

Synthesis of Heterotactic and Syndiotactic Polyacrylamides via Stereospecific Radical Polymerization of *N*-tert-Butoxycarbonylacrylamide in the Presence of Fluorinated Alcohols

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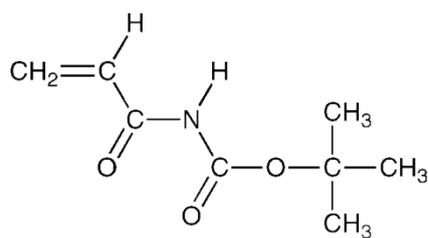
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INTRODUCTION

Polyacrylamide [poly(AAm)] has been widely used as a matrix for gel electrophoresis. The improvements in both resolution and reproducibility have contributed to the development of proteome analysis.¹⁻³ There are, however, limited number of reports on the syntheses of stereoregular poly(AAm)s, although the tacticity affects the properties of the polymer materials.

Recently, it has been reported that the syntheses of stereocontrolled poly(*N*-isopropylacrylamide)s [poly(NIPAAm)s] were achieved via anionic polymerization of protected NIPAAm monomers followed by deprotection.^{4,5} This strategy, however, is unsuitable for the syntheses of stereoregular poly(AAm)s, because double protections of the two N-H groups of AAm monomer are required before the anionic polymerization. To the best of our knowledge, the synthesis of isotactic poly(AAm) (*mm* = 65 %) by the radical polymerization in the presence of Lewis acids is the sole method for the preparation of stereoregular poly(AAm),⁶ except for the amidation of isotactic poly(phenyl acrylate).⁷

We have reported the stereocontrol in the radical polymerization of NIPAAm, which is one of *N*-monosubstituted acrylamides, utilizing the hydrogen-bond-assisted complex formation at low temperatures.⁸⁻¹¹ In the present work, we designed a new monomer, *N*-butoxycarbonylacrylamide (NBocAAm), as a protected AAm,¹² because the Boc groups of poly(NBocAAm)s are expected to be deprotected easily to afford poly(AAm)s. We conducted the radical polymerization of NBocAAm in the presence of fluorinated alcohols which induced heterotactic-specificity in the NIPAAm polymerization.^{11(b)} It was found that not only the resultant poly(NBocAAm)s were successfully converted into poly(AAm)s, but also the stereospecificity of the NBocAAm polymerization depended on the kinds of the added fluorinated alcohols. Here, we report the preliminary results of the syntheses of stereoregular poly(AAm)s via the radical polymerization of NBocAAm followed by deprotection.

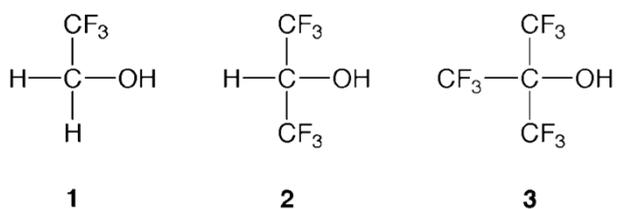


NBocAAM

EXPERIMENTAL

Materials

Toluene was purified through washing with sulfuric acid, water, and 5% aqueous NaOH; this was followed by fractional distillation. Dimethyl 2,2'-azobisisobutyrate (MAIB) (supplied by Otsuka Chemical Co., Ltd) was recrystallized from methanol. Acrylamide (Kanto Chemical Co., Inc.), sodium hydride (60% dispersion in paraffin liquid), and di-*tert*-butyl dicarbonate (Tokyo Kasei Kogyo Co.) were used without purification for monomer synthesis. 2,2,2-Trifluoroethanol (**1**) (Aldrich Chemical Co.), 1,1,1,3,3,3-hexafluoro-2-propanol (**2**) (supplied by Daikin Industries, Ltd.), and nonafluoro-*tert*-butanol (**3**) (Tokyo Kasei Kogyo Co.) were used without further purification for polymerization reactions.



Synthesis of NBocAAM¹³

The THF (500 mL) solution of acrylamide (14.2 g, 200 mmol) was placed in a 500 mL round-bottom flask equipped with a condenser and was magnetically stirred at 0 °C for 30 min. The solution was stirred for further 10 min under N₂ after the addition of NaH dispersed in paraffin liquid (60 %, 8.0 g, 200 mmol). To the stirred solution was added di-*tert*-butyl dicarbonate (25.0 g, 115 mmol) and the mixture was stirred at 0 °C for 3 h and at room temperature overnight. After the solvent was evaporated, the mixture was dissolved in ethyl acetate, washed with HCl and water, and dried over MgSO₄. After filtration, the solvent was evaporated again to yield crude NBocAAM. Recrystallization from ethyl acetate afforded pure NBocAAM (7.35 g, 37 %): m. p. 119-120 °C (decomp.), ¹H NMR (400 MHz, CDCl₃ at 35 °C), δ 1.51 (s, 9H), 5.84 (ddd, 1H, ²J = 1.7 Hz, ³J = 10.4 Hz, ⁵J = 0.6 Hz), 6.49 (dd, 1H, ²J = 1.7 Hz, ³J = 17.1 Hz), 7.05 (dd, 1H, ³J = 10.4 Hz, ³J = 17.1 Hz), 7.42 (bs, 1H), ¹³C NMR (100 MHz, CDCl₃ at 35 °C), δ 27.99, 82.77, 128.88, 130.76, 150.38, 165.88.

Polymerization

Typical polymerization procedure is as follows; NBocAAM (0.481 g, 2.8 mmol) and **1** (1.694 g, 16.9 mmol) were dissolved in toluene to prepare a 5 mL solution. MAIB (0.103 g, 0.40 mmol) was dissolved in toluene to prepare a 1 mL solution. Four milliliters of the former solution and one-half milliliter of the latter solution were transferred to the glass ampoule and cooled at -50 °C. The glass ampoule was degassed and filled with nitrogen three times, and sealed under vacuum. The polymerization was initiated by UV irradiation at the polymerization temperature. After 12 h, the polymerization mixture was

poured into a large amount of hexane/diethyl ether mixtures (1:1 vol:vol)¹⁴, and the precipitated polymer was collected by centrifugation, and dried *in vacuo*. The polymer yield was determined gravimetrically.

The NBocAAM monomer alone was insoluble in toluene at the polymerization temperatures and the addition of alkyl alcohols such as 3-methyl-3-pentanol, which significantly induced syndiotactic-specificity in NIPAAm polymerizations,^{11(a)} hardly improved the solubility of the monomer. The NBocAAM monomer, however, was soluble in toluene in the presence of fluorinated alcohols examined in this study. Monomer, polymer or both were precipitated during the polymerization reactions in the presence of **1** and **2** at $-40\text{ }^{\circ}\text{C}$.

Measurements

¹H and ¹³C NMR spectra were measured on an EX-400 spectrometer or an ECX-400 spectrometer (JEOL, Ltd.). Triad tacticities were determined from ¹³C NMR signals due to the methine groups in chain of the poly(AAM)s derived from poly(NBocAAM)s. Molecular weights and molecular weight distributions of the poly(NBocAAM)s were determined by size exclusion chromatography (SEC) (HLC 8220 instrument (Tosoh Co.)) equipped with TSK gels (SuperHM-M and SuperHM-H (Tosoh Co.)) using dimethylformamide (LiBr 10 mmol/L) as an eluent at $40\text{ }^{\circ}\text{C}$ ([polymer] = 1.0 mg/mL, flow rate = 0.35 mL/min). The SEC chromatogram was calibrated with standard polystyrene samples. IR spectra were recorded with FT/IR-460 plus (Jasco Co.).

RESULTS AND DISCUSSION

Radical Polymerization of NBocAAM in the Presence of Fluorinated Alcohols

The radical polymerization of NBocAAM in toluene at -40 or 0 °C for 12 h was carried out in the presence of sixfold amounts of fluorinated alcohols (**1-3**) to NBocAAM (Table 1). The polymers were obtained at relatively high yields. The molecular weights of the obtained polymers decreased as the number of fluorine atom and/or bulkiness of the fluorinated alcohols increased. This result suggests that the added fluorinated alcohols affected the stereospecificity of the NBocAAM polymerization through the hydrogen-bonding interaction.

<Table 1>

The obtained polymers were converted into poly(AAM)s by the deprotection to determine the tacticities.¹⁵ The details of the deprotection procedure is described later. Figure 1 displays the ^{13}C NMR spectra of the main-chain methine carbons of poly(AAM)s derived from poly(NBocAAM)s prepared at -40 °C. The signals were assigned at triad levels as in Figure 1, according to the literature.¹⁶ In the presence of **1**, almost atactic polymers were obtained, in particular by lowering the temperature to -40 °C. Interestingly, heterotactic and syndiotactic polymers were obtained with the addition of **2** and **3**, and such tendencies were enhanced at lower temperatures. These results contrast with the fact that heterotactic polymers were obtained by the NIPAAm polymerizations in the presence of **1-3**. Thus, it is assumed that such difference in the stereospecificities

between the NBocAm polymerizations and the NIPAAm polymerizations is attributed to the difference in the structures of the hydrogen-bond-assisted complexes between the monomers and the added fluorinated alcohols.

<Figure 1>

Deprotection of the *tert*-Butoxycarbonyl Group

The 0.1 g of poly(NBocAAm) prepared in toluene at 0 °C in the presence of **1** was dissolved in CF₃COOH (1 mL) at room temperature with stirring. After 1 h, the solution was poured into methanol (40 mL). The precipitate was collected by centrifugation. Figure 2 shows the IR spectrum of the precipitate together with those of the original poly(NBocAAm) and authentic poly(AAm). The absorbances at 1706 and 1778 cm⁻¹ (Figure 2c) disappeared after the deprotection (Figure 2b) and the spectrum of the deprotected polymer was consistent with that of poly(AAm) (Figure 2a). Further, the ¹³C NMR signal due to C=O of the deprotected polymer was observed as a single peak and agreed with that of poly(AAm). These results indicate that poly(NBocAAm) can be converted quantitatively into poly(AAm) under the acidic conditions, as expected.

<Figure 2>

CONCLUSION

We designed NBocAAm as a protected monomer and succeeded in indirect synthesis of

poly(AAm) by deprotection of poly(NBocAAm). Furthermore, it was revealed that the addition of fluorinated alcohols such as **2** and **3** significantly induced the heterotactic- and syndiotactic-specificities. To the best of our knowledge, these are the first syntheses of heterotactic and syndiotactic poly(AAm)s. Further works on the effect of the added amount of the fluorinated alcohols in addition to the structures of the hydrogen-bond-assisted complexes are in progress to revealed the mechanism of the stereospecific radical polymerizations of NBocAAm in the presence of the fluorinated alcohols.

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12. There were no concrete descriptions concerning both synthesis and polymerization of NBocAAM, although NBocAAM was included within the claim on the following patent; Urano, S.; Mizuguchi, R.; Tsuboniwa, N.; Aoki, K.; Suzuki, Y.; Itoh, T. (Nippon Paint Co., Ltd.). *Eur Pat Appl*, 177122, 1986.

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14. To determine the precipitant for poly(NBocAAM), we conducted SEC analysis of poly(NBocAAM) prepared in acetone at 0°C. The 0.1g of the polymerization mixture after the removal of acetone was dissolved into 1mL of THF, poured into diethyl ether containing 0, 25, and 50 vol% of hexane (40mL). The fractions of smaller molecular weights were not collected, when the polymerization mixture was poured into diethyl ether containing hexane less than 50 vol%. Thus, we determined hexane : diethyl ether (50 : 50 vol:vol) as the precipitant for poly(NBocAAM)s.
15. The dyad and/or triad tacticities were unable to be determined by ¹H NMR spectra of poly(NBocAAM)s measured in deuterated dimethyl sulfoxide at 90°C, because the signals due to the methine and methylene groups in chain overlapped with those of the solvent and the butoxy group, respectively.
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Table 1. Radical polymerization of NBocAAM in toluene at –40 or 0 °C for 12 h in the presence of fluorinated alcohols^a

Added alcohol	Temp.	Yield %	Triad tacticity / % ^b			M _n ^c	M _w ^c
	°C		<i>mm</i>	<i>mr</i>	<i>rr</i>	x 10 ⁻⁴	M _n
1	0	91	20	46	34	5.68	3.4
1	–40	95	23	52	25	10.8	4.0
2	0	79	15	54	31	2.52	1.6
2	–40	61	16	63	21	3.24	2.0
3	0	81	18	37	45	1.11	2.1
3	–40	65	11	44	45	1.00	1.6

a. [NBocAAM]₀ = 0.5 mol/L, [fluorinated alcohol]₀ = 3.0 mol/L, [MAIB]₀ = 0.05 mol/L.

b. Determined by ¹³C NMR signals due to methine groups of poly(AAm)s derived from poly(NBocAAM).

c. Determined by SEC (polystyrene standards).

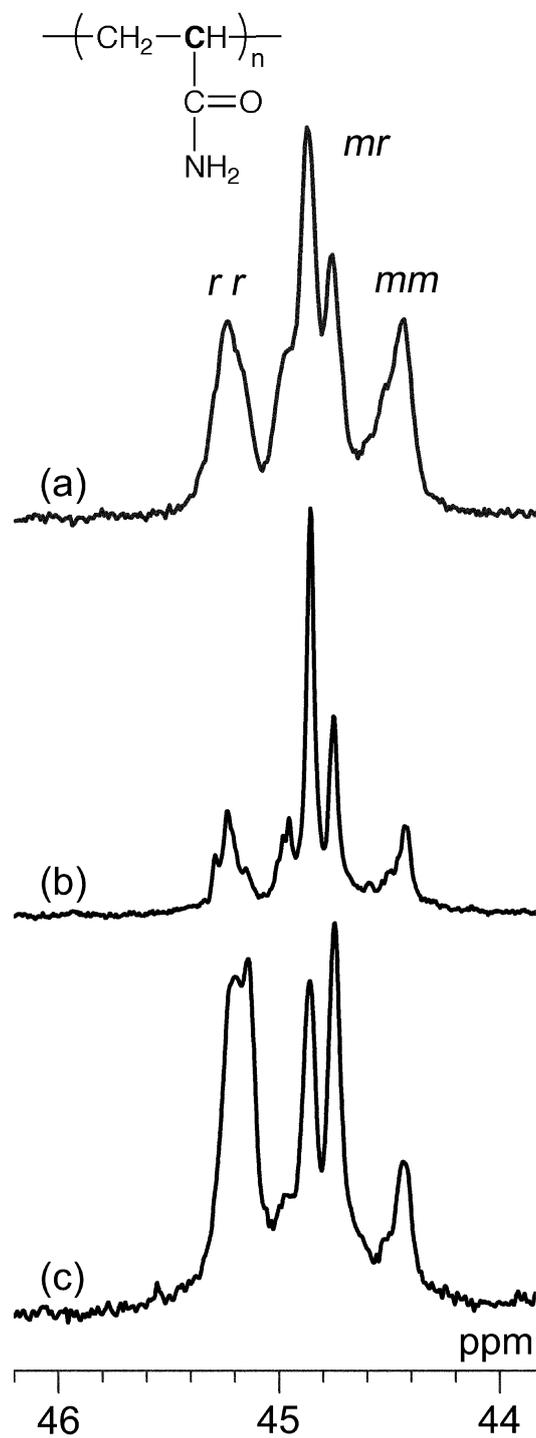


Figure 1. 100 MHz ^{13}C NMR spectra of the main-chain methine carbons of poly(AAm)s derived from poly(NBocAAm)s prepared at $-40\text{ }^\circ\text{C}$ in the presence of (a) **1**, (b) **2**, and (c) **3**, as measured in D_2O at $80\text{ }^\circ\text{C}$.

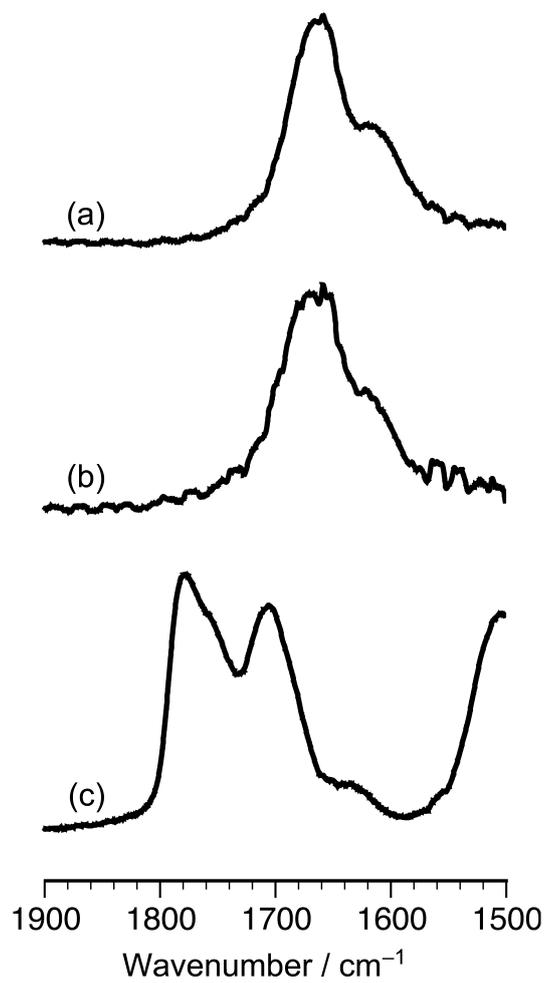


Figure 2. Expanded IR spectra of (a) poly(AAm), (b) the polymer derived from poly(NBocAAm), and (c) poly(NBocAAm).