part A: Polym. Chem.* **2002**, *40*, 2496−2500.
(54) Baraki, H.; Habaue, S.; Okamoto, Y. *Macromolecules* **2001**, *34*, 4724−4729.
(55) Isobe, Y.; Nakano, T.; Okamoto, Y. *J. Polym. Sci., Part A: Polym. Chem.* **2001**, *39*, 1463−1471.
(56) Morioka, K.; Suito, Y.; Isobe, Y.; Habaue, S.; Okamoto, Y. *J. Polym. Sci., Part A: Polym. Chem.* **2003**, *41*, 3354−3360.
(57) Isobe, Y.; Yamada, K.; Nakano, T.; Okamoto, Y. *Macromolecules* **1999**, *32*, 5979−5981.
(58) Isobe, Y.; Yamada, K.; Nakano, T.; Okamoto, Y. *J. Polym. Sci., Part A: Polym. Chem.* **2000**, *38*, 4693−4703.
(59) Miura, Y.; Satoh, T.; Narumi, A.; Nishizawa, O.; Okamoto, Y.; Kakuchi, T. *Macromolecules* **2005**, *38*, 1041−1043.

MA0509558