Macromolecules **2003,** *36,* 543−545 **543**

Synthesis of Isotactic Poly(*N*-isopropylacrylamide) by RAFT Polymerization in the Presence of Lewis Acid

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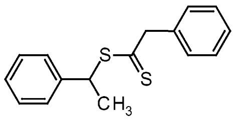
Received October 22, 2002
Revised Manuscript Received December 17, 2002

Introduction. Living radical polymerization[1] is the most significant and useful procedure to synthesize polymers with controlled molecular weight and narrow molecular weight distribution. Metal-catalyzed atom transfer radical polymerization,[2] nitroxide-mediated polymerization,[3] and reversible addition−fragmentation chain transfer (RAFT) polymerization[4] have been widely used for this purpose. Stereocontrol during polymerization is also very important as it may produce a polymer with better properties. Stereocontrolled polymers are often prepared by ionic or coordination polymerization with a catalyst containing a metal ion. Recently, one of our groups reported the stereocontrolled radical polymerization of acrylamides catalyzed by Lewis acids such as rare earth metal trifluoromethanesulfonates (OTf).[5,6] In our ongoing effort, we are interested in controlling both the stereostructure and molecular weight of the polyacrylamides.

This communication reports the first synthesis of stereocontrolled poly(*N*-isopropylacrylamide) with controlled molecular weight. The RAFT process was chosen since it has a very low interference with Lewis acids.[7] *N*-Isopropylacrylamide (NIPAM) was used as the monomer because it affords a water-soluble polymer[8] and has been widely studied as a polymer gel.[9] Ganachaud et al. recently reported the synthesis of poly(NIPAM) with controlled molecular weight by the RAFT polymerization using 2,2′-azobis(isobutyronitrile) (AIBN) initiator and two chain transfer agents, benzyl dithiobenzoate (in benzene) and cumyl dithiobenzoate (in 1,4-dioxane) at 60 °C.[10] Very recently, Schilli et al. reported the RAFT polymerization of NIPAM using benzyl 1-pyrrolecarbodithioate and cumyl 1-pyrrolecarbodithioate as the chain transfer agents and AIBN in 1,4-dioxane at 60 °C.[11] None of these examples, however, are for fine stereochemical control of polymers. In another context, we recently reported the synthesis of the highly isotactic poly(NIPAM) by radical polymerization in the presence of Lewis acids like rare earth metal triflates,[6] but the molecular weight control was not sufficient. The polymerization of NIPAM in methanol at −20 °C yielded a polymer with a high isotacticity ($m = 92\%$). Herein we thus choose 1-phenylethyl phenyldithioacetate (PEPD) as the chain transfer agent, which had been used for the RAFT polymerizations of methyl acrylate[12] and styrene[13] at room temperature. The solvent for the polymerization was a methanol−toluene (1:1) mixture because the polymerization of NIPAM in this medium was more quantitative than that in methanol.



1-Phenylethyl phenyldithioacetate (PEPD)

Experimental Section. 1-Phenylethyl phenyldithioacetate (PEPD) was synthesized according to the literature.[12] NIPAM (Wako, >98%) was recrystallized twice from hexane. AIBN (Kishida, 99%) was recrystallized from methanol. Y(OTf)$_3$ (Aldrich, 98%), Yb(OTf)$_3$ (Aldrich, 99.99%), and Sc(OTf)$_3$ (Aldrich, 99%) were dried under vacuum before use. Dehydrated methanol (Cica reagent, >99.8%) and dehydrated toluene (Cica reagent, >99.5%) were used as received.

The polymerization was carried out in a dry glass tube capped with a two-way glass stopper under dry nitrogen. For a typical polymerization, NIPAM (2.26 g, 20 mmol), PEPD (19.0 mg, 0.069 mmol), AIBN (3.8 mg, 0.023 mmol), and Y(OTf)$_3$ (1.25 g, 2.33 mmol) were placed in a dry glass tube and dried under vacuum for 1 h. Then toluene (10 mL) and methanol (10 mL) were added using a syringe. The obtained stock solution was divided into five dry glass polymerization tubes. The tubes were then placed in a thermostated bath at 60 °C for desired time. The reaction was stopped by cooling at −78 °C. The reaction mixture was precipitated in a large excess of diethyl ether and isolated by centrifugation. The isolated product containing the polymer and Y(OTf)$_3$ was dried overnight at 60 °C under vacuum. The polymer yields were gravimetrically determined from the ether-insoluble crude polymer sample and also by ^{1}H NMR of the reaction mixture. For the polymerization of NIPAM in the absence of a Lewis acid, the polymer was precipitated in hot water, isolated by centrifugation, and dried overnight at 60 °C under vacuum.

The average molecular weights and polydispersities of the polymers were measured by size exclusion chromatography (SEC) against polystyrene standard in DMF containing 0.1 mol/L LiCl with flow rate 0.5 mL/min at 40 °C on two polystyrene gel columns: TSK gel α-M (bead size 13 μm and measurable molecular weight range $10^{2.5}-10^7$) and TSK gel α-3000 (bead size 7 μm and measurable molecular weight range $10^{2.5}-10^5$) using JASCO RI-930 and JASCO UV-970 detectors. The ^{1}H NMR spectra were recorded on a Varian Gemini 2000 spectrometer (400 MHz). For the determination of the monomer conversion, the ^{1}H NMR spectrum of the polymerization mixture was measured in DMSO-d_6 at room temperature, and the integration of the monomer C=C−H peak at around 5.7 ppm was compared with the N−C−H peak intensity of the polymer and the monomer at around 4.1 ppm. The diad tacticity of poly(NIPAM) was determined from the methylene proton peaks of the polymer recorded in DMSO-d_6 at 170 °C.[6]

Results and Discussion. Figure 1 shows the pseudo-first-order kinetics plot with respect to the monomer concentration observed within 20−90% conversion. The

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10.1021/ma0257595 CCC: $25.00

Table 1. Results of RAFT Polymerization of *N*-Isopropylacrylamide (NIPAM) Using 2,2′-Azobis(isobutyronitrile) (AIBN) as Initiator and 1-Phenylethyl Phenyldithioacetate (PEPD) as Chain Transfer Agent in Methanol−Toluene (1/1, v/v) Mixture at 60 °C[a]

run	[NIPAM], M	[PEPD], mM	Lewis acid (*M*)	yield,[e] %	M_n(theor) × 10^{-4}	M_n(expt)[f] × 10^{-4}	M_w/M_n[f]	tacticity[g] *m*/*r*
1	1.0	3.47	$Y(OTf)_3$ (0.12)	100	3.26	2.95	1.82	81/19
2	1.0	3.47	$Y(OTf)_3$ (0.17)	91	2.97	2.78	1.76	83/17
3	1.0	3.47	$Yb(OTf)_3$ (0.17)	94	3.08	2.54	1.72	84/16
4	1.0	3.47	$Sc(OTf)_3$ (0.17)	87	2.85	2.72	1.57	67/33
5[b]	1.0	3.47	$Y(OTf)_3$ (0.12)	87	2.81	3.21	1.85	83/17
6[c]	1.0	3.47	$Y(OTf)_3$ (0.12)	15	0.50	10.07	3.89	60/40
7[d]	1.0	3.47	$Y(OTf)_3$ (0.20)	97	3.16	1.83	1.76	87/13
8	2.0	3.47	$Y(OTf)_3$ (0.20)	93	6.05	5.54	1.84	
9	2.0	9.17	$Y(OTf)_3$ (0.20)	86	2.12	2.28	1.39	

[a] [AIBN] = 1.2 mM, solvent = 4 mL, polymerization time = 4 h. [b] Solvent, methanol. [c] Solvent, toluene. [d] Temperature = 30 °C(UV), polymerization time = 24 h. [e] Diethyl ether-insoluble part. [f] Determined by SEC in DMF containing 0.1 M LiCl at 40 °C (PS standard). [g] Determined by ^1H NMR in DMSO-d_6 at 170 °C.

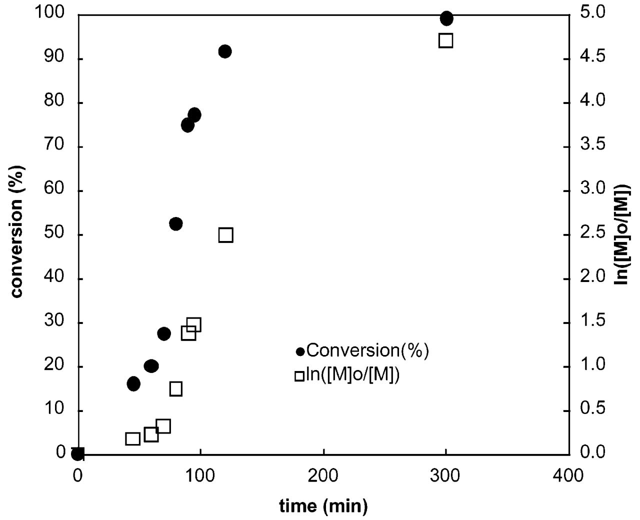

Figure 1. Plots of time−conversion and −ln($[M]_0$/[M]) (where $[M]_0$ = concentration of the monomer at $t = 0$ min and [M] = concentration of the monomer at the corresponding time) in the polymerization of *N*-isopropylacrylamide (NIPAM) using [NIPAM] = 1 M, [AIBN] = 1.2 mM, [PEPD] = 3.47 mM, $[Y(OTf)_3]$ = 0.12 M in 4 mL methanol/toluene (1/1, v/v) mixture at 60 °C (where AIBN = 2,2′-azobis(isobutyronitrile), PEPD = 1-Phenylethyl phenyldithioacetate and OTf = trifluoromethanesulfonate).

corresponding time−conversion plot is S-shaped. This type of observation has been reported for NIPAM polymerized by the RAFT process.[11]

Nevertheless, the polymerization led to a linear increase in molecular weight with conversion (Figure 2). The experimental molecular weight (M_n(expt)) is close to the theoretical one (M_n(theor)) calculated from the NIPAM/PEPD molar ratio and conversion of the monomer. However, the polydispersity increased with conversion and almost leveled off at around 1.8 after 50% conversion.[14] The increase in polydispersity with conversion was also observed in the RAFT polymerization of NIPAM using the cumyl dithiobenzoate/AIBN initiation system in 1,4-dioxane.[10] The formation of a three-arm star chain during polymerization reported by Kwak et al. may disturb the GPC molecular weight determination.[15] Such a possibility may be less important in our RAFT system with the PEPD chain transfer agent.[15]

The ^1H NMR of the resulting polymer in DMSO-d_6 at 170 °C clearly showed the presence of the aromatic protons of the dithioester end groups at around 7.1 ppm. In the SEC experiment, the RI detector and the UV detector monitoring the absorption due to the phenyl end groups in the polymer at 254 nm gave similar curves within the same elution time range. These results support the incorporation of a dithioester group into the polymer chain end. Moreover, reinitiation was successfully carried out using the poly(NIPAM) precursor (M_n = 16 900), NIPAM as the monomer, and AIBN as the initiator at 60 °C.[16] The resulting poly(NIPAM) had M_n = 59 400 and M_w/M_n = 2.2.

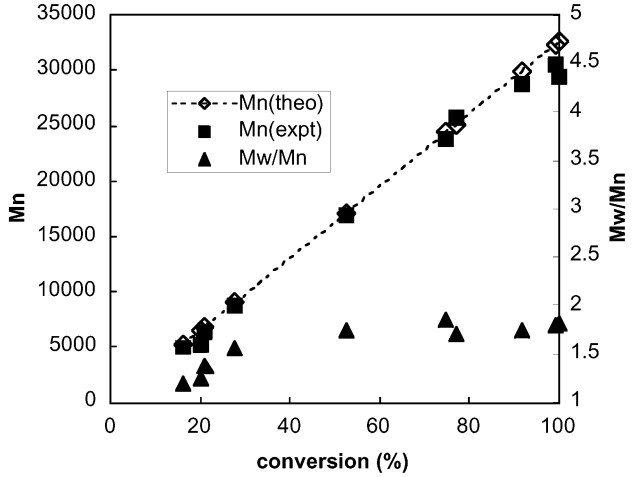

Figure 2. Plots of number-average molecular weight (M_n) and polydispersity (M_w/M_n) (where M_w = weight-average molecular weight) vs conversion in the polymerization of NIPAM. (Polymerization conditions are the same as shown in Figure 1.)

The tacticity of the poly(NIPAM) obtained in the kinetic study using 0.12 M $Y(OTf)_3$ was isotactic (*m* = 80−84%). The tacticity decreased slightly with an increase in the conversion. The tacticity of the poly(NIPAM) prepared under the same conditions in the absence of the Lewis acid was *m* = 47%.

Table 1 shows the results of the RAFT polymerization of NIPAM under different conditions. Increasing the concentration of $Y(OTf)_3$ from 0.12 to 0.17 M slightly increased the tacticity of the obtained polymer (runs 1 and 2). The polymer yield was almost quantitative, and the molecular weight of the obtained polymer was close to the calculated value. The effects of three triflates were compared in runs 2, 3, and 4. $Y(OTf)_3$ and $Yb(OTf)_3$ exhibited a similar isotacticity enhancing effect, but $Sc(OTf)_3$ gave the poly(NIPAM) with a lower tacticity (*m* = 67%). In these runs, the molecular weights were close to the calculated ones. The polymerization was also performed in pure methanol (run 5). The polymer yield was low (15%) in pure toluene (run 6). Under the same experimental conditions, the poly(NIPAM) prepared in methanol had a higher tacticity (*m* = 83%) (run 5) than those in toluene (m = 60%) (run 6) and in the methanol–toluene mixture (m = 81%) (run 1). The polymerization under UV irradiation at 30 °C resulted in the poly(NIPAM) with a high tacticity (m = 87%) (run 7). Although the polymer yield was almost quantitative, the observed molecular weight was lower than the calculated one, which may be ascribed to the formation of higher radical concentrations due to the dissociation of PEPD under UV irradiation in addition to initiator dissociation.[17] The increase in the monomer concentration, when all of the other conditions are the same, increased the molecular weight as expected (run 8). The increase in the concentration of PEPD, keeping the other conditions the same, decreased the polymer yield, molecular weight, and polydispersity (run 9) as expected. The observed molecular weights were close to the calculated ones (runs 8 and 9).

Thus, the isotacticity and molecular weight of poly(NIPAM) can be controlled simultaneously using the RAFT polymerization procedure in the presence of Lewis acids. This procedure may extend to the synthesis of the stereo-block homopolymer with different tacticity or block copolymer with other monomer having predetermined chain lengths. A study on the physical properties of the obtained stereo and molecular weight controlled poly(NIPAM) is under progress.

Conclusion. The RAFT polymerization of NIPAM in the presence of Lewis acids such as $Y(OTf)_3$ and $Yb(OTf)_3$ has led to the first example of stereocontrolled and molecular weight controlled poly(NIPAM) where the dyad isotacticity reached 87%. This procedure may be applicable to other (meth)acrylamides.

Acknowledgment. This work was partly supported by the New Energy and Industrial Technology Development Organization (NEDO) under the Ministry of Economy, Trade and Industry, Japan, through a grant for the “Nanostructure Polymer Project” in the project “Nanotechnology Materials Program” (2001–2008). B.R. thanks the Japan Society for the Promotion of Science (JSPS) for providing the Fellowship and Research Grant for this work.

Supporting Information Available: ^{1}H NMR spectra and SECs of obtained poly(NIPAM)s. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) The increase of polydispersity (M_w/M_n) with an increase in conversion observed at the early stage of the polymerization is inconsistent with the ideal RAFT kinetics. We also observed the increase of polydispersity with an increase in conversion in the polymerization of NIPAM in the absence of Lewis acid even up to 93% conversion using the same chain transfer agent (PEPD) under the same reaction conditions. The reason for these findings is presently not clear to us.

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(16) Experimental conditions: poly(NIPAM) = 0.12 g, AIBN = 0.12 mg, NIPAM = 0.28 g, methanol = 1 mL, toluene = 1 mL, temperature = 60 °C, time = 24 h, conversion = 90%.

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MA0257595