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# Syntheses and Radical Copolymerization Behavior of Optically Active Methacrylamides Having L- and D-Leucine Moieties. Interaction between L- and D-Forms

**Fumio Sanda, Masafumi Nakamura, and Takeshi Endo***

*Research Laboratory of Resources Utilization, Tokyo Institute of Technology, Nagatsuta-cho, Midori-ku, Yokohama 226, Japan*

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ABSTRACT: Syntheses and radical copolymerization behavior of *N*-methacryloyl-L-leucine methyl ester (MA-(L)-L-M) and its optical isomer (MA-(D)-L-M) have been examined. From their melting points and crystal X-ray analysis, MA-(L)-L-M and MA-(D)-L-M might be suggested to form a racemic compound associated at the amide moiety by a hydrogen bond. Radical copolymerizations of MA-(L)-L-M and MA-(D)-L-M were carried out using AIBN as an initiator (1 mol %) in chlorobenzene (1 M) to afford the corresponding copolymers as *n*-hexane-insoluble parts with $\bar{M}_n$ 77 000−120 000. The conversions of the monomers were almost quantitative in any case. The $T_g$ of the copolymer having an equimolar ratio of L- and D-units was lower than those of the corresponding homopolymers, while the solubility of the copolymer in ether was higher than those of the homopolymers. The total rate of radical copolymerization of MA-(L)-L-M and MA-(D)-L-M was smaller than those of the homopolymerizations of the both monomers.

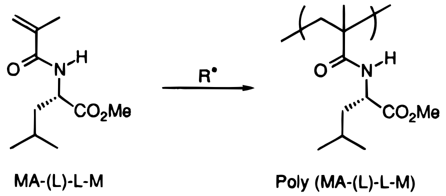
## Introduction

Various vinyl monomers having α-amino acid moieties have been reported.[1] Unique polymerization behavior, structure, and properties of the polymers based on chirality are expected. L-Leucine, one of the essential amino acids, has a strong hydrophobic nature based on its isobutyl group, and it plays an important role in α-helix formation and stabilization of peptides and proteins.[2] Poly(L-leucine) can form the α-helix by itself,[3] and therefore, it has been examined as a biocompatible material such as an artificial skin[4] and fiber.[5] We have developed amino acids and peptides as biocompatible materials as well as optical and chemical functional materials.[6] Recently, we have reported the synthesis and radical polymerization of a methacrylamide having an L-leucine methyl ester structure, *N*-methacryloyl-L-leucine methyl ester (MA-(L)-L-M) (Scheme 1).[7] The radical polymerization behavior of MA-(L)-M was unique and interesting. Namely, both inversion and increase of absolute value of specific rotation in the transformation from MA-(L)-L-M (+1.3 °) to poly(MA-(L)-L-M) (−35.7 °) could be observed. Moreover, the monomer reactivity ratio of MA-(L)-L-M was larger than that of methyl methacrylate, which is atypical for methacrylamides. Natural amino acids have the L-form, while in chemical syntheses, L- and D-amino acids form equivalently. The chirality of organic compounds is important, especially for drugs, and asymmetric synthesis draws much attention in organic chemistry. Therefore, the study of the polymerizations of L- and D-monomers, which are prepared from L- and D-amino acids, is important not only in polymer synthesis but also in organic synthesis. In this paper, the syntheses and radical copolymerization behavior of methacrylamides having L- and D-leucine methyl ester structures in the side chain (MA-(L)-L-M and MA-(D)-L-M) are described.

## Experimental Section

**Measurements.** $^1$H and $^{13}$C NMR spectra were recorded on JEOL JNM EX-90 and EX-400 spectrometers using tetramethylsilane (TMS) as an internal standard in deuterochloroform ($CDCl_3$) or benzene-$d_6$. FT-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 sodium lamp as a light source. Single crystal X-ray structure analysis was performed on a Rigaku AFC-5R system. Elemental analyses were performed on a Yanaco CHN Corder MT-5. Molecular weights ($\bar{M}_n$) and the distributions ($\bar{M}_w/\bar{M}_n$) were estimated by gel permeation chromatography (GPC) on a Tosoh HPLC HLC-8020 system with a data processor, equipped with four polystyrene gel columns (TSK gel, G6000H, G5000H, G4000H, and G2500H), using DMF (5.8 mM lithium bromide solution) as an eluent at a flow rate 1.0 mL/min, polystyrene calibration, and refractive index (RI) and ultraviolet (UV) detectors. Thermal analyses were performed on Seiko Instruments TG/DTA220 and DSC220C. The glass transition temperature ($T_g$), determined by differential scanning calorimetry (DSC), was taken as an inflection point on a trace at a heating rate of 10 °C/min. The 10% weight loss temperature ($T_{d10}$) was determined by thermogravimetric analysis (TGA) at a heating rate of 10 °C/min under a nitrogen atmosphere.

**Scheme 1**



**Materials.** 1-Ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDC·HCl) was a gift from Eiweiss Chemical Corp. Initiator, 2,2′-azobis(isobutyronitrile) (AIBN, Tokyo Kasei Kogyo Co.), was used as received. Chlorobenzene was distilled over calcium hydride after washing with concentrated sulfuric acid, aqueous sodium hydrogen carbonate, and water. *N,N*-Dimethylformamide (DMF) was distilled over calcium hydride.

**Synthesis of L-Leucine Methyl Ester Hydrochloride.** Thionyl chloride (40 mL, 550 mmol) was added dropwise to methanol (150 mL, 3.7 mol) at −10 °C. After stirring for 10 min, L-leucine (20 g, 110 mmol) was added to the solution, and the resulting mixture was stirred for 15 h at room temperature. The reaction mixture was concentrated by rotary evaporation, and the residue was precipitated with a large amount of ether to afford a white solid. The solid was filtered

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* To whom all correspondence should be addressed.

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off and dried under reduced pressure: yield 95%, $^1$H NMR $\delta$ (90 MHz, $CDCl_3$) 0.99 (d, $J$ = 5.72 Hz, 6 H, $CH(CH_3)_2$), 1.79−2.08 (m, 3 H, $-CH_2CH<$), 3.81 (s, 3 H, $CO_2CH_3$), 4.06−4.24 (m, 1 H, $>CHCH_2-$), 8.82 (br s, 3 H, $-NH_3$) ppm; IR (KBr) 2959, 1740 (C=O), 1591, 1510, 1251, 1231) cm$^{-1}$.

**Synthesis of D-Leucine Methyl Ester Hydrochloride.** The title compound was prepared from D-leucine similarly to L-leucine methyl ester hydrochloride (yield 96%). $^1$H NMR and IR spectra were similar to those of L-leucine methyl ester hydrochloride.

**Synthesis of *N*-Methacryloyl L-Leucine Methyl Ester (MA-(L)-L-M).** A solution of L-leucine methyl ester hydrochloride (20 g, 110 mmol), triethylamine (15.3 mL, 110 mmol), methacrylic acid (9.47 g, 110 mmol), and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (23.2 g, 120 mmol) in dichloromethane (200 mL) was stirred at room temperature for 10 h. The reaction mixture was washed with water (200 mL × 2), aqueous hydrochloric acid (1 M, 200 mL × 2), saturated aqueous sodium hydrogen carbonate (200 mL × 2), and water (200 mL × 1). The organic layer was separated and dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The residue was purified by recrystallization from *n*-hexane/ethyl acetate: yield 84%; mp 40−41 °C; $[\alpha]^{23}_D$ +3.0 ° ($c$ 1.00, $CHCl_3$); $^1$H NMR (90 MHz, $CDCl_3$) $\delta$ 0.95 (d, $J$ = 5.72 Hz, 6 H, $CH(CH_3)_2$), 1.47−1.80 (m, 3 H, $CH_2CH<$), 1.95−1.99 (m, 3 H, $CH_2{=}C(CH_3)$), 3.74 (s, 3 H, $CO_2CH_3$), 4.57−4.82 (m, 1 H, $>CHCO_2CH_3$), 5.31−5.39 (m, 1 H, $CH_2{=}C(CH_3)$), 5.70−5.78 (m, 1 H, $CH_2{=}C(CH_3)$), 6.42 (br d, $J$ = 7.9 Hz, 1 H, >NH); $^{13}$C NMR (22.5 MHz, $CDCl_3$) $\delta$ 18.57 ($CH_2{=}C(CH_3)$), 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 ($CH_2{=}C(CH_3)$), 139.74 ($CH_2{=}C(CH_3)$), 168.12 (>C=O (ester)), 173.72 (>C=O (amide)). IR (KBr) 3329 (N−H), 3266 (N−H), 2957 (C−H), 1746 (C=O (ester)), 1657 (C=O (amide)), 1618 (C=C), 1535 (N−H), 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.

**Synthesis of *N*-Methacryloyl D-Leucine Methyl Ester (MA-(D)-L-M).** The title compound was prepared from D-leucine methyl ester hydrochloride similarly to MA-(L)-L-M: yield 89%; mp 40−41 °C; $[\alpha]^{23}_D$ −3.0 ° ($c$ 1.00, $CHCl_3$). $^1$H NMR and IR spectra were similar to those of MA-(L)-L-M. Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.95; H, 8.98; N, 6.57. Found: C, 61.82; H, 9.18; N, 6.54.

**Radical Copolymerization of MA-(L)-L-M and MA-(D)-L-M.** To the monomers (total 3 mmol) in a polymerization tube was introduced AIBN (4.9 mg, 0.03 mmol), and subsequently chlorobenzene (3 mL). The tube was cooled, degassed, sealed off, and heated at 60 °C for 20 h. The resulting mixture was diluted with chloroform (3 mL) and poured into *n*-hexane (200 mL) to precipitate a polymer. The *n*-hexane-insoluble polymer was filtrated and dried at 60 °C in vacuo overnight. $^1$H NMR $\delta$ ($CDCl_3$) 8.1−7.4 (m, 1 H), 4.7−4.0 (m, 1 H), 3.9−3.6 (m, 3 H), 2.3−0.8 (m, 14 H) ppm.

**Molecular Orbital Calculations.** Semi empirical MO calculations were done on an Apple Power Macintosh 7100/80$_{AV}$ equipped with a 40 MIPS CXP coprocessor board with use of SONY Tektronix CAChe MOPAC 94 version 3.7, using the PM3 Hamiltonian. Ab initio MO calculations were done on a silicon Graphics 4D INDY with use of Biosym Technologies Turbomole version 2.3.

## Results and Discussion

**Monomer Syntheses.** The monomers, MA-(L)-L-M and MA-(D)-L-M, were prepared by the condensation reactions of methacrylic acid with L- and D-leucine methyl ester hydrochlorides, using EDC·HCl as a condensation reagent. L- and D-leucine methyl ester hydrochlorides were prepared by the reactions of L- and D-leucine with methanol in the presence of thionyl chloride (Scheme 2). MA-(L)-L-M and MA-(D)-L-M were purified by recrystallization from *n*-hexane/ethyl acetate. The optical isomers showed the same melting point (40−41 °C) and specific rotations of the opposite sign. The structures were determined by their spectral and analytical data.

**Scheme 2**

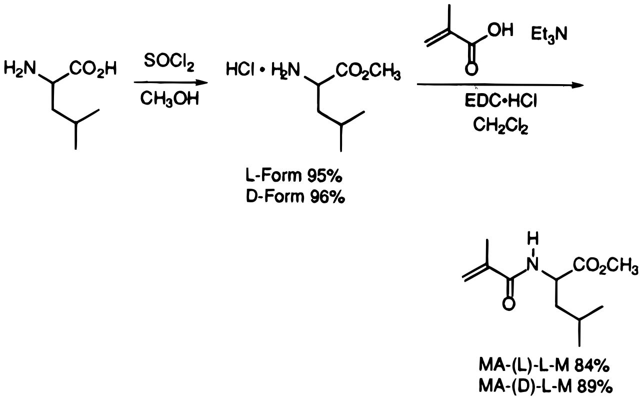

**Table 1. Specific Rotation and Melting Point of the Mixture of MA-(L)-L-M and MA-(D)-L-M**

| run | composition MA-(L)-L-M:MA-(D)-L-M | $[\alpha]^{21}_D$ $^a$ (deg) | mp$^b$ (°C) |
|---|---|---|---|
| 1 | 100:0 | +3.0 | 40−41 |
| 2 | 80:20 | | 35−67 |
| 3 | 60:40 | | 40−78 |
| 4 | 50:50 | 0 | 81−83 |
| 5 | 40:60 | | 40−79 |
| 6 | 20:80 | | 37−70 |
| 7 | 0:100 | −3.0 | 40−41 |

$^a$ Measured by polarimeter ($c$ 1.00, $CHCl_3$). $^b$ Measured by a micro melting point apparatus.

The specific rotations and melting points of the mixture of MA-(L)-L-M and MA-(D)-L-M in several compositions are summarized in Table 1. The mixtures of the L- and D-forms were prepared by evaporation of homogeneous solutions of L- and D-forms in chloroform. The ranges of melting points of the L- and D-forms (runs 1 and 7), and the equimolar mixture of L- and D-forms (run 4) were narrow (1−2 °C), while those of the other mixtures (runs 2, 3, 5, and 6) were wide (32−39 °C). The melting point of the equimolar mixture was higher by 41 °C than those of the L- and D-forms. This result suggests the formation of a racemic compound of L- and D-forms. X-ray analysis was carried out for a single crystal obtained by recrystallization of the equimolar mixture to confirm the formation of the racemic compound (Figure 1). L- and D- forms were confirmed to associate with each other by a hydrogen bond at the amide moieties (1.94 Å distance).

**Molecular Orbital Calculation.** Semiempirical and ab initio molecular orbital calculations were carried out to obtain the heats of formation of MA-(L)-L-M and MA-(L)-L-M/MA-(D)-L-M associate. The geometry which was obtained from the single crystal X-ray analysis was used as an initial one for the calculations. The results of the calculations are summarized in Table 2. The MA-(L)-L-M/MA-(D)-L-M associate was more stable by 2.83 kcal/mol [=−16.09 × 2 − (−35.01)] for PM3 and by 4.52 kcal/mol [=(−697.5617 × 2 − (−1395.1306)) × 627.5] for STO-3G than the system in which MA-(L)-L-M and MA-(D)-L-M existed separately. Figure 2 illustrates the heat of formation of a supermolecule consisting of MA-(L)-L-M and MA-(D)-L-M, which was calculated from 1.5 to 4.0 Å distance with 0.1 Å increments between the N−H hydrogen of MA-(L)-L-M and the amide carbonyl oxygen of MA-(D)-L-M. The total heat of formation showed a minimum at 1.9 Å distance for N−H···O=C, which well agreed with the result of single crystal X-ray

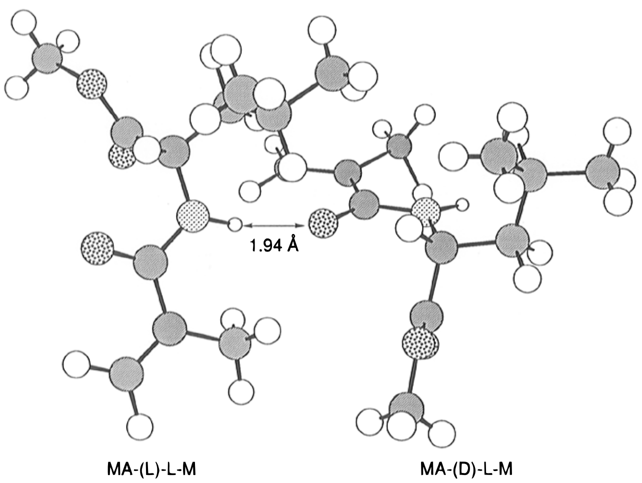

**Figure 1.** Crystal structure of the associate of MA-(L)-L-M and MA-(D)-L-M obtained by X-ray analysis.

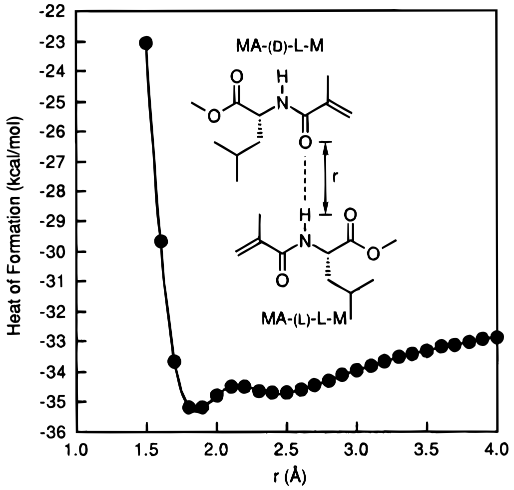

**Figure 2.** Intermolecular distance of MA-(L)-L-M and MA-(D)-L-M vs heat of formation of the total system.

**Table 2. Heat of Formation or Total Energy of MA-(L)-L-M/MA-(D)-L-M Associate and MA-(L)-L-M**

| method | MA-(L)-L-M/MA-(D)-L-M associate | MA-(L)-L-M |
|---|---|---|
| PM3 | −35.01 kcal/mol | −16.09 kcal/mol |
| STO-3G | −1395.1306 Hartree | −697.5617 Hartree |
| 6-31G** | | −706.5310 Hartree |

analysis (1.94 Å). In conclusion, MA-(L)-L-M and MA-(D)-L-M were confirmed to form a racemic compound by hydrogen bonding of the amide moiety.

**Radical Copolymerization of MA-(L)-L-M and MA-(D)-L-M.** Radical copolymerizations of MA-(L)-L-M and MA-(D)-L-M were carried out in the presence of 1 mol % of 2,2′-azobis(isobutyronitrile) (AIBN) at 60 °C in chlorobenzene. The results of the copolymerizations are summarized in Table 3. The obtained polymers were isolated by reprecipitation with *n*-hexane. Both the conversion of the total monomers and the yield of the copolymer were nearly quantitative. The molecular weight of the copolymer was 77 000−120 000. The structure of the obtained copolymer was determined by $^1$H NMR spectra. A linear relationship was observed between the monomer feed ratio and the specific rotation of the copolymer, while the $T_g$ of the copolymer having an equimolar ratio of L- and D-units was lower than those of the homopolymers (Figure 3). The difference between the $T_g$ values of the homopolymer and copolymer might be caused by the difference in rigidness of the polymers. Figure 4 illustrates the relationship between MA-(L)-L-M in feed vs recovery of the copolymer as an ether-insoluble part. The triad tacticity of the polymer was estimated by $^{13}$C NMR as syndio:hetero:iso = 46:41:13;[8] the isotactic ratio was slightly larger than for poly(methyl methacrylate) obtained by radical polymerization under similar conditions (syndio:hetero:iso = 59:36:5). Both of the ether-soluble and

**Table 3. Radical Copolymerization of MA-(L)-L-M and MA-(D)-L-M[a]**

| run | monomer (L):(D) | conv.[b] (%) | yield[c] (%) | $\bar{M}_n$[d] | $\bar{M}_n/\bar{M}_n$[d] | $T_g$[e] (°C) | $[\alpha]^{27}{}_D$[f] (deg) |
|---|---|---|---|---|---|---|---|
| 1 | 100:0 | 96 | 91 | 120 000 | 2.34 | 160 | −34.4 |
| 2 | 80:20 | 95 | 93 | 95 000 | 2.04 | 133 | −21.8 |
| 3 | 60:40 | 96 | 90 | 85 000 | 2.13 | 129 | −6.8 |
| 4 | 50:50 | 95 | 88 | 79 000 | 2.12 | 125 | 0 |
| 5 | 40:60 | 95 | 92 | 77 000 | 1.83 | 120 | +8.0 |
| 6 | 20:80 | 96 | 92 | 83 000 | 2.28 | 140 | +22.5 |
| 7 | 0:100 | 97 | 91 | 100 000 | 2.33 | 164 | +37.3 |

[a] Conditions: monomer, 3 mmol; initiator, 2,2′-azobis(isobutyronitrile) (AIBN), 1 mol %; solvent, chlorobenzene, 3 mL; 60 °C; 20 h. [b] Determined by $^1$H NMR. [c] *n*-Hexane-insoluble part. [d] Estimated by GPC on the basis of the polystyrene standard; eluent, LiBr solution in DMF (5.8 mM). [e] Determined by DSC. [f] Measured by polarimeter (*c* 1.00, $CHCl_3$).

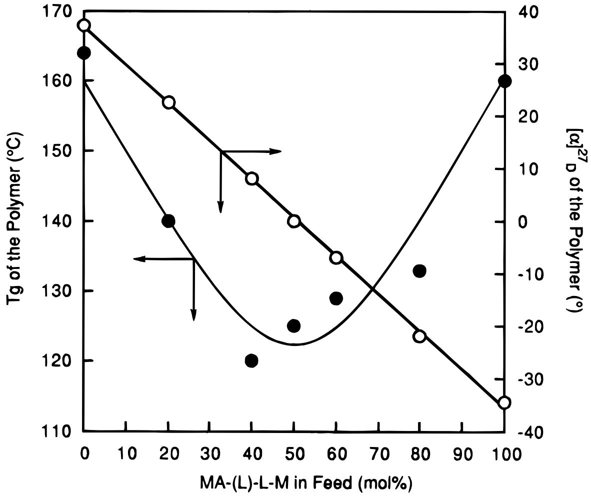

**Figure 3.** MA-(L)-L-M in feed vs $T_g$ (●) and $[\alpha]^{27}{}_D$ (○) of the copolymer.

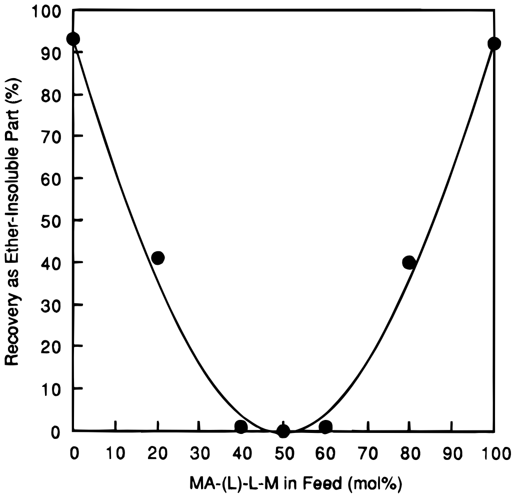

**Figure 4.** Recovery as an ether-insoluble part of the copolymer of MA-(L)-L-M and MA-(D)-L-M isolated by reprecipitation with *n*-hexane. The polymers were obtained by the polymerization summarized in Table 3.

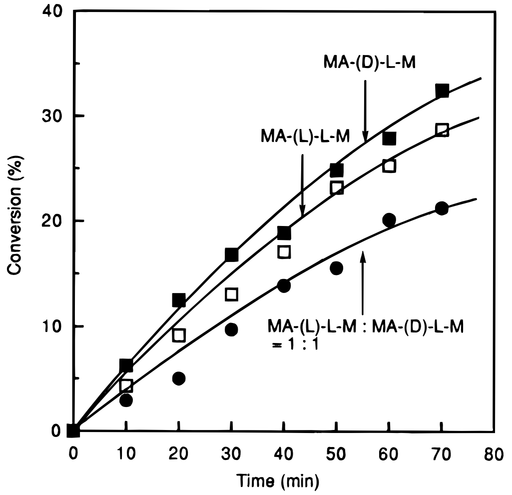

**Figure 5.** Time−conversion relationships of MA-(L)-L-M, MA-(D)-L-M, and an equimolar mixture of MA-(L)-L-M and MA-(D)-L-M in the polymerizations in benzene-$d_6$. Polymerization conditions: total monomer, 1 M; AIBN, 1 mol %; 60 °C.

insoluble polymers showed similar tacticity values and specific rotations. These results suggest that the tacticity of the polymer does not affect the solubility of the copolymers. The molecular weight of the ether-insoluble polymer was higher than that of the ether-soluble polymer.[9] The drastic differences of the solubilities of the homopolymer and copolymer in ether may also suggest the difference of the rigidness. Interaction by hydrogen bonding between L- and D-units in the copolymer and/or unit sequence might affect the $T_g$ and solubility of the copolymer.[10]

As described above, the $T_g$s and solubilities of the homopolymer and copolymer of MA-(L)-L-M and MA-(D)-L-M were drastically different. Time−conversion relationships of MA-(L)-L-M, MA-(D)-L-M, and an equimolar mixture of MA-(L)-L-M and MA-(D)-L-M in the polymerizations in benzene-$d_6$ were monitored by $^1$H NMR spectra (Figure 5) to obtain some information on the interaction between the L- and D-forms. The total rate of copolymerization of MA-(L)-L-M and MA-(D)-L-M was smaller (ca. $^2/_3$) than those of the homopolymerizations. Aggregation of MA-(L)-L-M and MA-(D)-L-M might decrease the rate of copolymerization,[11] probably because the acryloyl groups of the monomers are placed in opposite directions, as shown in Figure 1. In the $^1$H NMR spectra of MA-(L)-L-M, MA-(D)-L-M, and an equimolar mixture of MA-(L)-L-M and MA-(D)-L-M, which were measured in benzene-$d_6$ (1 M) at 60 °C, the N−H proton signal of the equimolar mixture appeared at higher field in 0.02 ppm than those of MA-(L)-L-M and MA-(D)-L-M (Figure 6). The stronger hydrogen bond between the L- and D-forms than those of the L- and L- or D- and D-forms might cause the higher field shift of the N−H proton signal. In the IR spectra of MA-(L)-L-M and MA-(D)-L-M in benzene (0.5 M), the absorption derived from hydrogen bonding of N−H was observed at 3378 cm$^{-1}$, while that of the equimolar mixture of MA-(L)-L-M and MA-(D)-L-M was observed at 3372 cm$^{-1}$. This shift may strongly support the presence of a stronger interaction between L- and D-forms than between L- and L- or D- and D-forms.

## Summary

In this paper, methacrylamides having L- and D-leucine structures in the side chains, *N*-methacryloyl L- and D-leucine methyl esters (MA-(L)-L-M and MA-(D)-L-M), were synthesized, and their radical copolymerization behavior was examined. The higher melting point of an equimolar mixture of MA-(L)-L-M and MA-(D)-L-M (81−83 °C) than that of each monomer (40−41 °C) and single crystal X-ray analysis confirmed the formation of a racemic compound of L- and D-forms which aggregated at amide N−H and carbonyl moieties by hydrogen bonding. The racemic compound was estimated to be stabilized by 2.83 and 4.52 kcal/mol by PM3 and ab initio calculations, respectively. The radical copolymerization proceeded in nearly quantitative conversion to yield the corresponding copolymer. A linear relationship was observed between the monomer feed ratio and the specific rotation of the copolymer, while the $T_g$ of the copolymer having an equimolar ratio of L- and D-units was lower than those of the homopolymers. Moreover, the solubility of the copolymer having equimolar units of L- and D-forms was drastically higher than those of the homopolymers. Interaction by hydrogen bonding between L- and D-units in the copolymer and/or unit sequence might affect the $T_g$ and solubility of the copolymer. The total rate of copolymerization of MA-(L)-L-M and MA-(D)-L-M was smaller (ca. $^2/_3$) than those of the homopolymerizations, probably due to the aggregation of the L- and D-forms, which was supported by the $^1$H and IR spectra.

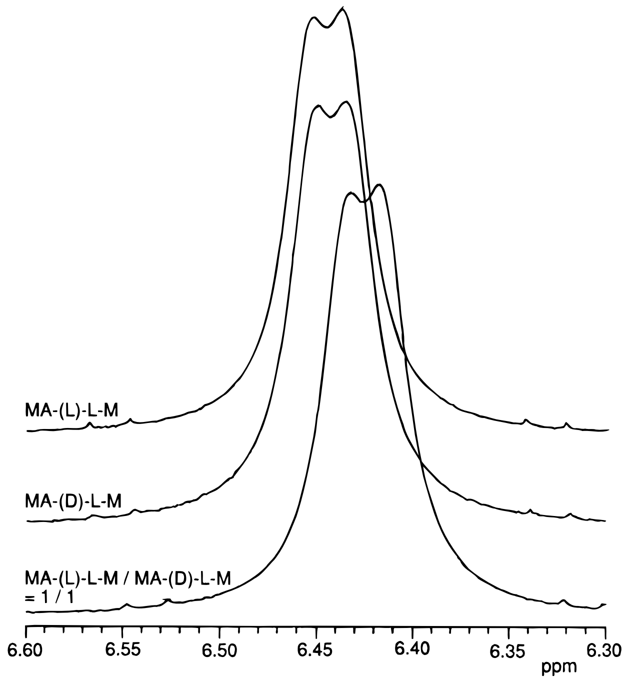

**Figure 6.** N−H signals in the $^1$H NMR spectra of MA-(L)-L-M, MA-(D)-L-M, and an equimolar mixture of MA-(L)-L-M and MA-(D)-L-M in benzene-$d_6$ (1 M) measured at 60 °C.

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