Radical Polymerization Behavior of a Proline-Substituted Acrylamide. Effect of s-*Cis*−s-*Trans* Isomerization on the Polymerization

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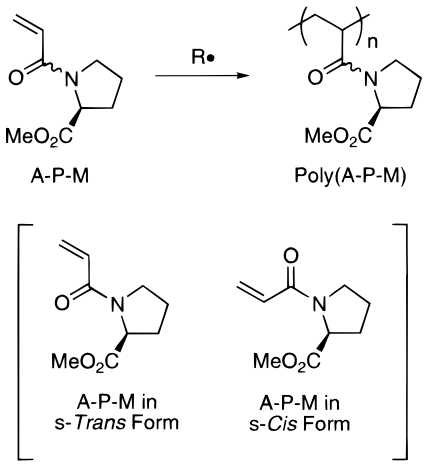
ABSTRACT: Synthesis and radical polymerization of a proline-substituted acrylamide, *N*-methacryloyl-L-proline methyl ester (A-P-M) were carried out. The isomerization of A-P-M between s-*cis* and s-*trans* forms of A-P-M was analyzed by ^{1}H NMR spectroscopy and molecular dynamics simulation, and the effect of the *cis*−*trans* isomerization on the radical polymerization of A-P-M was examined. The content of s-*cis* form of A-P-M increased with the NMR measuring temperature. The radical polymerization of A-P-M at higher temperature afforded the polymer with a higher s-*cis* content and a lower absolute value of specific rotation. It was suggested that the s-*cis*/s-*trans* ratio and the tacticity of the polymer affected the optical properties.

Introduction

The isomerization of the proline amide moiety between s-*cis* and s-*trans* forms has been widely studied from both experimental and theoretical points of view in the fields of protein and peptide chemistry.[1] In synthetic polymer chemistry, vinyl polymers based on amino acids and peptides have been developed directing to chemically functional materials such as polymeric electrolytes,[2] optically active adsorbents,[3] photochromic materials,[4] drug delivery materials,[5] and thermosensitive materials.[6] The mostly common amino acid-based vinyl polymers are poly(*N*-acryl- and poly(methacrylamides), which can be easily prepared by the radical polymerization of the corresponding *N*-acryl and methacrylamides.[7] We have examined the synthesis and radical polymerization of these monomers to find some unique properties concerning the polymerizability, specific rotation, glass transition temperature, and solubility.[8] However, radical polymerization of proline-substituted acrylamides has been scarcely studied, much less the effect of *cis*−*trans* isomerization of the proline amide moiety on the polymerization behavior and polymer properties so far. This paper deals with conformation analysis of a proline-substituted acrylamide, *N*-methacryloyl-L-proline methyl ester (A-P-M) by NMR spectroscopy and molecular dynamics calculation, and the effect of *cis*−*trans* isomerization on the radical polymerization of A-P-M (Scheme 1).

Scheme 1



Experimental Section

Measurements. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM EX-90, EX-400, and GX-500 spectrometers using tetramethylsilane (TMS) as an internal standard in chloroform-*d* ($CDCl_3$) or *N*,*N*-dimethylformamide-d_7 (DMF-d_7). IR spectra were obtained with a JASCO FT/IR-5300. Melting points (mp) were measured by a Yanaco micro melting point apparatus. Specific rotations ($[\alpha]_D$) were measured on a JASCO DIP-1000 digital polarimeter using a sodium lamp as a light source. Circular dichroism (CD) spectra were measured on a JASCO J-720 spectropolarimeter. Elemental analysis was performed on a Yanaco CHN Corder MT-5. Number average molecular weights (M_n) and polydispersity ratios (M_w/M_n) were estimated by gel permeation chromatography (GPC) on a Tosoh HPLC HLC-8020 system, equipped with consecutive four polystyrene gel columns (TSK gels G6000H, G5000H, G4000H, and G2500H), using DMF (5.8 mM lithium bromide solution) as an eluent at a flow rate of 1.0 mL/min, a polystyrene calibration, and refractive index (RI) and ultraviolet (UV) detectors. Thermal analysis was performed on Seiko Instruments TG/DTA220 and DSC220C. Glass transition temperatures (T_g) were taken as inflection points on traces by differential scanning calorimetry (DSC) at a heating rate of 10 °C/min. Temperatures (T_{d10}) with 10% weight loss were determined by thermogravimetric analysis (TGA) at a heating rate of 10 °C/min under a nitrogen atmosphere.

Materials. L-Proline methyl ester hydrochloride (Eiweiss Chemical Co.), acryloyl, methacryloyl, and isobutyryl chlorides (Tokyo Chemical Industry Co.) were used as received. Initiators, 2,2′-azobis(isobutyronitrile) (AIBN, Tokyo Chemical Industry Co.), 1,1′-azobis(cyclohexanecarbonitrile) (V-40, Wako Pure Chemical Industries, Ltd.), di-*tert*-butyl peroxide (Nacalai Tesque, Inc.), *tert*-butyl hydroperoxide (TBHP, Nacalai Tesque, Inc.) were used as received. Chlorobenzene (CB) was distilled over calcium hydride after washing with concentrated sulfuric acid, aqueous sodium hydrogen carbonate, and water. DMF and *N*-methylformamide (MF) were distilled over calcium hydride.

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Synthesis of *N*-Acryloyl-L-proline Methyl Ester. To a solution of L-proline methyl ester hydrochloride (16.5 g, 100 mmol) and triethylamine (21 g, 210 mmol) in dichloromethane (28.9 mL) was added acryloyl chloride (8.7 mL, 110 mmol) at 0 °C, and the resulting mixture was stirred at room temperature overnight. The reaction mixture was washed with 1 M HCl (200 mL × 2), saturated aqueous solutions of $NaHCO_3$ (200 mL × 2), and NaCl (200 mL × 1). The organic layer was dried over anhydrous $MgSO_4$ and filtered, and the filtrate was concentrated by rotary evaporation. A part (1.5 g) of the residue was distilled in the presence of copper(I) chloride (150 mg) by a Kugel rohr apparatus; yield 0.9 g (69%), bp 170 °C/1.2 mmHg, $[\alpha]_D^{25}$ −121.3° (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 6.25−6.40 (m, 2 H, $-CH{=}CH_2$), 5.71 (dd, J = 7.9 and 4.5 Hz, 1 H, $-CH{=}CH_2$), 4.51−4.63 (m, 1 H, $>CHCO_2CH_3$), 3.74 (s, 3 H, $-CO_2CH_3$), 3.60−3.79 (m, 2 H, $>NCH_2-$), 1.95−2.32 (m, 4 H, $-CH_2CH_2-$) ppm. ^{13}C NMR ($CDCl_3$): δ 172.5 (−CONH−), 164.4 ($-CO_2CH_3$), 128.3 ($-CH{=}CH_2$), 128.0 ($-CH{=}CH_2$), 59.2 ($>CHCO_2-$, s-*cis*), 58.8 ($>CHCO_2-$, s-*trans*), 52.4 ($-CO_2CH_3$, s-*cis*), 52.1 ($-CO_2CH_3$, s-*trans*), 46.4 ($>NCH_2-$, s-*cis*), 46.8 ($>NCH_2-$, s-*trans*), 31.3 ($>CHCH_2-$, s-*cis*), 29.0 ($>CHCH_2-$, s-*trans*), 22.5 ($-CH_2CH_2CH_2-$, s-*cis*), 24.7 ($-CH_2-CH_2CH_2-$, s-*trans*) ppm. IR (KBr): 2955 (C−H), 1744 (C=O (ester)), 1651, 1615, 1435, 1198, 1177 cm^{-1}. Anal. Calcd for $C_9H_{13}NO_3$: C, 59.00; H, 7.15; N, 7.65. Found: C, 58.76; H, 7.16; N, 7.65.

Synthesis of *N*-Isobutyryl-L-proline Methyl Ester. The title compound was prepared from L-proline methyl ester hydrochloride with isobutyryl chloride similarly to A-P-M; yield 75%, bp 170 °C/1.2 mmHg (Kugel), $[\alpha]^{25}_D$ −92.7° (*c* 1.00, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 4.48−4.50 (m, 1 H, $>CHCO_2CH_3$), 3.72 (s, 3 H, $-CO_2CH_3$), 3.64−3.76 (m, 2 H, $>NCH_2-$), 3.54−3.60 (m, 1 H, $(CH_3)_2CH-$), 1.91−2.20 (m, 4 H, $>CHCH_2CH_2-$), 1.1−1.17 (m, 6 H, $(CH_3)_2CH-$) ppm. ^{13}C NMR ($CDCl_3$): δ 175.9 (−CONH−), 173.0 ($-CO_2CH_3$), 59.3 ($>CHCO_2-$, s-*cis*), 58.7 ($>CHCO_2-$, s-*trans*), 52.5 ($-CO_2CH_3$, s-*cis*), 52.1 ($-CO_2CH_3$, s-*trans*), 46.4 ($>NCH_2-$, s-*cis*), 46.7 ($>NCH_2-$, s-*trans*), 32.3 ($-CH(CH_3)_2$, s-*cis*), 32.6 ($-CH(CH_3)_2$, s-*trans*), 31.5 ($>CHCH_2-$, s-*cis*), 29.1 ($>CHCH_2-$, s-*trans*), 22.5 ($-CH_2CH_2CH_2-$, s-*cis*), 24.9 ($-CH_2CH_2CH_2-$, s-*trans*), 19.7 ($-CH(CH_3)_2$, s-*cis*), 18.9 ($-CH(CH_3)_2$, s-*trans*) ppm. IR (KBr): 2972 (C−H), 1745 (C=O (ester)), 1649, 1429, 1197, 1174 cm^{-1}. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.60; N, 7.03. Found: C, 59.92; H, 8.52; N, 6.87.

Radical Polymerization of A-P-M. Typical Procedure. To the monomer (3 mmol) in a polymerization tube was introduced an initiator (0.03 mmol), and subsequently a dry solvent (3 mL), if required. The tube was cooled, degassed, sealed off, and heated at a set temperature for 20 h. The resulting mixture was diluted with chloroform (3 mL) and poured into ether (200 mL) to precipitate a polymer. The ether-insoluble polymer was filtrated and dried at 60 °C in vacuo overnight. ^1H NMR ($CDCl_3$): δ 4.1−5.0 (m, 1 H), 3.2−4.0 (m, 5 H), 1.0−2.8 (m, 7 H) ppm. ^{13}C NMR ($CDCl_3$): δ 172−174 (−CONH−, $-CO_2CH_3$), 59 ($>CHCO_2-$), 52 ($-CO_2CH_3$), 48 ($>NCH_2-$), 37−39 ($-CH_2CH<$ (main chain)), 29 ($>CHCH_2-$), 25 ($-CH_2CH_2CH_2-$) ppm. IR (KBr): 2955 (C−H), 2245, 1744 (C=O (ester)), 1642, 1437, 1197 cm^{-1}.

Molecular Dynamics Calculation. Molecular dynamics (MD) calculation was done on a Silicon Graphics Indigo2 IMPACT 10000 with use of Molecular Simulations Discover version 2.97. The geometries were optimized using the conjugate gradient method in 1000 steps at 298 K.

Results and Discussion

Conformation Study of A-P-M. *N*-Acetylproline has been reported to exist in two conformation isomers, s-*cis* and s-*trans* conformers.[9] ^1H NMR spectra (400 MHz) of A-P-M were measured to determine the ratio of the two conformers in DMF-d_7 at −40 to +120 °C to find that the signal assignable to s-*cis* form shifted to the higher field from 4.94 to 4.70 ppm and that to the s-*trans* form shifted to the lower field from 4.42 to 4.46 ppm with an increase in the measuring temperature. The integration ratio of the s-*cis* signal increased from 16.3 to 23.9% at temperatures from −50 to +80 °C. These signals of s-*cis* and -*trans* conformers coalesced into one at ca. 100 °C, which indicated that the rotational barrier between the two conformers was ca. 18 kcal/mol.[10] The conformation of A-P-M was also analyzed by MD calculation, which suggested that the rotational energy barrier between the s-*cis* and -*trans* forms was 15.7 kcal/mol. The higher rotational energy barrier determined by NMR spectroscopy compared with that calculated by the MD method may be due to the interaction between A-P-M molecules and the solvent DMF molecules, because it does not consider the intermolecular interaction, which may somewhat hinder the bond rotation of A-P-M. The MD calculation indicated that the s-*trans* conformer was 0.80 kcal/mol more stable than the s-*cis* one, which agreed well with the value (1.10 kcal/mol) experimentally obtained by the Boltzmann distribution based on the NMR integration ratio of the two isomers.

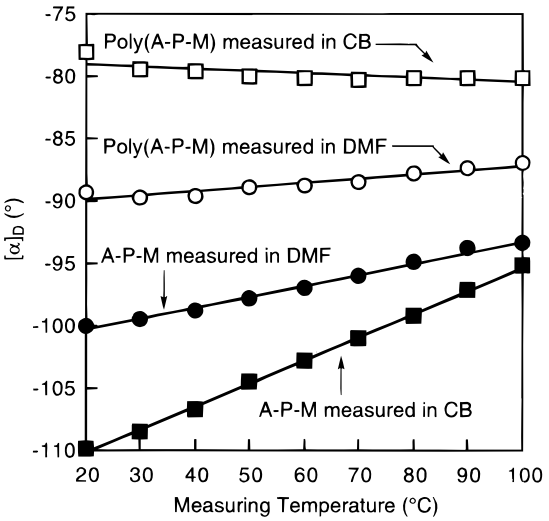

Figure 1. Relationships between the measuring temperature and specific rotations (*c* 1.0, DMF and CB) of A-P-M and poly(A-P-M) obtained by the polymerization with AIBN (1 mol %) at 60 °C in DMF (1 M) for 20 h.

Further, the specific rotations of A-P-M and poly(A-P-M) were measured in DMF and CB at 20−100 °C to estimate the effect of s-*cis*/s-*trans* ratio of A-P-M on the specific rotations (Figure 1). The absolute values of the specific rotations of A-P-M increased with the measuring temperature in both solvents, while those of poly(A-P-M) changed little. The steric hindrance of the polymer main chain might increase the rotational barrier between the s-*cis* and -*trans* forms to restrain the transformation.[11]

Radical Polymerization of A-P-M. Radical polymerization of A-P-M was carried out in the presence of an appropriate initiator (1 mol %) at 60−160 °C for 20 h in bulk, DMF, MF, and CB. The polymer was isolated by precipitation from ether. The ^1H and ^{13}C NMR and IR spectra of the obtained polymer confirmed that the structure of the polymer was the corresponding polyacrylamide, poly(A-P-M). Table 1 summarizes the conditions and results of the polymerization, along with the optical and thermal properties of the polymers obtained.[12] In DMF, the conversion of A-P-M and the yield of the polymer decreased as the polymerization temperature was raised, while M_n decreased slightly (runs 2−5). In MF, the M_n remarkably decreased as the

Table 1. Radical Polymerization of A-P-M (Conditions: Monomer, 3 mmol; Solvent, 3 mL; Initiator, 1 mol %; 20 h)

run	solv[a]	init[b]	temp (°C)	conv[c] (%)	yield[d] (%)	M_n[e]	M_w/M_n[e]	$[\alpha]_D$[f] (deg)	T_g[g] (°C)	T_{d10}[h] (°C)
1	none	AIBN	60	82	82	74 000	2.43	−93.2	152	348
2	DMF	AIBN	60	100	78	55 000	1.76	−97.5	155	357
3	DMF	V-40	80	100	89	36 000	1.84	−96.4	151	355
4	DMF	DTBP	120	78	72	43 000	1.32	−96.2	140	340
5	DMF	TBHP	160	55	53	47 000	1.42	−95.1	144	*i*
6	MF	AIBN	60	*i*	87	97 000	1.96	−100.7	159	*i*
7	MF	V-40	80	*i*	87	74 000	1.73	−100.3	155	*i*
8	MF	DTBP	120	*i*	91	42 000	1.52	−94.3	145	*i*
9	MF	TBHP	160	*i*	85	13 000	1.03	−77.3	127	*i*
10	CB	AIBN	60	100	88	63 000	1.92	−102.5	155	359
11	CB	V-40	80	100	90	65 000	2.83	−101.7	153	355
12	CB	DTBP	120	100	86	106 000	2.93	−97.4	154	355
13	CB	TBHP	150	100	86	69 000	2.71	−95.3	153	355

[a] DMF; *N*,*N*-dimethylformamide, MF; *N*-methylformamide, CB; chlorobenzene. [b] AIBN; 2,2′-azobis(isobutyronitrile), V-40; 1,1′-azobis(cyclohexanecarbonitrile), DTBP; di-*tert*-butyl peroxide, TBHP; *tert*-butyl hydroperoxide. [c] Determined by ^{1}H NMR. [d] Ether-insoluble part. [e] Estimated by GPC based on polystyrene standards, eluent; LiBr solution in DMF (5.8 mM). [f] Measured by a polarimeter at 25 °C (*c* 1.00, $CHCl_3$). [g] Determined by DSC. [h] Determined by TGA under nitrogen. [i] Not determined.

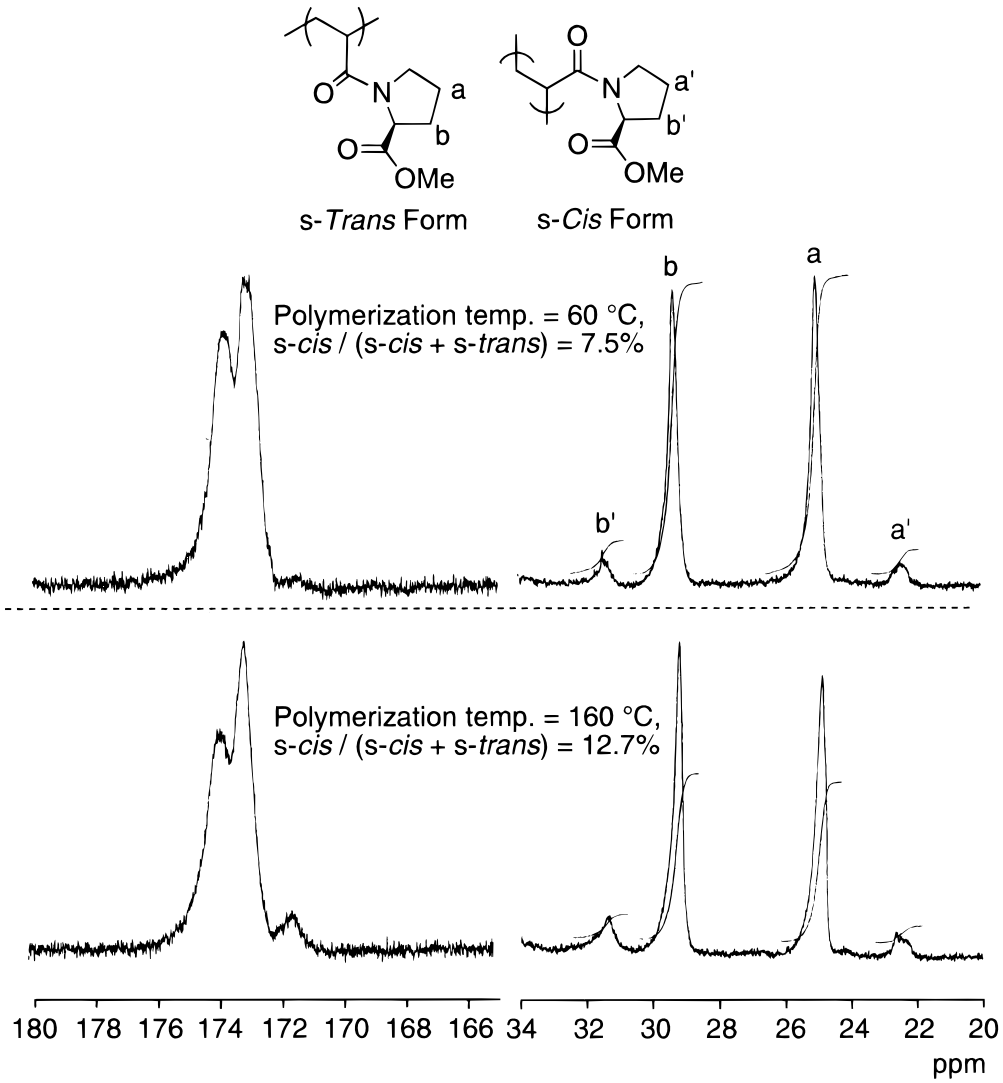

Figure 2. Effect of polymerization temperature on the s-*cis*/s-*trans* ratio of poly(A-P-M). ^{13}C NMR spectra (solvent $CDCl_3$, 125 MHz) of poly(A-P-M) obtained in the polymerizations in DMF (1 M) for 20 h at 60 and 160 °C in the presence of 1 mol % of AIBN and TBHP (runs 2 and 5 in Table 1), respectively.

polymerization temperature was raised, while the yield of the polymer was independent of the polymerization temperature (runs 6−9). In these cases, $|[\alpha]_D|$ and T_g tended to decrease with M_n. In CB, the yield and M_n of the polymer were independent of the polymerization temperature, while $|[\alpha]_D|$ decreased as the temperature was raised (runs 10−13). The s-*cis*/s-*trans* ratios of the proline units in the polymers were estimated by ^{13}C NMR spectroscopy to examine the assumption that the s-*cis*−s-*trans* isomerization of the proline moiety might affect the polymerization behavior. Figure 2 illustrates the carbonyl carbon and pyrrolidine ring carbon regions

Table 2. s-*Cis* and s-*Trans* Ratio of Poly(A-P-M) Obtained in the Radical Polymerizations of A-P-M in DMF and CB at 60 and 160 °C (Polymerizations Carried Out in 1 M Monomer Concentration for 20 h at 60 and 160 °C in Presence of 1 mol % of AIBN and TBHP, Respectively)

				CD band[b]	
run	polymerization temp (°C)	polymerization solvent	s-*cis*/(s-*cis* + s-*trans*)[a] (%)	λ_{max} (nm)	[θ] at λ_{max} (deg·cm^2/dmol)
1	60	DMF	7.5	235	1174
2	60	CB	5.6	230	3431
3	160	DMF	12.7	230	3348
4	160	CB	10.7	230	3342

[a] Determined by ^{13}C NMR spectra (solvent $CDCl_3$, 125 MHz). [b] Measured in 2,2,2-trifluoroethanol with 5 mM concentration at room temperature. λ_{max} and [θ] at λ_{max} of *N*-isobutyryl-L-proline methyl ester were 226 nm and 2211 deg·cm^2/dmol, respectively.

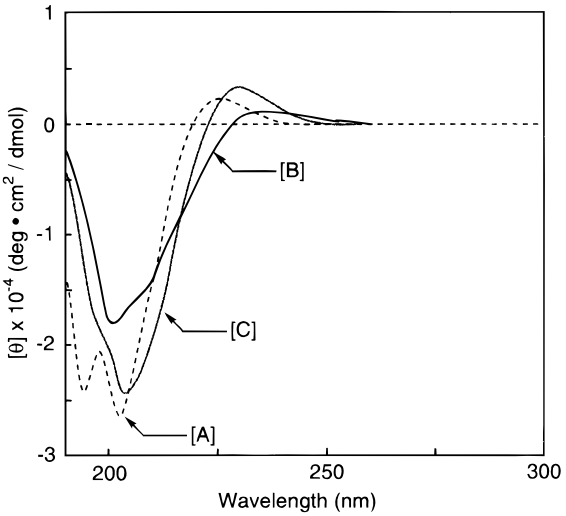

Figure 3. CD spectra (measured in 2,2,2-trifluoroethanol with 5 mM concentration at room temperature) of [A] *N*-isobutyryl-L-proline methyl ester and poly(A-P-M) obtained in the polymerizations in DMF at [B] 60 and [C] 160 °C (runs 2 and 5 in Table 1).

in the ^{13}C NMR spectra of the polymers obtained in the polymerizations in DMF at 60 and 160 °C. The split signals *a*, *b*, and *a*′, *b*′ are assigned as the pyrrolidine carbons in s-*trans* and s-*cis* forms, respectively.[13] Table 2 summarizes the ratios between the s-*cis* and -*trans* forms calculated by the ^{13}C NMR integration ratio. The polymerization in both DMF and CB afforded a polymer with a larger s-*cis* content at a higher polymerization temperature. This might be reasonable because the proline moiety in the s-*cis* form increased with temperature as described above. Since the amount of the s-*cis* isomer in the polymer was lower than that exhibited in the monomer, it might be unlikely that the polymer composition was directly related to the ground-state geometry and more likely it reflected the rates for reaction of the s-*cis* and -*trans* isomers. The transition from the s-*cis* form to -*trans* one seemed to be restricted in the polymer, probably due to the polymer effect, which agreed with the smaller change of the specific rotation value of poly(A-P-M) than that of A-P-M at various temperatures, as shown in Figure 1.

CD Spectral Analysis of the Monomers, Polymers, and Model Compounds of the Polymers. Figure 3 illustrates the CD spectra of the model compound of the repeating unit of the polymer: *N*-isobutyryl-L-proline methyl ester ([A]) and poly(A-P-M) obtained in the polymerizations in DMF at 60 and 160 °C ([B] and [C]). The polymers obtained at 60 and 160 °C showed positive Cotton effects at 235 and 230 nm, which were 9 and 4 nm longer than *N*-isobutyryl-L-proline methyl ester. This result may indicate the presence of some specific structures in the polymers which are somewhat dependent on the polymerization temperature. The difference of the s-*cis* and -*trans* ratio of the proline moiety between the two polymers may be the one factor to change the CD patterns, since the polymers obtained by the polymerizations in DMF and CB at 160 °C, whose *cis*/*trans* ratios are nearly equal, showed similar positive Cotton effect with λ_{max} and [θ] at λ_{maxCD} (runs 3 and 4 in Table 2). The difference in tacticities of the polymers might also affect the CD patterns, since the carbonyl carbon signal showed different patterns in the ^{13}C NMR spectra of the polymers obtained by the polymerizations in DMF at 60 and 160 °C (Figure 2).[14]

Conclusion

In this paper, we examined the conformation of the proline-substituted acrylamide (A-P-M) and its effect on the radical polymerization behavior. The content of the s-*cis* form in the proline amide moiety and the specific rotation of A-P-M increased with the measuring temperature. When the radical polymerization of A-P-M was carried out in DMF at the temperature ranging from 60 to 160 °C, the conversion of A-P-M and the yield of the polymer decreased as the polymerization temperature was raised. From the ^{13}C NMR spectra of the polymers obtained in the polymerization at 160 °C, it was confirmed that the presence of the proline unit in the s-*cis* form was larger than that at 60 °C. The polymer contained the smaller amount of the s-*cis* unit than that expected from the s-*cis*/s-*trans* ratio of the monomer, which might suggest that the rates for the reaction of the s-*cis* and -*trans* isomers contributed more than the ground-state geometry of A-P-M. The difference of the s-*cis*/s-*trans* ratio of the proline amide moiety as well as the tacticity of the polymers would affect the CD patterns of the polymers obtained in the polymerizations at the different temperatures.

Supporting Information Available: Figure showing the ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of poly(A-P-M) obtained in the polymerization with AIBN (1 mol %) in DMF (1 M) at 60 °C for 20 h (run 2 in Table 1). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Sandström, J. *Dynamic NMR Spectroscopy*; Academic Press: London, 1982; Chapter 6.

(11) The changes in specific rotation values of *N*-methacryloyl-L-leucine methyl ester and its polymer were ±1 °C in the similar measurement, which were much smaller than that of A-P-M.

(12) We also synthesized the corresponding proline-substituted methacrylamide (MA-P-M) and examined the radical polymerization in a fashion similar to that with A-P-M. The conversion of MA-P-M was much lower than that of A-P-M (24 and 14% in the similar conditions of runs 1 and 2 in Table 1, respectively). The low polymerizability of MA-P-M might be caused by the absence of an amide hydrogen, which has been reported to increase the radical polymerizability by hydrogen bonding effect.[8b]

(13) The ^{13}C NMR signals *a*, *a*′, *b*, and *b*′ of the polymer were assigned on the basis of the ^{13}C NMR chemical shifts of A-P-M and proline, along with the paper concerning the assignment of the ^{13}C NMR signals of the s-*cis* and *trans* proline moieties (Goodman, M.; Mierke, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 3489). The corresponding signals of A-P-M to the signals *a*, *a*′, *b*, and *b*′ of poly(A-P-M) were observed at 22.5, 24.7, 29.0, and 31.3 ppm, respectively. The ^{13}C NMR signals of proline corresponding to *a* (*a*′) and *b* (*b*′) carbons of poly(A-P-M) were observed at 25.0 and 30.3 ppm (Kalinowski, H.-O.; Berger, S.; Braun, S. *Carbon-13 NMR Spectroscopy*; John Wiley & Sons: Chichester, U.K., 1988; p 229).

(14) The tacticity of the polymer could not be determined from the amide carbonyl carbon signal of poly(A-P-M) around 174 ppm in the ^{13}C NMR spectra, because the signal overlapped the ester carbonyl carbon signal.

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