# Radical Polymerization of Styrene Derivatives Bearing *N*-Free Amino Acid Side Chains, Synergic Effect of Chirality, and Hydrogen Bonding for Stereoselective Polymerization

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**ABSTRACT**: Radical polymerization of styrene derivatives having a series of amino acid, alanine, glycine, leucine, valine, Boc-leucine, and Boc-valine, in the side chain bound at the C-terminal was conducted to regulate the stereoinduction system in the propagation step. Isotacticity increased in the polymer main chain, especially in the polymerization of monomers bearing *N*-free L-leucyl and L-valyl esters in THF or DMF at 50 °C, by the synergic stereoregulation with chirality control and hydrogen bonding between the radical polymer terminal and the monomer. © 2010 Wiley Periodicals, Inc. J Polym Sci Part A: Polym Chem 48: 5593–5602, 2010

**KEYWORDS**: amino acid-bound polyolefine; isotactic; NMR; polystyrene; radical polymerization; stereoinduced polymers

**INTRODUCTION** Induction of chirality into the backbone of polyolefins synthesized by free radical polymerization has been a challenging target for a long time and many chemists have tried to solve it.[1,2] Until now, using monomers having chiral auxiliaries[3–6] is one of the efficient methods for stereospecific or stereoregulated radical polymerization. Moreover, chiral bioactive substituents in polymer side chains, such as amino acids, peptides, and sugars, can also play important roles as functional bioactive groups in part.[7–14] However, it is still unclear how stereoselection is regulated by such chiral auxiliaries. Porter et al. reported that a penultimate group of the growing radical terminal effects on stereocontrol of chiral-monomer addition,[15] whereas a recent study discussed that radical chain end can control the stereochemistry.[16] Using monomers bearing chiral amino acid, North and coworkers reported that the specific rotation of copolymers varied in a nonlinear manner with the proportion of chiral amino acid, indicating the capability of chiral induction.[17] Although steric hindrance between the hindered group in acrylates and the growing radical terminal was regarded as the important regulating factor in the chirality induction system, hydrogen bonding, which is a characteristic interaction with amino acid derivatives, has rarely been focused as an important factor. Quite recently, Bag et al. reported importance of hydrogen-bonding interaction between monomer and growing polymer terminal in the radical polymerization of L-leucine-substituted acrylamide, though chirality induction mechanism was not clear.[18]

We noticed that the synergic effect of chirality and intermolecular hydrogen bonding between amino acid in the monomer side chain and the growing polymer terminal is expected to induce stereocontrol in the polymer main chain to some extent, because stereoregulation might be conducted if the chiral monomer accesses to the prochiral radical terminal with selecting a suitable route (path A in Fig. 1) via formation of intermolecular hydrogen-bonding interaction, other than paths B–D, in which the synergic stereocontrol system does not work appropriately. Analogous chiral induction system was performed for polymerization of amino-acid substituted isocyanides.[19]

In our preliminary study exploring synthetic polymers with the ammonium residues exhibiting antibiotic activity adsorbing on the bacterial cell walls, we reported an efficient preparative method for a styrene derivative bearing *N*-free alanyl ester.[20] The designed structure of the polymers is different from the amino-acid bound *N*-acrylamides or *N*-methacrylamides reported previously[7–14] in the following two points: (1) the amino group in amino acid is free, and (2) not acrylate but styrene derivatives were used as monomers. Stereoselective radical polymerization of styrene and its derivatives has rarely been reported until now. Here, we report AIBN-initiated radical polymerization of the styrene derivatives bearing (L)-alanine, glycine, (L)-leucine, (*rac*)-leucine, (L)-valine, Boc-(L)-leucine, and Boc-(L)-valine at 50 °C to form new polystyrene derivatives bearing amino acid in the side chain. As a result, we can observe significant increase of $^{13}C$ signals due to the *m* diads or the *mm* triads showing isotacticity in the polystyrenes, which were made from the polymers bearing (L)-leucine and (L)-valine, whereas, interestingly,

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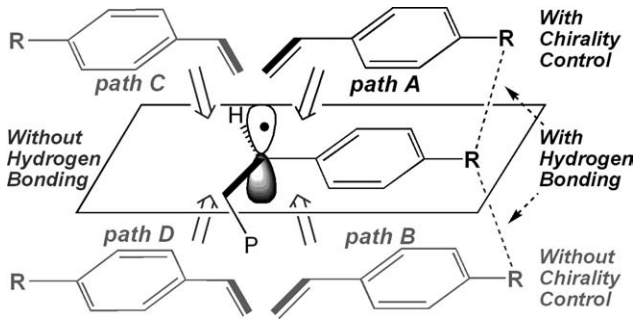



**FIGURE 1** Supposed routes of the styrene derivatives for the polymer terminal.

monomers with glycine, (*rac*)-leucine, Boc-leucine, and Boc-valine or those which were polymerized at 80 °C were not much suitable for stereoselective polymerization. This shows that the synergic interaction of chirality and hydrogen bonding is one of the appropriate ways to achieve the stereoselective radical polymerization.

## EXPERIMENTAL

### Materials

AIBN and 4-(chloromethyl)styrene were used as purchased from Aldrich. Boc-(L)-alanine and the other Boc-protected amino acids were used as purchased from Watanabe Chemical. THF or DMF for radical polymerization was dried over sodium benzophenone ketyl or calcium hydride and distilled just before use. Other solvents were used as purchased.

### Techniques

$^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on a VARIAN Mercury Y plus 400 MHz spectrometer at room temperature in $CDCl_3$, $D_2O$, or $CD_3OD$. IR spectra were recorded in $cm^{-1}$ on a PERKIN ELMER Spectrum One spectrometer equipped with a universal diamond ATR. Size exclusion chromatography analysis of the polymers was carried out using a JASCO HPLC system equipped with a RI-2031Plus differential refractometer and an UV-2075Plus UV-VIS detector (254 nm) using two Shodex KF-804L+KF-804L columns at 40 °C. THF was used as an eluent (1.0 mL $min^{-1}$). Calibration was carried out using standard samples of polystyrene. The optical rotations were measured with a JASCO DIP-140 digital polarimeter in methanol at 25 °C. The concentration was at 1 g $dL^{-1}$. The path length was 0.1 cm, and the light source was sodium D line. The circular dichroism (CD) spectra were recorded on a JASCO J-600 spectropolarimeter at 25 °C over the range of 195–260 nm using a quartz cell of 0.1 cm path length at a sample concentration of $1 \times 10^{-3}$ M. Electrospray ionization time-of-flight mass spectrometry (ESI-TOF MS) was carried out on a JEOL JMS-T100 mass spectrometer. The sample solutions in methanol were directly infused using methanol as solvent stream.

### Preparation of Boc-Amino Acid Styrenes, 1a–1d

In a typical example, to a 50-mL round-bottom flask, Boc-(L)-alanine (3.78 g, 20.0 mmol), 4-(chloromethyl)styrene (3.05 mL, 20.0 mmol), sodium carbonate (1.05 g, 10.0 mmol), and DMF (150 mL) containing 1% water (1.5 mL) were added and stirred at 60 °C for 6 h. Complete consumption of the starting materials was confirmed by means of $^1$H NMR measurement of the crude mixture in $CDCl_3$. After removal of the solvent under reduced pressure, water (80 mL) was added and extracted with ethyl acetate (50 mL × 3). Most of the cases, additional purification was not necessary. If further purification of the resulting mixture is required (containing a small amount of 4-(chloromethyl)styrene and DMF), washing with petroleum ether gave a white solid, **1a** (4.29 g, 3.28 mmol, 78% yield).

**1a**: Anal. $C_{17}H_{23}NO_4$: Calcd. C 66.86, H 7.59, N 4.59; Found C, 66.91; H, 7.47; N, 4.69. $^1$H NMR ($CDCl_3$): $\delta$ = 7.41 (d, $J$ = 8.0 Hz, 2H, Ph), 7.31 (d, $J$ = 8.0 Hz, 2H, Ph), 6.71 (dd, $J$ = 10.8 Hz, 1H, —CH=), 5.78 (t, $J$ = 17.6 Hz, 1H, =$CH_2$), 5.28 (d, $J$ = 6.40 Hz, 1H, =$CH_2$), 5.17 (AB pattern, 2H, $CH_2$), 5.10 (t, $J$ = 21.6 Hz, 1H, NH), 4.35 (quint, $J$ = 6.80 Hz, 1H, CH), 1.40 (d, $J$ = 16.4 Hz, 3H, $CH_3$), 1.44 (s, 9H, $^t$Bu). $^{13}$C NMR ($CDCl_3$): $\delta$ = 172.9, 154.9, 137.5, 136.1, 134.7, 128.3, 126.2, 114.3, 79.8, 66.7, 49.3, 28.4, 18.7. IR: 3384 (s, NH), 1719 $cm^{-1}$ (vs, C=O).

**1b** (coupled with Boc-glycine at 90 °C for 50 min, yield 75%): ESI-MS Calcd. ($C_{16}H_{21}NO_4$) 314.1362 (M + $Na^+$); Found 314.1351. $^1$H NMR ($CDCl_3$): $\delta$ = 7.40 (d, $J$ = 8.0 Hz, 2H, Ph), 7.31 (d, $J$ = 8.0 Hz, 2H, Ph), 6.71 (dd, $J$ = 10.8, 17.6 Hz, 1H, —CH=), 5.76 (t, $J$ = 17.6 Hz, 1H, =$CH_2$), 5.27 (d, $J$ = 10.8 Hz, 1H, =$CH_2$), 5.16 (s, 2H, $CH_2$), 5.01 (br, 1H, NH), 3.95 (d, $J$ = 5.2 Hz, 1H, CH), 1.45 (s, 9H, $^t$Bu). $^{13}$C NMR ($CDCl_3$): $\delta$ = 170.3, 155.7, 137.8, 136.2, 134.6, 128.6, 126.4, 114.5, 80.0, 66.8, 42.5, 28.3. IR: 3375 (s, NH), 1748 $cm^{-1}$ (sh, C=O), 1700 $cm^{-1}$ (vs, C=O).

**1c** [coupled with Boc-leucine at 45 °C for 24 h, yields 89% (for L form) and 90% (for racemate)]: ESI-MS Calcd. ($C_{20}H_{29}NO_4$) 370.1989 (M + $Na^+$); Found 370.1930. $^1$H NMR ($CDCl_3$): $\delta$ = 7.40 (d, $J$ = 8.0 Hz, 2H, Ph), 7.30 (d, $J$ = 8.0 Hz, 2H, Ph), 6.71 (dd, $J$ = 10.8, 17.6 Hz, 1H, —CH=), 5.76 (t, $J$ = 17.6 Hz, 1H, =$CH_2$), 5.27 (d, $J$ = 10.8 Hz, 1H, =$CH_2$), 5.14 (AB pattern, 2H, $CH_2$), 4.88 (d, $J$ = 8.4 Hz, 1H, NH), 4.35 (br, 1H, CH), 1.75–1.55 (m, 3H, $CH_3$), 1.43 (s, 9H, $^t$Bu), 0.92 (d, $J$ = 6.4 Hz, 3H, $CH_3$), 0.92 (d, $J$ = 6.4 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$): $\delta$ = 173.4, 155.4, 137.6, 136.3, 134.9, 128.4, 126.3, 114.4, 79.8, 66.6, 52.2, 41.7, 28.3, 24.7, 22.8, 21.9. IR: 3370 (s, NH), 1710 $cm^{-1}$ (vs, C=O).

**1d** (coupled with Boc-valine at 60 °C for 6 h, yield 90%): ESI-MS Calcd. ($C_{19}H_{27}NO_4$) 356.1832 (M + $Na^+$); Found 356.1648. $^1$H NMR ($CDCl_3$): $\delta$ = 7.40 (d, $J$ = 8.4 Hz, 2H, Ph), 7.31 (d, $J$ = 8.4 Hz, 2H, Ph), 6.71 (dd, $J$ = 10.8, 17.6 Hz, 1H, —CH=), 5.76 (t, $J$ = 17.6 Hz, 1H, =$CH_2$), 5.27 (d, $J$ = 10.8 Hz, 1H, =$CH_2$), 5.15 (AB pattern, 2H, $CH_2$), 5.02 (d, $J$ = 9.2 Hz, 1H, NH), 4.27 (dd, $J$ = 9.2, 4.4 Hz, 1H, CH), 2.14 (sept, $J$ = 5.2 Hz, 1H, CH), 1.44 (s, 9H, $^t$Bu), 0.93 (d, $J$ = 6.8 Hz, 3H, $CH_3$), 0.85 (d, $J$ = 7.2 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$): $\delta$ = 172.0, 155.5, 137.5, 136.1, 134.7, 128.4, 126.1, 114.2, 79.64, 66.3, 58.4, 31.1, 28.1, 18.8, 17.3. IR: 3380 (s, NH), 1710 $cm^{-1}$ (vs, C=O).

### Preparation of 2a–2d

In a typical example, to a 200-mL flask, **1a** (1.97g, 6.45 mmol) and a toluene solution of trifluoroacetic acid (TFA,

25%, 130 mL) were added and stirred at room temperature for 1 h. The solution was concentrated with $N_2$ gas bubbling and then evaporated under reduced pressure. The resulting yellow oil was dissolved in a small amount of water, and aqueous sodium hydrocarbonate (4%) was added to the solution at 0 °C to raise its pH up to 7–8. After extraction with ethyl acetate (50 mL × 3) and salting out from aqueous solution, the ethyl acetate solution was dried over anhydride sodium sulfate and evaporation of the solvent gave a pale yellow solid, **2a** (1.05 g, 5.16 mmol, 80% yield). The product was not able to purified further using column chromatography with neutralized silica, because of hydrolysis of the ester, forming alanine and 4-vinylbenzylalcohol.

**2a**: ESI-MS Calcd. ($C_{12}H_{15}NO_2$) 206.1176 ($M + H^+$); Found 206.1130. $^1$H NMR ($CDCl_3$): $\delta$ = 7.37 (d, $J$ = 8.41 Hz, 2H, Ar), 7.25 (d, $J$ = 8.41 Hz, 2H, Ar), 6.68 (dd, $J$ = 11.2, 17.6 Hz, 1H, —CH=), 5.74 (d, $J$ = 17.6 Hz, 1H, CH=), 5.27 (d, $J$ = 11.2 Hz, 1H, CH=), 5.13 (AB pattern, 2H, $CH_2$), 4.04 (q, $J$ = 21.6 Hz, 1H, CH), 1.56 (d, $J$ = 7.21 Hz, 3H, $CH_3$). $^{13}$C NMR ($CDCl_3$): $\delta$ = 173.3, 140.7, 138.8, 137.0, 131.6, 129.2, 117.8, 70.9, 51.5, 17.8. IR: 1749 (vs, C=O), 1611 $cm^{-1}$ (s, HNH).

**2b** (yield: 88%): ESI-MS Calcd. ($C_{11}H_{13}NO_2$) 192.1019 ($M + H^+$); Found 192.1013. $^1$H NMR ($CD_3OD$): $\delta$ = 7.45 (d, $J$ = 8.00 Hz, 2H, Ph), 7.38 (d, $J$ = 8.40 Hz, 2H, Ph), 6.74 (dd, $J$ = 10.8, 17.6 Hz, 1H, —CH=), 5.80 (d, $J$ = 17.6 Hz, 1H, CH=), 5.27 (s, 2H, $CH_2$—), 5.26 (d, $J$ = 10.8 Hz, 1H, CH), 3.87 (s, 2H, CH). $^{13}$C NMR ($CD_3OD$): $\delta$ = 168.5, 139.4, 137.5, 135.9, 130.0, 127.4, 114.8, 68.6, 41.1. IR: 1751 (vs, C=O), 1602 $cm^{-1}$ (s, HNH).

**2c** [yields: 73% (for L form) and 85% (for racemate)]: ESI-MS Calcd. ($C_{15}H_{21}NO_2$) 270.1464 ($M + Na^+$); Found 270.1527. $^1$H NMR ($CDCl_3$): $\delta$ = 7.38 (d, $J$ = 8.40 Hz, 2H, Ph), 7.26 (d, $J$ = 8.0 Hz, 2H, Ph), 6.69 (dd, $J$ = 10.8, 17.6 Hz, 1H, —CH=), 5.75 (d, $J$ = 17.6 Hz, 1H, CH=), 5.27 (d, $J$ = 10.8 Hz, 1H, CH=), 5.14 (AB pattern, 2H, $CH_2$), 3.98 (t, $J$ = 6.8 Hz, 1H, CH), 1.76 (m, 3H, $CH_2$, CH), 0.92–0.90 (m, 6H, $CH_3$). $^{13}$C NMR ($CDCl_3$): $\delta$ = 171.5, 138.1, 136.3, 134.3, 128.8, 126.6, 114.7, 67.7, 51.9, 40.6, 28.5, 24.5, 22.3. IR: 3375 (s, NH), 1731 $cm^{-1}$ (vs, C=O).

**2d** (yield: 96%): ESI-MS Calcd. ($C_{14}H_{19}NO_2$) 234.1494 ($M + H^+$); Found 234.1489. $^1$H NMR ($CDCl_3$): $\delta$ = 7.37 (d, $J$ = 8.00 Hz, 2H, Ph), 7.28 (d, $J$ = 8.0 Hz, 2H, Ph), 6.68 (dd, $J$ = 10.8, 17.6 Hz, 1H, —CH=), 5.75 (d, $J$ = 17.6 Hz, 1H, CH=), 5.27 (d, $J$ = 10.8 Hz, 1H, CH=), 5.21 (d, $J$ = 12 Hz, 1H, gem-CH), 5.11 (d, $J$ = 12 Hz, 1H, gem-CH), 3.87 (m, 1H, CH), 2.31 (m, 1H, CH), 1.00 (d, $J$ = 6.8 Hz, 6H, $CH_3$). $^{13}$C NMR ($CDCl_3$): $\delta$ = 169.1, 138.2, 136.3, 134.0, 129.1, 126.6, 114.8, 68.0, 58.5, 30.0, 17.9, 17.7. IR: 3321 (s, NH), 1733 $cm^{-1}$ (vs, C=O).

### Radical Polymerization of 2a–2d

In a typical example, to a 10-mL ampule was added a solution of monomer **2a** (1.05 g, 5.11 mmol) in THF (1.0 mL) and AIBN (8.0 mg, 51.1 $\mu$mol). The ampule was degassed, sealed under reduced pressure, and stirred at 50 °C for 24 h. The solution became viscous and after cooling to room temperature, polymers were precipitated, and the solution was washed with THF (ca. 20 mL) and was dried under reduced pressure to form a pale yellow precipitate, **3a** (0.894 g, 85% yield).

**3a**: $^1$H NMR ($CD_3OD$): $\delta$ = 7.07 (Ph), 6.48 (Ph), 5.14 (—$CH_2$—O—), 4.10 ($NH_2$—CH—CO), 1.51 ($CH_3$), 1.8–1.1 (—CH—$CH_2$—). $^{13}$C NMR ($D_2O$ containing HCOOH): $\delta$ = 170.7, 145, 132, 128, 68.1, 49.0, 40, 15.3. IR: 3423 (brw, NH), 1655 $cm^{-1}$ (vs, C=O).

**3b** (yield: 78%): $^1$H NMR ($CD_3OD$): $\delta$ = 7.03 (Ph), 6.43 (Ph), 5.16 (—$CH_2$—O—), 3.91 ($NH_2$—$CH_2$—CO), 2.0–1.1 (—CH—$CH_2$—). IR: 3365 (brw, NH), 1748 $cm^{-1}$ (vs, C=O). The $^{13}$C NMR spectrum for **3b** could not be obtained because of low solubility of **3b** in common solvents.

**3c** (yield: 92% for L form) and **3i** (yield: 69% for racemate)): $^1$H NMR ($CD_3OD$): $\delta$ = 7.06 (Ph), 6.44 (Ph), 5.18 (—$CH_2$—O—), 4.06 ($NH_2$—CH—CO), 1.71 ($CH_2CH(CH_3)_2$), 2.3–1.1 (—CH—$CH_2$—), 0.90 ($CH(CH_3)_2$). $^{13}$C NMR ($CD_3OD$): $\delta$ = 170.1, 134, 130, 129, 68.9, 59.3, 41–42, 31.1, 26.5, 18.7, 18.3. IR: 3365 (brw, NH), 1733 $cm^{-1}$ (vs, C=O).

**3d** (yield: 82%): $^1$H NMR ($CD_3OD$): $\delta$ = 7.06 (Ph), 6.40 (Ph), 5.17 (—$CH_2$—O—), 3.96 ($NH_2$—CH—CO), 2.25 ($CH(CH_3)_2$), 1.8–1.2 (—CH—$CH_2$—), 0.90 ($CH(CH_3)_2$). IR: 3379 (brw, NH), 1728 $cm^{-1}$ (vs, C=O). The $^{13}$C NMR spectrum for **3d** could not be obtained because of low solubility of **3d** in common solvents.

### Radical Polymerization of 1c and 1d

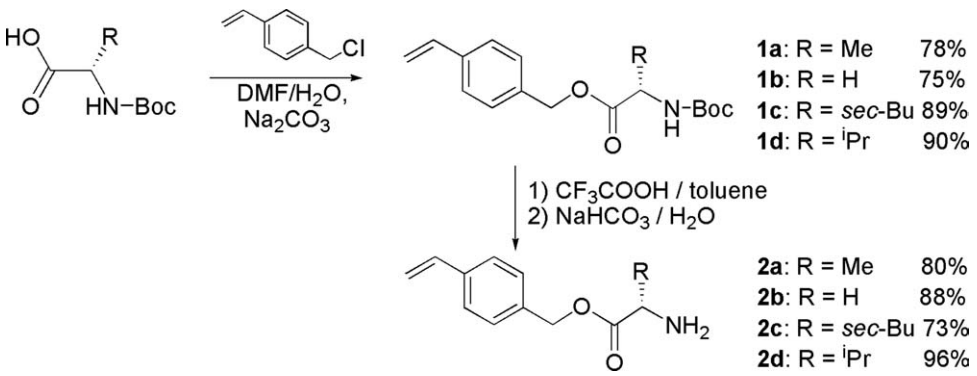
In a typical example, to a 10 mL ampoule, a solution of monomer **1d** (2.00 g, 5.99 mmol) in THF (2.0 mL) and AIBN (9.0 mg, 59.9 $\mu$mol) was added and degassed. The ampule was sealed under reduced pressure and stirred at 50 °C for 24 h. The solution was added dropwise into stirring hexane (30 mL) to form a pale yellow precipitate, **3f** (1.64 g, 82% yield).

**3e** (from **1c**, 1.72 g, 86% yield): $^1$H NMR ($CDCl_3$): $\delta$ = 7.09 (Ph), 6.84 (Ph), 6.56–6.44 (Ph), 5.11 (—$CH_2$—O—), 4.23 ($NH_2$—CH—CO), 1.68 (CH), 1.57 (CH), 1.68–1.30 (—$CH_2$—CH—), 1.42 ($C(CH_3)_3$), 0.89 ($CH_3$). $^{13}$C NMR ($CD_3OD$): $\delta$ = 173.6, 155.6, 145.2, 133.2, 127.8, 77.8, 66.6, 52.3, 46.3, 41.7, 40.3, 28.5, 24.9, 23.1, 22.0. IR: 3364 (brw, NH), 1709 $cm^{-1}$ (vs, C=O).

**3f**: $^1$H NMR ($CDCl_3$): $\delta$ = 7.11 (Ph), 6.54–6.70 (Ph), 5.12 (—$CH_2$—O—), 4.10 ($NH_2$—CH—CO), 2.09 (CH), 1.43–1.29 (—CH—$CH_2$—), 1.43 ($C(CH_3)_3$), 0.89 ($CH_3$). $^{13}$C NMR ($CDCl_3$): $\delta$ = 172.4, 155.8, 145.0, 133.1, 128.0, 79.8, 66.7, 58.6, 46.2, 40.3, 31.5, 28.5, 19.2, 17.7. IR: 3374 (brw, NH), 1709 $cm^{-1}$ (vs, C=O).

### Hydrolysis of 3a–3i

To a 50-mL round-bottom flask, a solution of polymer **3a** (0.105 mg) in methanol (10 mL) was added and a 40% solution of sodium hydroxide (1.25 mL) was added dropwise. After stirring for 1 h, addition of excess amount of water gave white precipitate, which was filtered (**4a**: 53% yield). $(C_9H_{10}O)_n$: Calcd. C, 80.56; H, 7.51; Found C, 78.78; H, 7.53.




**SCHEME 1** Synthesis of **1a–1d** and **2a–2d**.

The nitrogen content ratio in the polymer was 0.60%, suggesting that amino acid barely remained. The carbon content ratio was a little smaller than the theoretical one, because some amount of water may persistently remained in the polymer. $^1$H NMR ($CD_3OD$): $\delta$ = 7.06 (br, 2H, Ar), 6.54 (br, 2H, Ar), 4.54 (br, 2H, $CH_2$), 1.80 (br, 1H, CH), 1.5 (br, 2H, $CH_2$). IR: 3309 cm$^{-1}$ (brs, OH). The other polymers also showed the same spectra after hydrolysis.

### Acetylation of 4a–4i

To a 100-mL round-bottom flask, poly(4-hydroxymethylstyrene) **4c** (131.5 mg) and acetic anhydride (20 mL) were added and refluxed for 18 h. The addition of water (20 mL) followed by stirring at 90 °C at 1 h gave a white precipitate, which was filtered (**5c**: 159.6 mg, 92% yield).

$^1$H NMR ($CDCl_3$): $\delta$ = 7.04 (br, 2H, Ar), 6.47 (br, 2H, Ar), 5.00 (br, 2H, Ar-$CH_2$—), 2.09 (s, 3H, $COCH_3$), 1.69 (br, 1H, $\alpha$-CH), 1.32 (br, 2H, $\beta$-$CH_2$). $^{13}$C NMR ($CDCl_3$): $\delta$ = 170.8 (CO), 144.8 ($4^o$-Ph), 133.3 ($4^o$-Ph), 128.0 (Ph), 127.7 (Ph), 66.0 (Ar-$CH_2$—), 46.0, 43.6, 42.6, 42.2 (br, $\alpha$-CH), 40.2 ($\beta$-$CH_2$), 21.0 ($CH_3$). IR: 1732 cm$^{-1}$ (vs, C=O).

## RESULTS AND DISCUSSION

### Preparation of a Series of Amino Acid-Bound Styrene

To prepare the amino acid-substituted styrene, in this study, a simple coupling method was used using inexpensive 4-(chloromethyl)styrene and *N*-*tert*-butoxycarbonyloxy(Boc)-protected amino acids in DMF containing a small amount of water with $Na_2CO_3$ to form benzyl esters, *N*-Boc-protected styrene derivatives of alanine (**1a**: 78%), glycine (**1b**: 75%), leucine [**1c**: 89% (for L form) and 90% (for racemate)], and valine (**1d**: 90%) (Scheme 1).[21] The *N*-Boc group, which is easily deprotected by acids, is more favored than the other types of protecting groups, because undesirable hydrolysis of benzyl ester does not proceed under acidic condition. As a result, monomers (**2a–2d**) without the Boc group were successfully obtained in high yields [**2a** (alanyl ester): 80%, **2b** (glycyl ester): 88%, **2c** (leucyl ester): 73% (for L form) and 85% (for racemate), **2d** (valyl ester): 96%] after treatment of **1a–1d** with 25% TFA in toluene. More acidic conditions using aqueous solution of some carboxylic acids, which are generally used for deprotection of the Boc group in peptide synthesis,[22] resulted in hydrolysis of the benzyl ester to some extent in addition to the deprotection. Compounds **1** and **2** were characterized on the basis of NMR, IR, and ESI-Mass spectra and were confirmed on the basis of elemental analysis. The NMR spectra for these monomers bearing chiral amino acid showed characteristic AB patterns around $\delta$ 5 assigned as the diastereotopic benzyl methylene protons (Fig. 2), except for the monomer having achiral glycine in the side chain. Further, a set of three signals assigned as the vinyl protons appeared at 5–7 ppm. Deprotection of the *N*-Boc group was confirmed by the disappearance of a sharp, singlet $^1$H resonance because of the methyl protons in the *tert*-butyl group around $\delta$ 1.4 ppm (Fig. 2).

IR resonances of the amino-acid substituted styrene monomers with or without *N*-Boc group in the side chain gave significant information about intermolecular hydrogen-bonding interaction between secondary Boc-amide or primary amine N—H moiety and carbonyl groups in the amino acid side chains. As shown in Figure 3, a single band at 3370 cm$^{-1}$ for the Boc-protected monomers (e.g., **1c**) was out of the range assigned as secondary amide N—H absorbance with hydrogen bonding (3330–3060 cm$^{-1}$; Fig. 3). In contrast, two bands for the deprotected monomers (e.g., **2c**) at 3375 and 3305 (sh) cm$^{-1}$ were in the range of the primary amine N—H absorbance with hydrogen bonding (3400–3250 cm$^{-1}$). The results showed that hydrogen-bonding interaction may be efficient for the amino-acid bound monomers after removal of the Boc group, whereas Boc protection of amino acid in the side chain disturbs hydrogen bonding between amide N—H and carbonyl groups.

### Radical Polymerization

Free radical polymerization of monomers, **2a–2d**, **1c**, and **1d**, was conducted (Scheme 2) in degassed THF with AIBN, which initiated the polymerization at 50 °C under reduced pressure to form the polystyrene derivatives, **3a–3d** from **2a–2d** and **3e** and **3f** from **1c** and **1d**, efficiently (Table 1, entries 1–6). Particularly, the (L)-valine-substituted monomer **2d** was also polymerized at higher temperature, 80 °C, forming a polymer **3g** (entry 7). DMF was also used instead of THF as a solvent for the polymerization of **2d** to form a polymer **3h** (entry 8). In addition to use achiral glycine-substituted styrene **2b**, racemic amino acid-substituted styrene, a DL-leucine derivative **(*rac*)-2c**, was also polymerized to form polymer **3i** to evaluate necessity of chirality in the monomer side chain for stereoselective polymerization (Table 1, entry

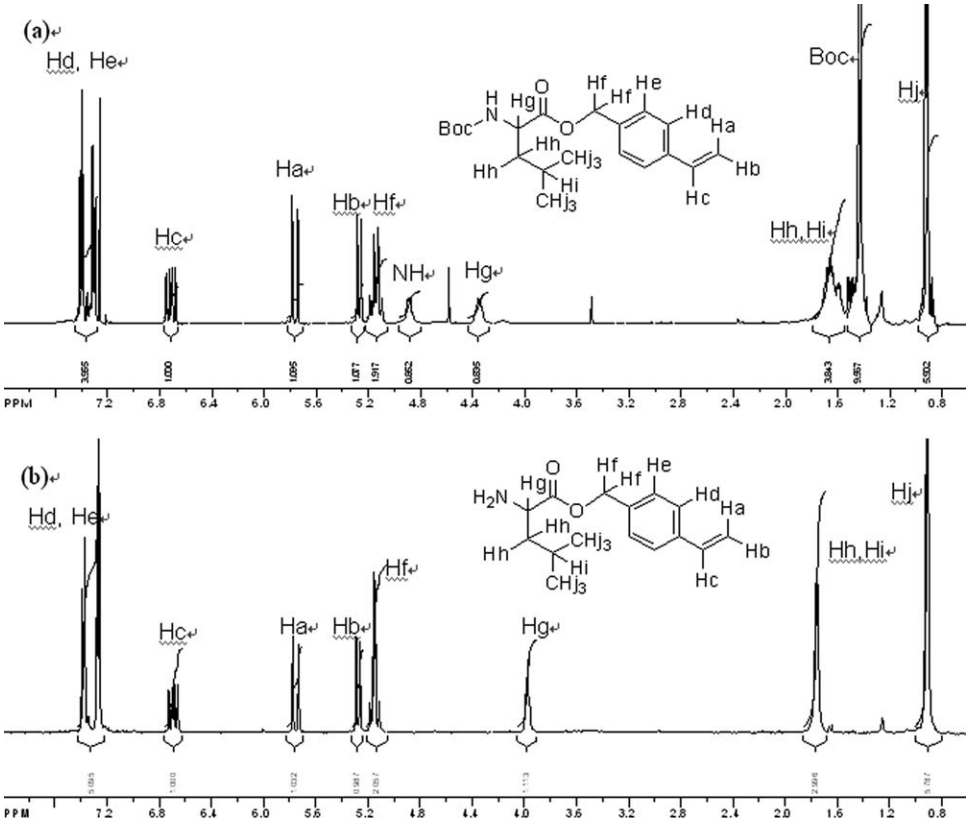



**FIGURE 2** Representative examples of the $^1$H NMR spectra (in $CDCl_3$, 400 MHz) for (a) **1c** and (b) **2c**.

9 and Scheme 3). The polystyrene derivatives, **3a–3d** and **3g–3i**, bearing no Boc groups could be dissolved in methanol, DMSO, or DMF, but were only swelled in toluene, THF, or chloroform, suggesting that intramolecular strong hydrogen bonding between amine and carbonyl moieties in the side chains prevents dissolution in nonpolar solvents. In contrast, the Boc-protected polymers **3e** and **3f** were soluble even in nonpolar solvents. Thus, in the polymerization of **2a–2d** in THF resulted in production of the swelled polymers, which were precipitated in hexane, yielding polymers **3a–3d** and **3g–3i**, whereas the other Boc-substituted polymers **3e** and **3f** were precipitated in methanol after polymerization. Because of the poor solubility in THF, molecular weight of these amino acid-bound polystyrenes could not be determined by SEC analysis. The $^1$H NMR analysis of these polymers in $CD_3OD$ (for **3a–3d** and **3g–3i**) or $CDCl_3$ (for **3e** and **3f**) demonstrated the disappearance of the characteristic set of the three signals due to the vinyl protons of the monomers and appearance of broadened characteristic signals around $\delta$ 6–7 and 1–2 ppm, assigned as phenylene and alkyl chain groups, respectively, in 4-substituted polystyrene as shown in Figure 4.

### Hydrolysis and Acetylation

To evaluate the tacticity of the polymers from responsible NMR spectra, we removed amino acid side chain. As shown in Scheme 2, polymers **3a–3i** were hydrolyzed with NaOH in methanol and water (1 mol $L^{-1}$) solution at room temperature to remove amino acid in the side chains and then acetylated with acetic anhydride under reflux condition for 18 h to form corresponding polymers **4a–4i** and **5a–5i** in good yields (Scheme 2 and Table 1). The absence of amino acid groups in these polymers was confirmed on the basis of the NMR and IR spectra. Elemental analysis data of the

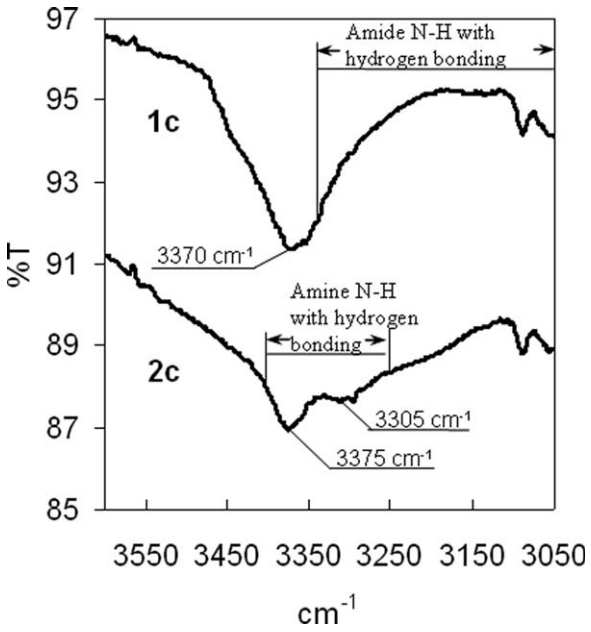
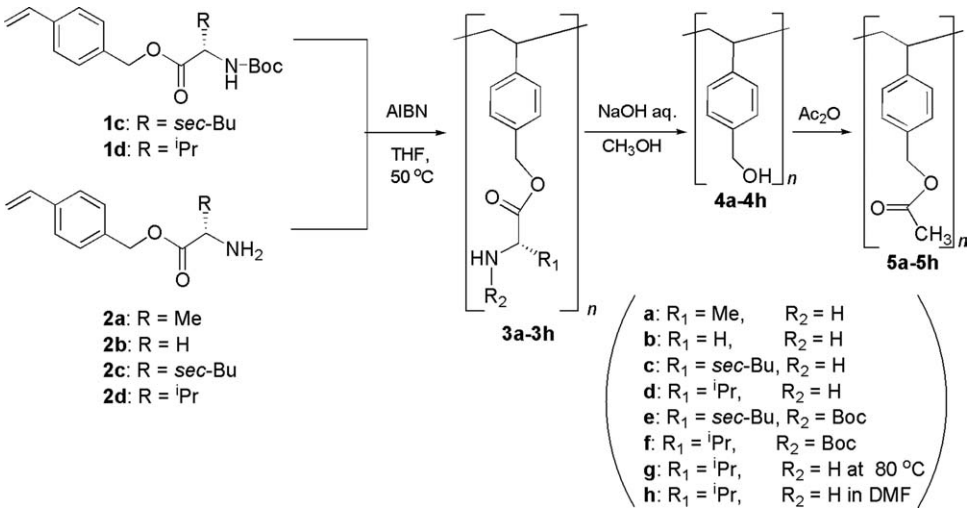



**FIGURE 3** Representative examples of IR spectra (solid state) for **1c** and **2c** in the region of N—H stretching (3100–3600 $cm^{-1}$). Small bands at 3084 $cm^{-1}$ in the both spectra were assigned as $sp^2$ C—H stretching.




**SCHEME 2** Radical polymerization of **1a**, **1d**, and **2a–2d** to form **3a–3h**, which were hydrolyzed and acetylated to form **4a–4h** and **5a–5h**.

hydrolyzed polymer **4** also supported the disappearance of amino acid. The ratio of nitrogen content in the hydrolyzed polymer **4** was 0.60%, suggesting that a little amount of amino acid remained. The ratio of carbon content was 78.78%, which was a little smaller than the theoretical one, because some amount of water may persistently remained in the polymer. Detailed spectroscopic analysis of polymers **4a–4i** was difficult, because these polymers were not dissolved in nonpolar solvents and slightly soluble in polar solvents, such as methanol and DMF. IR spectra for **4a–4i** in the solid state showed broad absorbance around 3309 $cm^{-1}$ assignable to OH stretching band. In contrast, acetylated polymers **5a–5i** were easily dissolved in THF and chloroform, so that the molecular weight of acetylated polymers was finally determined as 3.2–27 kg $mol^{-1}$ by means of the SEC analysis using polystyrene as a calibrating standard as shown in Table 1. The $^{1}H$ and $^{13}C$ resonances due to the methyl protons and carbon ($H_g$ and $C_i$ in Fig. 5) in the acetyl group for **5a–5i** appeared at $\delta$ 2.09 and 21.0, showing that the polymers **4a–4i** were completely acetylated. Existence of the carbonyl group in **5a–5i** was confirmed by the $^{13}C$ NMR resonance, in which the corresponding signal was observed at $\delta$ 170.8 and the IR resonance due to the carbonyl stretching band at 1732 $cm^{-1}$.

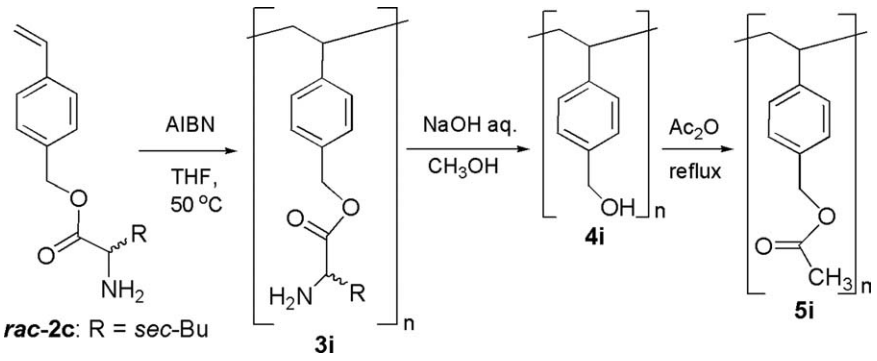
### Stereochemistry

Unfortunately, we could not measure specific rotations of the soluble acetylated polymers because of some coloration

**TABLE 1** Synthetic and Analytical Results in Polymers **3–5**

| | | | | | **3**[a] | | **4**[a] | | **5**[a] | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Entry | Monomer | Temperature (°C) | Time (h) | Solvent | Product | Yield (%) | Product | Yield (%) | Product | Yield (%) | $M_n$[b] (kg $mol^{-1}$) | $M_w/M_n$ | *mm*:*mr*:*rr* (*m*:*r*)[c] |
| 1 | **2a** (L-Ala) | 50 | 24 | THF | **3a** | 85 | **4a** | 52 | **5a** | 80 | 6.7 | 4.2 | 8:35:57 (26:74) |
| 2 | **2b** (Gly) | 50 | 48 | THF | **3b** | 69 | **4b** | 54 | **5b** | 89 | 3.8 | 3.4 | 6:41:53 (26:74) |
| 3 | **2c** (L-Leu) | 50 | 48 | THF | **3c** | 92 | **4c** | 58 | **5c** | 92 | 3.2 | 2.3 | 18:31:51 (34:66) |
| 4 | **2d** (L-Val) | 50 | 48 | THF | **3d** | 100 | **4d** | 57 | **5d** | 88 | 7.4 | 3.1 | 13:44:43 (35:65) |
| 5 | **1c** (Boc) | 50 | 48 | THF | **3e** | 86 | **4e** | 100 | **5e** | 80 | 10.3 | 2.3 | 10:30:60 (25:75) |
| 6 | **1d** (Boc) | 50 | 48 | THF | **3f** | 82 | **4f** | 64 | **5f** | 85 | 11.6 | 1.8 | 9:42:49 (30:70) |
| 7 | **2d** (L-Val) | 80 | 24 | THF | **3g** | –[d] | **4g** | 56 | **5g** | 67 | 3.7 | 1.9 | 9:38:53 (28:72) |
| 8 | **2d** (L-Val) | 50 | 24 | DMF | **3h** | 100 | **4h** | 61 | **5h** | 90 | 26.6 | 2.2 | 10:45:45 (33:67) |
| 9 | ***rac*-2c** | 50 | 24 | THF | **3i** | 69 | **4i** | 34 | **5i** | 47 | 13.8 | 1.4 | 10:32:58 (26:74) |

[a] The compounds **3**, **4**, and **5** are polystyrene with amino acid side chain, poly(4-hydroxymethyl-styrene) after hydrolysis, and poly(4-acetyloxymethyl-styrene) after acetylation, respectively.
[b] Molecular weight was determined by means of size-exclusion chromatography (SEC) in THF, calibrated with polystyrene standard.
[c] The ratios of the tacticity were determined by a curve-fitting program[23] using the $^{13}C$ NMR spectra, according to those of a similar polystyrene analog in the literature.[17] The ratios between *mr* and *rr* include some error (about 5%) because of large overlap of these signals.
[d] The yield could not be determined because the product and the monomer could not be separated because of these high solubility in various organic solvents, such as methanol, THF, and hexane.




**SCHEME 3** Polymer synthesis using a monomer containing a racemic isomer of leucine, ***rac*-2c**.

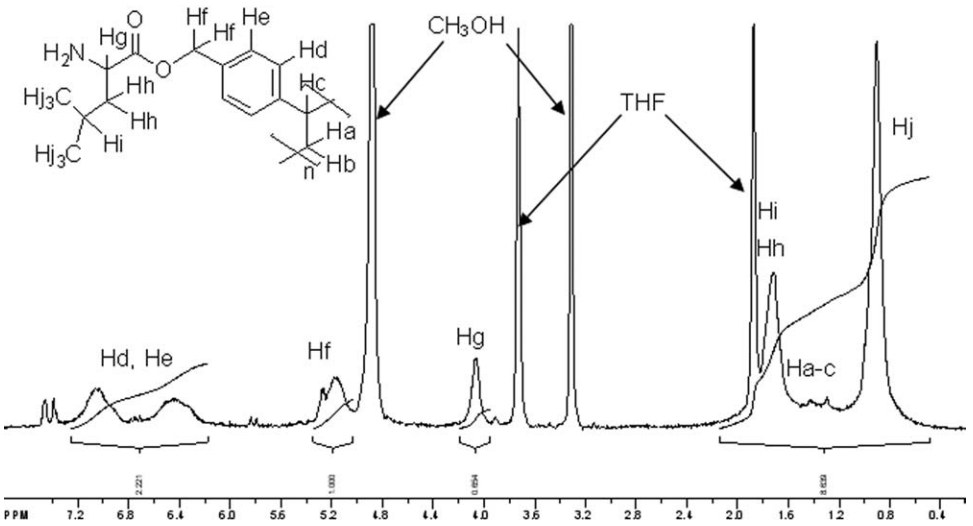



**FIGURE 4** Representative example of the $^{1}H$ NMR spectrum (in $CD_3OD$, 400 MHz) for **3c**.

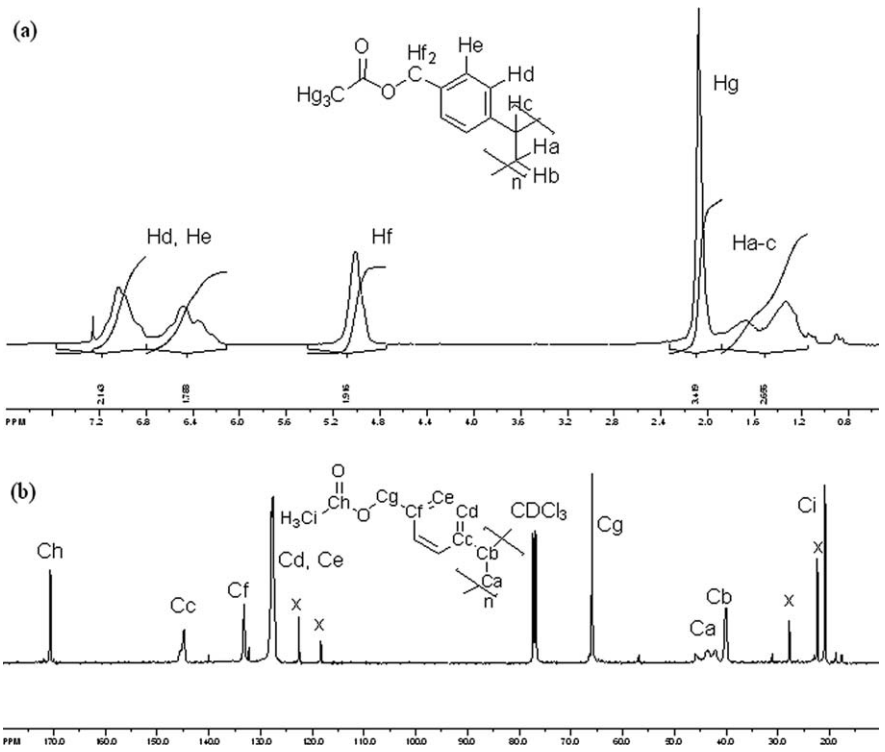



**FIGURE 5** (a) $^{1}H$ and (b) $^{13}C$ NMR spectra (in $CDCl_3$) for acetylated polymer **5**.

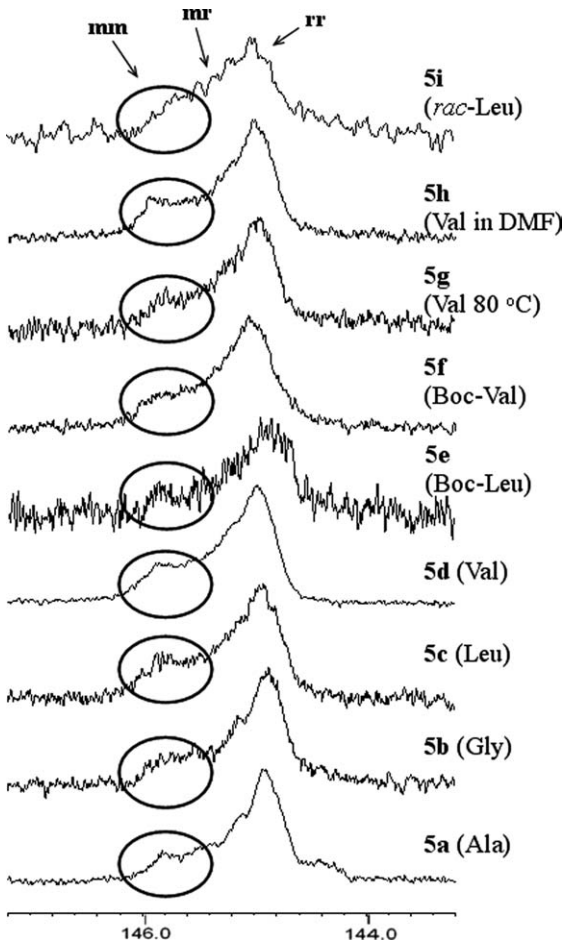



**FIGURE 6** Partial $^{13}C$ NMR spectra for **5a–5i** around $\delta$ 144–146 in the aromatic *ipso*-carbon region.

during acetylation and also could not observe the crystallinity in **5a–5i** by powder X-ray diffraction studies, probably attributed to the inappropriate polymer side-chain length of the acetyloxymethylphenyl group for the formation of crystals. Thus, we observed the $^{13}C$ NMR spectra for **5a–5i** (Fig. 6) to determine the tacticity of these polymers. The tacticity of the $^{13}C$ resonance was assigned according to that for a similar polymer, poly(4-methoxymethyl-styrene).[23] As shown in Figure 6, the shape of the signals around $\delta$ 144–146 ppm assigned as a quaternary phenylene carbon adjacent to the main-chain carbon in the $^{13}C$ NMR spectra for **5a–5i** shows increase and decrease of the *mm* triad contents, which demonstrated an isotactic sequence of three monomer unit in the polymer main chain. Curve fitting simulation was conducted using an NMR analyzing program, 1D NMR ver. 3. 7. 16.[24] Gaussian distributions were applied and optimized by the least-squares method. Representative examples are shown in Figure 7. Five or four resonances were found in the overlapped signals: the lowest-field signal at $\delta$ 145.8 was assigned as the *mm* triad, and the highest ones at $\delta$ 144.9 were assigned as the *rr* triads, of which these integrated ratios in the curve-fitting simulation roughly agreed with the known values of polystyrene (Table 1). The ratios between *mr* and *rr* include some error (about 5%) because of large overlap of these signals. Only in the case of **5a** from alanine-containing polystyrene, unknown signal was contaminated at $\delta$ 144.4. Remarkably, we found significant increase of the low-field signal due to the *mm* triad of the aromatic carbon up to 13–20% in the polymers **5c** and **5d** at $\delta$ 145-6, which were synthesized from the polymers having (L)-leucine and (L)-valine. In contrast, the *mm* contents of the other polymers, **5a**, **5b**, **5e**, **5f**, **5g**, and **5i**, were under 10% and did not broadly differ from each other. The solvent, DMF, was also effective for the stereoselective polymerization in part, probably because the hydrogen-bonding interaction with DMF might link the CO and NH groups between the monomer side chain and the growing polymer terminal during propagation step to form **3h**.

Increase of isotacticity in **5c** and **5d** demonstrated that stereochemistry was successfully controlled to some extent in

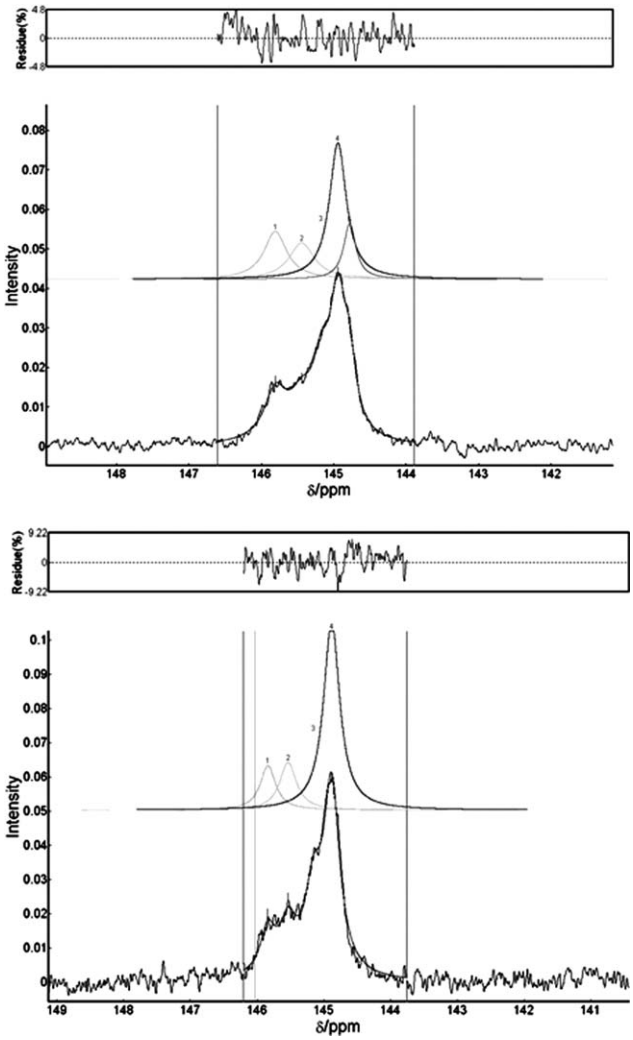



**FIGURE 7** Examples of curve-fitting experimental results using $^{13}C$ NMR spectra for **5c** (leucine) and **5b** (glycine) around $\delta$ 144–146 in the aromatic *ipso*-carbon region, indicating that the lowest field signal assigned as *mm* triad for **5c** increased in comparison with that for **5b**.

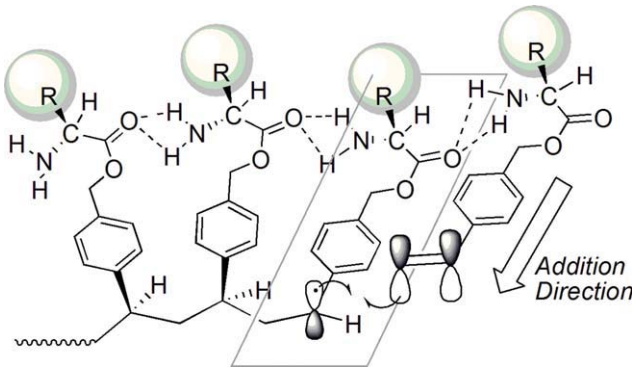



**FIGURE 8** One of the models in the stereoselection of free radical carbon with monomer. One-dimensional hydrogen-bonding network exists in the main chain, and similar mode of hydrogen bonding between the side chains of monomer and polymer α-end.

the polymerization of the styrene derivatives containing chiral amino acids, expectedly. Moreover, the synergic effect of chirality and intermolecular hydrogen-bonding interaction between the amino acid-containing monomer and the polymer α-end was indicated from the tacticity of the polymers **5a–5i**. Critical differences in the monomer structures and polymerization conditions of the poorly controlled polymers, **5a**, **5b**, **5e**, **5f**, **5g**, and **5i** from those of the more isotactic polymers, **5c**, **5d**, and **5h**, were (1) using amino acid without chirality, glycine or (*rac*)-leucine, (2) presence of the Boc-amide moiety, and (3) at higher temperature, 80 °C, for unsuccessful stereoselective polymerization. The above factor (1) may affect stereoselection with chirality, whereas (2) and (3) may affect that with hydrogen bonding as expected in Figure 1. Figure 8 shows one of the models in the stereoselection of free radical carbon in the growing terminal with monomer. Polymer side chains containing amino acid may make strong one-dimensional hydrogen-bonding network using carbonyl and amine moiety. When vinyl carbon in the monomer makes an approach to the radical carbon, hydrogen-bonding interaction between the side chains of monomer and the polymer α-end, before the radical addition, may restrict the way to two of the four approaches as shown in Figure 1. In addition, chiral alkyl group in the monomer side chain may select one of the two approaches, the faces of the $sp^2$ radical carbon (Fig. 8). Chirality of (L)-alanine in **2a** may be insufficient to control the stereoselection. The *N*-Boc protection at the amino group in the styrene derivatives **1c** and **1d** also had difficulty in stereoselective polymerization due to weak hydrogen-bonding interaction, as indicated in the IR resonances for the monomers **1a–1d** (Fig. 3), probably because steric hindrance of the Boc substituent disturbed the hydrogen bonding to some extent. In other words, both chirality and hydrogen-bonding interaction of chiral amino acid in the monomer with those in the radical terminal play the crucial roles in controlling the tacticity. In comparison with earlier cases, in which only the chirality or hydrogen-bonding interactions could control the tacticity in radical polymerization under 0 °C,[3] this synergic control works even at higher temperature (50 °C). It is a significant result, demonstrating that our hypothesis can be actualized in free radical polymerization of styrene derivatives.

## CONCLUSIONS

In summary, stereoselective radical polymerization of styrene derivatives having *N*-free amino acids in the side chain bound at the C-terminal was conducted successfully to form chirality-induced polystyrenes by the synergic stereoregulation with chirality and hydrogen-bonding interaction between the polymer radical terminal and the monomer. Remarkably, this synergic control works even at high temperature (50 °C). The stereoselectivity may increase when the polymerization is conducted at low temperature and the steric hindrance of the amino acid residues increased. We are now researching clarification of the detailed mechanism in stereoregulation and applications of these polymers.

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