SHORT COMMUNICATIONS

Synthesis of Highly Isotactic Poly(*N*-isopropylacrylamide) by Anionic Polymerization of a Protected Monomer

Tatsuki KITAYAMA, Wataru SHIBUYA, and Ken-ichi KATSUKAWA

*Department of Chemistry, Graduate School of Engineering Science, Osaka University,
1-3 Machikaneyama, Toyonaka, Osaka 560-8531, Japan*

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Stereoregularity of vinyl polymers often affects significantly their properties and functions, and thus stereospecific polymerization has been important from the view points of both polymer chemistry and industry. In vinyl polymerization ionic and coordination processes have been considered favorable for the stereocontrol, in which proper selection of initiators, catalysts, additives and solvents may provide us with a handle for controlling stereoregularity in a wide variety. For example, we have shown that highly isotactic, syndiotactic, and heterotactic polymethacrylates could be prepared in toluene by using several anionic initiators; *tert*-butylmagnesium bromide (*t*-BuMgBr) for isotactic polymerization^{1,2} *tert*-butyllithium (*t*-BuLi) / trialkylaluminum (R_3Al) for syndiotactic one^{3,4} and *t*-BuLi / bis(2,6-di-*tert*-butylphenoxy)methylaluminum [MeAl(ODBP)₂] for heterotactic one.^{5–13}

Polymers of acrylamide and its derivatives including *N*-isopropylacrylamide (NIPAm) are widely used in industry, agriculture and medicine due to their remarkable properties including good biocompatibility and low toxicity.^{14,15} Electron-withdrawing nature of amide groups might provide the monomers with potential reactivity favorable for anionic polymerization. However, the presence of acidic hydrogen in acrylamide itself and monosubstituted acrylamide inhibits the anionic vinyl polymerization. Thus radical polymerization has been so far the only means to obtain the corresponding polymers with few exceptions such as hydrogen-transfer polymerization of α -(aminomethyl)acrylates¹⁶ and *N*-acryloylurea derivatives with potassium *tert*-butoxide or 1,8-diazabicyclo[5.4.0]undec-7-ene.^{17–21} As a consequence, stereospecific anionic polymerization of acrylamide derivatives have only been known for *N,N*-disubstituted ones.^{22–28} Nakahama

and his coworkers have reported successful stereospecific anionic polymerization of *N,N*-diethylacrylamide (DEA) in tetrahydrofuran (THF) by careful selection of Lewis-acid additives and counter cations. A syndiotactic poly(DEA) was prepared with alkyl-lithium initiator [1,1-bis(4'-trimethylsilylphenyl)-3-methylpentyllithium]/diethylzinc (Et_2Zn), an isotactic one with *t*-BuMgBr/ Et_2Zn , and a heterotactic one with diphenylmethylpotassium (Ph_2CHK)/ Et_2Zn .^{29–34} In 1996, Okamoto and his coworkers³⁵ reported the anionic polymerization of *N,N*-diphenylacrylamide with *t*-BuMgBr in toluene at $-78^\circ C$, which gave an isotactic polymer with *m* diad of 80%. More recently, they also found that, in radical polymerizations of acrylamide and its derivatives, rare-earth metal trifluoromethanesulfonates (triflates) as Lewis-acid additives promoted stereospecific polymerization and, in particular, isotactic poly(NIPAm)s with *m* diad content of 92% were obtained with lutetium and yttrium triflates in methanol at $-20^\circ C$.³⁶ Here, we report synthesis of highly isotactic poly(NIPAm) *via* an anionic polymerization of a trimethylsilyl-protected NIPAm derivative (TMS-NIPAm). Particularly interesting is that the isotactic poly(NIPAm) derived from the poly(TMS-NIPAm) has much lower solubility in water, methanol, and even in dimethyl sulfoxide (DMSO) as compared with that obtained radically.

EXPERIMENTAL

According to the procedure reported for the trimethylsilylation of amides,³⁷ NIPAm and chlorotrimethylsilane (Me_3SiCl) were reacted in the presence of triethylamine (Et_3N). Me_3SiCl (2 equiv.) was added dropwise to a mixture of NIPAm (1 equiv., 1 mmol / mL) and Et_3N (2 equiv.) in diethyl ether under dried

Figure 1. 500 MHz ^1H NMR spectra of TMS-NIPAm measured in CDCl_3 (a) and in toluene- d_8 (b) at 30°C .

nitrogen at 0°C with stirring for 1 h, and the mixture was kept at 20°C for further 5 h with stirring. Then the ammonium salt precipitated was removed by filtration under nitrogen. The filtrate was concentrated under reduced pressure, followed by twice distillation; bp $39.4^\circ\text{C} / 6\text{ mmHg}$, yield 41%. TMS-NIPAm thus obtained was identified by GC, MS, IR, ^1H NMR, and ^{13}C NMR. ^1H , ^{13}C , and ^{29}Si NMR spectra of the monomer consisted of two isomers (major / minor) as described later; ^1H NMR (CDCl_3 , 30°C): δ 5.49 / 5.44 (dd, 1H, $\text{CH}_2=\text{CH}$), 5.96 / 5.73 (dd, 1H, $\text{CH}_2=\text{CH}$), 6.37/6.21 (m, 1H, $\text{CH}_2=\text{CH}$), 1.04/1.08 (d, 6H, $(\text{CH}_3)_2\text{CH}-\text{N}$), 3.68/3.83 (m, 1H, $(\text{CH}_3)_2\text{CH}-\text{N}$), 0.22/0.24 (s, 9H, $(\text{CH}_3)_3\text{Si}$); ^{13}C NMR (CDCl_3 , 30°C): δ 154.37/152.00 (C=N), 123.26/134.94 (CH=), 123.68/121.84 ($\text{CH}_2=$), 24.54/23.54 ($(\text{CH}_3)_2\text{CH}-\text{N}$), 47.76/46.89 ($(\text{CH}_3)_2\text{CH}-\text{N}$), 0.46/0.62 ($(\text{CH}_3)_3\text{Si}$); ^{29}Si $\{^1\text{H}\}$ NMR (CDCl_3 , 30°C): 18.5 / 18.0 ppm (from $(\text{CH}_3)_4\text{Si}$). IR (liquid): 2966 (C-H), 1656 (C=N), 1600 (C=C), 1403 (C-O), 1282 (C-Si), 1051 cm^{-1} (O-Si). MS (EI): m/z 185 (M^+), 184 (M^+-H), 170 (M^+-CH_3), 142 ($\text{M}^+-\text{CH}_2\text{CH}$), 73, 55. HRMS (EI): calcd for $\text{C}_9\text{H}_{19}\text{ONSi}$ (M^+), 185.1236; found, 185.1265.

All the anionic polymerizations were carried out in glass ampoules filled with dried nitrogen passed through Molecular Sieves (MS) 4A cooled at -78°C . Polymerization reactions were initiated by adding the monomer slowly to initiator solutions at the polymerization temperatures. After the prescribed period of time, the reaction was terminated with methanol at the polymerization temperatures. The reaction mixtures were poured into a large amount of Et_2O , and the precipitated polymers were collected by filtration, washed with Et_2O and subsequently with water as far as the polymer was insoluble in water, and dried under high vacuum at 40°C . In the case of radical polymerization, the reaction was initiated by raising

the temperature of the mixture of the monomer and 2,2'-azobisisobutyronitrile (AIBN) to 60°C . Number-average molecular weights, $\overline{M}_n$'s, of the polymers except for those obtained with AIBN were estimated by ^1H NMR spectroscopic end-group analysis from *t*-butyl proton signals and the main-chain methylene proton signals based on the assumption that the polymerization is initiated from *t*-BuLi or *t*-BuMgBr and proceeds without chain-transfer reaction.

RESULTS AND DISCUSSION

Figure 1a shows ^1H NMR spectrum of TMS-NIPAm in CDCl_3 at 30°C , which consists of two sets of signals due to two isomers in the ratio of 1:0.79. ^{13}C NMR spectrum also exhibits a similar characteristics. The ^1H NMR spectrum measured in toluene- d_8 at 30°C also showed two sets of peaks due to the isomers but in a different ratio, that is, 1:0.14 (Figure 1b). The ratio was almost constant in the temperature range from -78 to 80°C (1:0.11 to 1:0.20). Thus in the polymerization medium (toluene), one of the isomers exists predominantly over the other. The ^{13}C NMR resonances at 154.4 ppm (major) and 152.0 ppm (minor) are likely due to imino carbon instead of carbonyl one. ^1H -decoupled ^{29}Si NMR spectrum measured in CDCl_3 at 30°C showed two peaks at 18.5 and 18.0 ppm, which are due to $(\text{CH}_3)_3\text{Si}-\text{O}$ group similar to that observed for *N,O*-bis(trimethylsilyl)acetamide (16.8 ppm). NOESY spectrum of the monomer in toluene- d_8 at 30°C showed a correlation between H(c) (vinyl methine proton) and H(d) (isopropyl methine proton) only for the major isomer, suggesting that the major isomer is depicted by the structure A with the *E* configuration at C=N bond.

TMS-NIPAm was polymerized by radical and anionic initiators in toluene and the results are summa-

Table I. Polymerization of TMS-NIPAm in toluene^a

Run	Initiator system	Temp.	Time	Yield	$\overline{M}_n^b$	Tacticity ^b /%	
		°C	h	%	(NMR)	<i>m</i>	<i>r</i>
1	AIBN ^c	60	2	100	—	42.4	57.6
2	AIBN	60	6	87	—	44.8	55.2
3	<i>t</i> -BuMgBr	−40	24	33	10700	80.4	19.6
4	<i>t</i> -BuLi	−40	24	52	14100	31.8	68.2
5	<i>t</i> -BuLi/Et ₃ Al	−20	24	53	18300	93.3	6.7
6	<i>t</i> -BuLi/ <i>n</i> -Pr ₃ Al	−20	24	65	24800	96.0	4.0
7	<i>t</i> -BuLi/ <i>n</i> -Bu ₃ Al	−78	24	0	—	—	—
8	<i>t</i> -BuLi/ <i>n</i> -Bu ₃ Al	−60	80	16	34900	47.0	53.0
9	<i>t</i> -BuLi/ <i>n</i> -Bu ₃ Al	−40	24	39	13000	97.3	2.7
10	<i>t</i> -BuLi/ <i>n</i> -Bu ₃ Al	−20	24	91	22600	95.9	4.1
11	<i>t</i> -BuLi/ <i>n</i> -Bu ₃ Al	0	24	100	9000	95.1	4.9
12	<i>t</i> -BuLi/ <i>n</i> -O _c ₃ Al	−20	24	51	12500	91.1	8.9
13	<i>t</i> -BuLi/EtAl(ODBP) ₂ ^d	−40	24	0	—	—	—
14	<i>t</i> -BuLi/EtAl(ODBP) ₂	0	24	28	15100	93.1	6.9
15	<i>t</i> -BuLi/EtAl(ODBP) ₂	20	24	48	12400	85.3	14.7

^aMonomer 5 mmol, initiator 0.1 mmol, toluene 5 mL, Li/Al = 1/5. ^bDetermined by ¹H NMR spectroscopic end-group analysis (DMF-*d*₇, 110°C), with the assumption that no chain-transfer reaction takes place. ^cMonomer; NIPAm. ^dEtAl(ODBP)₂; bis(2,6-di-*tert*-butylphenoxy)ethylaluminum.

rized in Table I. The radical polymerization with AIBN at 60°C gave a polymer in a good yield as the polymerization of NIPAm itself. When the reaction mixture was treated with methanol, the trimethylsilyl group was readily eliminated and the de-protected polymer was recovered as poly(NIPAm) though 0.3% of silyl groups was detected in its ¹H NMR spectrum. ¹H NMR spectroscopic determination of tacticity of the polymer (*cf.* Figure 2c) revealed that the poly(TMS-NIPAm) has almost the same tacticity as poly(NIPAm) directly obtained from NIPAm and is almost atactic. The polymerization with *t*-BuMgBr at −40°C for 24 h gave a polymer rich in isotacticity (*m* diad content, 80%). In contrast, the polymerization with *t*-BuLi gave a syndiotactic-rich polymer. Several aluminum compounds, which have been known effective for stereocontrol in anionic polymerizations of methacrylates^{3–13} and acrylates,^{38, 39} have been examined in combination with *t*-BuLi. *t*-BuLi/R₃Al (R = ethyl, *n*-propyl, *n*-butyl, and *n*-octyl) is known to promote syndiotactic-specific

living polymerization of methacrylates.^{3, 4} The polymerization of TMS-NIPAm with *t*-BuLi/R₃Al (1/5) at −20°C (runs 5, 6, 10, and 12 in Table I) gave polymers with high isotacticity. As an example, ¹H NMR spectrum of poly(NIPAm) derived from poly(TMS-NIPAm) obtained with *t*-BuLi/*n*-Pr₃Al (run 6) is shown in Figures 2a and 2b together with that obtained with AIBN (Figure 2c). The methylene proton signals are observed clearly as split peaks typical of non-equivalent *meso* methylene groups as the major component with a minor signal observed between them, revealing high isotacticity of the polymer. Diad tacticity determined from these signals is shown in Table I. Among R₃Al's examined at −20°C, *n*-Pr₃Al and *n*-Bu₃Al gave the highest isotacticity of *m* = 96%.

Temperature dependence of the polymerization was examined by using *t*-BuLi/*n*-Bu₃Al (1/5) as an initiator in the range from −78 to 0°C. The polymerization at −78°C gave no polymer for 24 h. At −60°C, a polymer obtained in a low yield was found to be almost atactic instead of isotactic. For the temperature range from −40 to 0°C, highly isotactic polymers were formed with the highest *m* diad content of 97.3% at −40°C. As described previously, TMS-NIPAm consists of two isomers. C=N carbon resonance of TMS-NIPAm measured in toluene-*d*₈ at −40°C showed two peaks at 154.5 and 150.7 ppm due to the major and minor isomers, respectively. The ¹³C NMR spec-

Figure 2. 500 MHz ^1H NMR spectra of poly(NIPAm)s derived from poly(TMS-NIPAm)s prepared with $t\text{-BuLi}/n\text{-Pr}_3\text{Al}$ (1/5) in toluene at -20°C (a), (b) and with AIBN at 60°C (c). The spectra were measured in $\text{DMF}-d_7$ at 110°C . The signal marked with $\times$ is due to water, and that $*$ due to the remaining $(\text{CH}_3)_3\text{Si}$ group (0.3%).

trum of a mixture of TMS-NIPAm and $n\text{-Bu}_3\text{Al}$ (2:1) showed additional signals at 174.6 and 177.0 ppm; the chemical shift values are even larger than that of dialkylacrylamide (e.g., 165.1 ppm for diisopropylacrylamide) and likely due to carbonyl carbon coordinated with $n\text{-Bu}_3\text{Al}$. The results suggest that TMS-NIPAm isomerizes by the action of the Lewis acid to an N,N -disubstituted acrylamide, the carbonyl group of which is coordinated by $n\text{-Bu}_3\text{Al}$. The peak intensity decreased at -60 and -78°C , at which temperatures the isotactic polymer was not formed. The results imply a possibility that the highly isotactic polymer is formed *via* the isomerization of the monomer by the aluminum compound as an important step toward the high stereospecificity of this polymerization.

A bulky aluminum Lewis acid, $\text{EtAl}(\text{ODBP})_2$, which is also known effective for living and stereospecific polymerizations of methacrylates⁹ and acrylates,^{38,39} was examined as an additive for the polymerization of TMS-NIPAm. Though it was not effective at -40°C , the polymerizations at 0 and 20°C gave isotactic polymers with a little lower m diad contents than those obtained with $t\text{-BuLi}/n\text{-Bu}_3\text{Al}$. The polymer yields were lower than those for the polymerization with $t\text{-BuLi}/\text{R}_3\text{Al}$ under the same conditions, probably due to the exceeding bulkiness of $\text{EtAl}(\text{ODBP})_2$ which might hinder the propagation reaction.

The highly isotactic poly(NIPAm)s exhibited quite different solubility from that obtained by radical polymerization. The solubility of the poly(NIPAm) with m content of 95.9% (run 10 in Table I) was

examined by placing 10 mg of the polymer sample in 1 mL of solvents such as toluene, acetone, chloroform, dichloromethane, methanol, water, DMSO, N,N -dimethylformamide (DMF), N -methyl-2-pyrrolidone (NMP), tetrahydrofuran (THF), 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP), ethyl acetate, Et_3N , and acetonitrile. As reported previously,³⁶ the isotactic polymer is insoluble in water in contrast to atactic poly(NIPAm) prepared radically. Among the solvents examined, the polymer was dissolved in DMF and in NMP at least at 80°C . Due to the limited solubility of highly isotactic poly(NIPAm), information on the molecular weight distribution is not yet available, which is needed to clarify whether this polymerization system is living or not. Nevertheless, the present study demonstrates that high-level control of stereoregularity of poly(NIPAm) brings about unique properties.

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