Synthesis of Novel Optically Active Polymethacrylamide Having L-Leucine Structure in the Side Chain

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Various vinyl monomers having α-amino acid moieties in the side chains have been reported.[1] Unique polymerization behavior, structure, and properties of the polymers based on the chirality will be expected. L-Leucine, one of the essential amino acids, has a strong hydrophobic nature caused by its isobutyl group, and it plays an important role in α-helix formation and stabilization of peptides and proteins.[2] Meanwhile, its corresponding polymer poly(L-leucine) shows several useful properties. Poly(L-leucine) can form α-helix by itself,[3] and, therefore, it has been examined as biocompatible materials such as artificial skin,[4] fiber,[5] and so on. Poly(L-leucine) catalyzes asymmetric epoxidation of chalcone with approximately quantitative optical purity.[6] Peptides consisting of L-leucine and L-lysine show artificial enzymatic behavior in decarboxylation of oxaloacetate.[7] As described above, polymers consisting of L-leucine structure are intended to show novel properties. In this paper, synthesis, radical polymerization of methacrylamide having L-leucine methyl ester structure in the side chain, *N*-methacryloyl-L-leucine methyl ester (MLM), the curious optical property, and the monomer reactivity ratios with methyl methacrylate (MMA) are described.

The monomer MLM was prepared by the reaction of L-leucine methyl ester with methacryloyl chloride in the presence of triethylamine in 62% yield (Scheme 1). MLM (mp 39–41 °C, $[\alpha]^{27}_D$ +1.3° (*c* 1.00, $CHCl_3$)) was obtained as a colorless needlelike crystal by column chromatographic purification. The structure was determined by its spectral and analytical data.[8]

Radical polymerization of MLM was carried out in the presence of 2,2′-azobis(isobutyronitrile) (AIBN; 1 mol%) at 60 °C for 20 h in bulk, chlorobenzene, and DMF. *n*-Hexane-insoluble polymer was obtained as a white fibrous solid. The structure of the obtained polymer was determined as poly(MLM) (PMLM) by its ^{1}H NMR spectrum (Figure 1). The tacticity of PMLM could not be determined because of the overlap of the signals derived from methyl protons in the main chain and those in the leucine side chain.

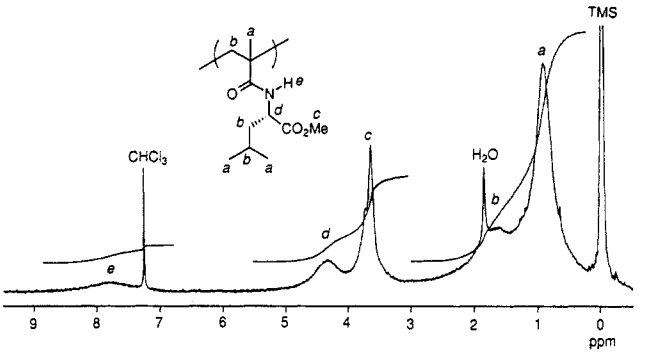
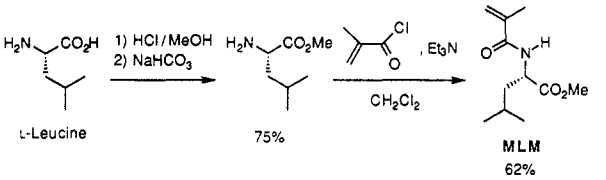
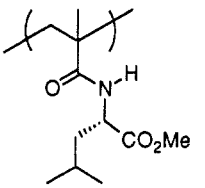


Figure 1. ^{1}H NMR spectrum of PMLM (run 1 in Table 1, solvent $CDCl_3$, 90 MHz).

Scheme 1





PMLM

The results and conditions of the polymerizations of MLM are summarized in Table 1. The molecular weight and its distribution were determined by gel permeation chromatography (GPC) using a LiBr/DMF solution (5.8 mM) as an eluent by comparison to polystyrene standard samples. Intense tailing of chromatographic peaks of the polymers was observed in GPC measurement using tetrahydrofuran as an eluent. The molecular weight of the polymer obtained in the bulk polymerization (run 1) was higher than those of the solution polymerization (runs 2 and 3). The value of 372 000 for $\bar{M}_n$ (run 1) seems to be high considering the initiator percent.[9] The glass transition temperature (T_g) of PMLM was relatively high (160–165 °C), similar to other polymers obtained from *N*-monosubstituted methacrylamides such as poly(*N*-*tert*-butylmethacrylamide)[10] and poly[*N*-[4-(alkoxycarbonyl)phenyl]methacrylamide].[11] The 10% weight loss temperature ($T_{d_{10}}$) of PMLM under nitrogen was 302–317 °C. It is quite interesting that both inversion and increase of the absolute value of specific rotation in the transformatiom from MLM (+1.3°) to PMLM (−35.7 to −42.2°) were observed. Since the specific rotation of the analogue of the monomer unit in the polymer chain, *N*-pivaloyl-L-leucine methyl ester was as small (−1.6°) as that of MLM, some kind of stereostructure of PMLM should cause the large specific rotation of PMLM as reported in polymerizations of optically active α-olefins.[12]

Copolymerization parameters r_1 and r_2 of MLM (M_1) and MMA (M_2) were examined by copolymerizations in chlorobenzene (1 M) using AIBN (1 mol %) as an

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Table 1. Radical Polymerization of MLM[a]

run	solvent[b] (M)	yield[c] (%)	$\bar{M}_n$[d]	$\bar{M}_w/\bar{M}_n$[d]	T_g[e] (°C)	$T_{d_{10}}$[f] (°C)	$[\alpha]_D$[g] (deg)
1	none	77	372 000	1.78	162	317	−35.7
2	CB (1)	85	49 000	2.24	165	317	−40.5
3	DMF (1)	61	38 000	1.56	160	302	−42.2

[a] Conditions: monomer, 3 mmol; initiator, 2,2′-azobis(isobutyronitrile)(AIBN), 1 mol%; 60 °C; 20 h. [b] CB = chlorobenzene, DMF = *N,N*-dimethylformamide. [c] *n*-Hexane-insoluble part. [d] Estimated by GPC based on polystyrene standards; eluent, LiBr in DMF (5.8 mM). [e] Determined by DSC. [f] Determined by TGA under nitrogen. [g] Measured by polarimeter at 27 °C (*c* 1.00, $CHCl_3$).

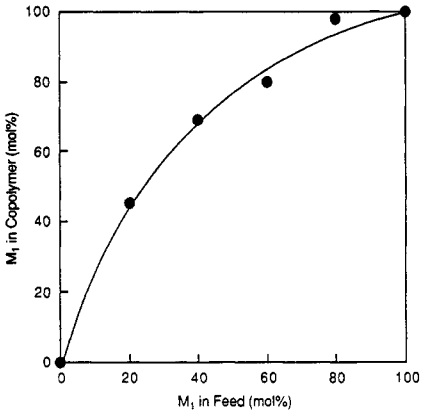

Figure 2. Copolymer composition curve of MLM (M_1) and MMA (M_2): (●) experimental points; (—) calculated curve using the copolymerization parameters $r_1 = 3.531$ and $r_2 = 0.364$.

initiator at 60 °C for 8 min. The conversions of the monomers were kept below 6% in every case to facilitate the determination of the parameters. The compositions of the obtained copolymers were determined by the integration ratio of the $CHCO_2CH_3$ proton (4.4 ppm) of the MLM unit to CO_2CH_3 protons of both units (MLM, 3.7 ppm; MMA, 3.6 ppm) in the ^1H NMR spectra. The copolymerization parameters r_1 and r_2 calculated by a nonlinear least-squares method[13] were estimated as 3.531 and 0.364, respectively. The monomer feed ratio–copolymer composition curve calculated using these parameters is shown in Figure 2 with the plots of the experimental data obtained. The much higher reactivity of MLM than MMA is particularly surprising in view of the fact that reactivities of the usual methacrylamide derivatives are lower than that of MMA.[14] Intermolecular interaction caused by a L-leucine unit between a propagating polymer chain and MLM should increase its reactivity. This should be one of the reasons for the high molecular weight of PMLM. Further examinations on the tacticity of the polymer, higher order structure, asymmetric induction to the main chain of the polymer, and so on are now under investigation.

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(8) Mp 39–41 °C; $[\alpha]^{27}_D$ +1.3° (*c* 1.00, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 0.96 (d, $J = 5.49$ Hz, 6 H, $CH(CH_3)_2$), 1.45–1.80 (m, 3 H, CH_2 and $CH(CH_3)_2$), 1.89–2.00 (m, 3 H, CH_3 (allyl)), 3.75 (s, 3 H, CO_2CH_3), 4.57–4.82 (m, 1 H, $CHCO_2CH_3$), 5.31–5.39 (m, 1 H, CH (olefin)), 5.70–5.78 (m, 1 H, CH (olefin)), 6.29 (br d, $J = 9.0$ Hz, 1 H, NH); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 18.57 (CH_3, allyl), 22.04 ($CH(CH_3)_2$), 22.82 ($CH(CH_3)_2$), 25.01 ($CH(CH_3)_2$), 41.68 (CH_2), 50.90 (CO_2CH_3), 52.27 ($CHCO_2CH_3$), 119.98 (CH_2=C), 139.74 (CH_2=*C*), 168.12 (C=O (ester)), 173.72 (C=O (amide)); IR (KBr) 3329 (NH), 3266 (NH), 2957 (CH), 1746 (C=O (ester)), 1657 (C=O (amide)), 1618 (C=C), 1535 (NH), 1204, 1152, 937 cm^{-1}. Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.64; H, 8.98; N, 6.55.

(9) $\bar{M}_w$ of PMLM obtained by bulk polymerization (run 1 in Table 1) determined by gel permeation chromatography–low angle laser light scattering (GPC–LALLS) was 783 000, which well agreed with $\bar{M}_w$ estimated by ordinary GPC ($\bar{M}_w$, 662 000).

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(14) For examples, reactivity ratios of methacrylamide (r_1) with MMA (r_2), *N*-methylmethacrylamide (r_1) with MMA (r_2), *N*-(methoxymethyl)methacrylamide (r_1) with MMA (r_2), and *N*-phenylmethacrylamide (r_1) with MMA (r_2) are reported as r_1, 0.49, r_2, 1.65;[a] r_1, 0.24, r_2, 1.54;[a] r_1, 0.27, r_2, 1.66;[a] and r_1, 0.63, r_2, 1.51,[b] respectively. (a) Müller, E.; Dinges, K.; Graulich, W. *Makromol. Chem.* **1962**, *57*, 27. (b) Otsu, T.; Inoue, M. *Kobunshi Ronbunshu* **1974**, *31*, 250.