Highly Radical-Polymerizable Methacrylamide Having Dipeptide Structure. Synthesis and Radical Polymerization of *N*-Methacryloyl-L-leucyl-L-alanine Methyl Ester

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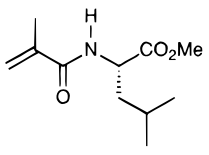
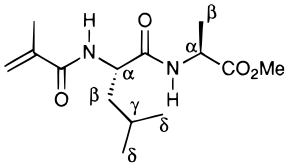
ABSTRACT: Synthesis and radical polymerization of methacrylamide having an L-leucyl-L-alanine methyl ester structure, *N*-methacryloyl-L-leucyl-L-alanine methyl ester (MA-LA-M), were carried out. Radical polymerization of MA-LA-M in the presence of AIBN (1 mol %) in chlorobenzene (1.0 mol/L) afforded the corresponding polymer (poly(MA-LA-M)) with $\bar{M}_n$ 196 000. The 10% weight loss temperature of poly(MA-LA-M) under nitrogen was 300 °C. Increase of the absolute value of specific rotation in the transformation from MA-LA-M (−48.0°) to poly(MA-LA-M) (−76.5°) could be observed. The rate of radical polymerization of MA-LA-M was 4−6 times larger than that of *N*-methacryloyl-L-leucine methyl ester (MA-L-M) in benzene-d_6 (1.0 mol/L), whereas the activation energy (E_a) of MA-LA-M (51.4 kJ/mol) was larger than that of MA-L-M (29.7 kJ/mol). The absolute value of the activation entropy ($\Delta S^{\ddagger}$) in the radical polymerization of MA-LA-M (−144 J/(K·mol)) was smaller than that of MA-L-M (−221 J/(K·mol)). These parameters for the both monomers were nearly equal in the polymerizations in DMSO-d_6. From the IR and ^{1}H NMR analyses, MA-LA-M in benzene might be suggested to be more strongly aggregated each other by intermolecular hydrogen bonds than MA-L-M.

Introduction

Synthetic peptides are important in the field of medicines, foods, fibers, and so on, since they show high biocompatibility and optical activity. Peptides generally form inherent high ordered structures and show various characteristic functions based on the amino acid composition and sequence. As an application of peptides having useful properties described above, various vinyl monomers bearing peptide moieties in the side chain have been synthesized, and the corresponding polymers have been expected as functional materials.[1] We have already reported that methacrylamide having L-leucine methyl ester structure, *N*-methacryloyl-L-leucine methyl ester (MA-L-M), shows high radical polymerizability in bulk, and both inversion and increase of the absolute value of specific rotation in the transformation before and after the polymerization.[2] In this paper, synthesis and radical polymerization behavior of methacrylamide having dipeptide structure, *N*-methacryloyl-L-leucyl-L-alanine methyl ester (MA-LA-M), are disclosed. In addition, the difference of radical polymerizabilities between MA-LA-M and MA-L-M is discussed based on the effect of aggregation by intermolecular hydrogen bonds on radical polymerization. The sequence, L-leucyl-L-alanine (LA) is interesting since a series of oligopeptides Nps-$(LA)_n$-OEt have been prepared and the relationship between the chain length of the peptides and the higher order structure has been studied.[3]



MA-L-M



MA-LA-M

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Experimental Section

Measurements. ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM EX-90 and EX-400 spectrometers using tetramethylsilane (TMS) or hexamethyldisiloxane as an internal standard in deuteriochloroform ($CDCl_3$), deuteriobenzene (benzene-d_6), or deuteriodimethyl sulfoxide (DMSO-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. Molecular weights ($\bar{M}_n$) and its 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 of 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) 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.

Materials. *N*-(*tert*-Butoxycarbonyl)-L-leucine (Boc-Leu-OH), L-alanine methyl ester hydrochloride (HCl·Ala-OMe), and 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDC·HCl) were obtained from Eiweiss Chemical Corp. 1-Hydroxybenzotriazole (HOBt), trifluoroacetic acid (TFA), and 2,2′-azobis(isobutyronitrile) (AIBN) were purchased from Tokyo Kasei Kogyo Co. Benzene was distilled over sodium. Chlorobenzene was distilled over calcium hydride after washing with concentrated sulfuric acid, aqueous sodium hydrogen carbonate, and water. *N*,*N*-Dimethylformamide (DMF) and dimethyl sulfoxide (DMSO) were distilled over calcium hydride.

Synthesis of Monomer. (A) *N*-(*tert*-Butoxycarbonyl)-L-leucyl-L-alanine Methyl Ester. To a mixture of L-alanine methyl ester hydrochloride (14.0 g, 100 mmol), triethylamine (15.6 mL, 110 mmol), *N*-(*tert*-butoxycarbonyl)-L-leucine (30.0 g, 120 mmol), and HOBt (18.4 g, 120 mmol) in dichloromethane (300 mL) was added EDC·HCl (23.0 g, 120 mmol) at 0 °C, and the resulting mixture was stirred at room temperature overnight. The reaction mixture was washed with water (200 mL), 1 M HCl (200 mL), saturated aqueous solution of $NaHCO_3$ (200

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mL), and a saturated aqueous solution of NaCl (200 mL). The organic layer was dried over anhydrous $MgSO_4$, filtrated, and concentrated by rotary evaporation. The residue was purified by recrystallization from ethyl acetate/*n*-hexane (volume ratio 1/3): yield 29.7 g (94%); mp 116−117 °C (lit.[4] 114−116 °C); $[\alpha]_D^{20}$ −32.3° (*c* 1.00 $CHCl_3$); ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.93 (d, J = 6.40 Hz, 6 H, Leu$^\delta$), 1.39 (d, J = 7.20 Hz, 3 H, Ala$^\beta$), 1.44 (s, 9 H, $(CH_3)_3CCO$), 1.50 (m, 1 H, Leu$^\gamma$), 1.66 (m, 2 H, Leu$^\beta$), 3.73 (s, 3 H, CO_2CH_3), 4.13 (broad d, Leu-NH), 4.56 (m, 1 H, Leu$^\alpha$), 4.97 (d, J = 8.00 Hz, 1 H, Ala$^\alpha$), 6.70 (broad d, J = 7.02 Hz, 1 H, Ala-NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.22 (Ala$^\beta$), 21.98 and 22.93 (Leu$^\delta$), 24.69 (Leu$^\gamma$), 28.29 ((*C*H_3)C), 41.33 (Leu$^\beta$), 47.70 (Ala$^\alpha$), 52.34 (Leu$^\alpha$), 53.00 (CO_2CH_3), 80.01 ((CH$_3$)*C*), 155.70 (C═O (urethane)), 172.26 (C═O (Ala, ester)), 173.17 (C═O (Leu, amide)); IR (KBr) 3314 (N−H), 2962 (C−H), 1755 (C═O (ester)), 1688 (C═O (urethane)), 1651 (C═O (amide)), 1552 (N−H), 1203, 1167, 951, 875, 760 cm^{-1}.

(B) *N*-Methacryloyl-L-leucyl-L-alanine Methyl Ester (MA-LA-M). To a solution of Boc-LA-M (25.0 g, 79 mmol) in dichloromethane (200 mL), at 0 °C, was added TFA (50 mL, 296 mmol), and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated by rotary evaporation and dried in vacuo. To the residual compound were added triethylamine (17.0 mL, 120 mmol), methacrylic acid (8.6 mL, 95 mmol), HOBt (14.7 g, 95 mmol), dichloromethane (200 mL), and then EDC·HCl (18.5 g, 95 mmol) at 0 °C, and the resulting mixture was stirred at room temperature overnight. The reaction mixture was washed with water (200 mL), 1 M HCl (200 mL), a saturated aqueous solution of $NaHCO_3$ (200 mL), and a saturated aqueous solution of NaCl (200 mL). The organic layer was dried over anhydrous $MgSO_4$, filtrated, and concentrated by rotary evaporation. The residue was purified by recrystallization from ethyl acetate/*n*-hexane (volume ratio 1/9): yield 20.5 g (94%); mp 156−158 °C, $[\alpha]_D^{20}$ −48.0° (*c* 1.00 $CHCl_3$); ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.89 (d, J = 4.68 Hz, 6 H, Leu$^\delta$), 1.32 (d, J = 7.30 Hz, 3 H, Ala$^\beta$), 1.61−1.67 (m, 3 H, Leu$^\beta$ and Leu$^\gamma$), 1.91 (s, 3 H, CH_3 (allyl)), 3.70 (s, 3 H, CO_2CH_3), 4.39−4.66 (m, 2 H, Leu$^\alpha$ and Ala$^\alpha$), 5.29−5.32 (m, 1 H, CH (olefin)), 5.71−5.72 (m,1 H, CH (olefin)), 6.72 (broad d, J = 8.46 Hz, 1 H, Leu-NH), 7.34 (broad d, J = 7.02 Hz, 1 H, Ala-NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.01 (Ala$^\beta$), 18.56 (CH_2═C(*C*H_3)), 22.28 and 22.89 (Leu$^\delta$), 24.85 (Leu$^\gamma$), 41.53 (Leu$^\beta$), 48.13 (Ala$^\alpha$), 51.68 (Leu$^\alpha$), 52.45 (CO_2CH_3), 120.39 (*C*H_2═C), 139.46 (CH_2═*C*), 168.27 (C═O (Ala, ester)), 171.89 (C═O (Leu, amide)), 173.11 (C═O (methacrylamide)); IR (KBr) 3295 (N−H), 2959 (C−H), 1755 (C═O (ester)), 1657 and 1651 (C═O (amide)), 1613 (C═C), 1547 (N−H), 1208, 1169, 934 cm^{-1}. Anal. Calcd for $C_{14}H_{24}N_2O_4$: C, 59.14; H, 8.51; N, 9.85. Found: C, 58.77; H, 8.36; N, 10.00.

Polymerization of MA-LA-M. To MA-LA-M (284 mg, 1.0 mmol) in a polymerization tube were introduced AIBN (1 mol %) and solvent (1.0 mL). The tube was cooled, degassed, sealed off, and heated at 60 °C for 20 h. The resulting mixture was diluted with methanol (50 mL) and precipitated with ether (300 mL). The solvent-insoluble part was filtered off and dried at 50 °C in vacuo overnight.

Measurements of Time Conversion of MA-LA-M and MA-L-M. Time conversions of MA-LA-M and MA-L-M with AIBN (1 mol %) in benzene-d_6 or DMSO-d_6 (1.0 mol/L) in degassed sealed NMR sample tubes were monitored by the ^{1}H NMR (90 MHz) spectra following the decrease of signals of olefin protons toward internal standard (hexamethyldisiloxane) at 60, 70, and 80 °C, respectively. The ^{1}H NMR spectra were measured first at room temperature. After that, the sample tube was ejected from the NMR probe, and the probe was heated to the set temperature. The time conversion measurement was started with inserting the sample tube into the probe. The conversions of the monomers were estimated based on the ^{1}H NMR spectra measured at room temperature. The kinetic parameters were reproduced within ±4%.

Results and Discussion

Synthesis of MA-LA-M. The monomer MA-LA-M was prepared by the condensation reaction of L-leucyl-L-alanine methyl ester trifluoroacetate (TFA·Leu-Ala-OMe) with methacrylic acid using EDC·HCl and HOBt as coupling reagents in the presence of triethylamine, as shown Scheme 1. TFA·Leu-Ala-OMe was prepared by the coupling reaction of L-alanine methyl ester hydrochloride (HCl·Ala-OMe) and *N*-(*tert*-butoxycarbonyl)-L-leucine (Boc-Leu-OH) using the EDC·HCl−HOBt method, followed by deprotection of Boc group by TFA. MA-LA-M was purified by recrystallization from ethyl acetate/*n*-hexane (volume ratio, 1/9). The structure of the monomer was determined by the ^{1}H and ^{13}C NMR, IR spectra, and elemental analysis.

Scheme 1

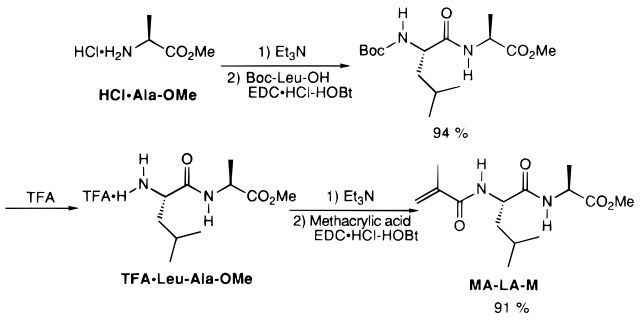
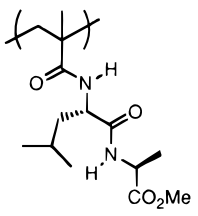


Table 1. Radical Polymerization of MA-LA-M[a]

run	solvent[b] (M)	conversion[c] (%)	yield[d] (%)	$\bar{M}_n$[e]	$\bar{M}_w/\bar{M}_n$[e]	T_{d10}[f] (°C)	$[\alpha]_D$[g] (deg)
1	benzene(1)	97	82	132 000	3.30	314	−75.5
2	CB(1)	99	88	196 000	1.76	300	−76.5
3	DMF(1)	98	90	75 000	2.22	311	−75.2
4	DMSO(1)	99	80	79 000	3.50	308	−78.9

[a] Conditions: monomer, 1 mmol; initiator, 2,2′-azobis(isobutyronitile) (AIBN), 1 mol %; 60 °C; 20 h. [b] CB = chlorobenzene, DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide. [c] Estimated by ^{1}H NMR. [d] Ether-insoluble part. [e] Estimated by GPC based on polystyrene standards; eluent, LiBr in DMF (5.8 mM). [f] Determined by TGA under nitrogen. [g] Measured by polarimeter at 25 °C (*c* 1.00, $CHCl_3$).

Radical Polymerization of MA-LA-M. Radical polymerization of MA-LA-M was carried out in the presence of AIBN (1 mol %) at 60 °C for 20 h in benzene, chlorobenzene, DMF, and DMSO (1.0 mol/L). The obtained polymer was isolated by reprecipitation with ether. The conversion of the polymerization was estimated to be 97−99% by the ^{1}H NMR. The structure of the polymer obtained was determined as poly(MA-LA-M) by its ^{1}H NMR spectrum.[5] The conditions and results of the polymerizations are summarized in Table 1. The molecular weights of the polymer obtained in the polymerizations in benzene and chlorobenzene (runs 1 and 2) were higher than those of the polymerizations in DMF and DMSO (runs 3 and 4). This result might be caused by the chain transfer reaction and decrease of aggregation by intermolecular hydrogen bond of MA-LA-M in DMF or DMSO. In the polymerization of MA-LA-M, large increase of absolute value of specific rotation in the transformation from monomer (−48.0°) to polymer (−76.5°) was observed similarly to the polymerization of MA-L-M.[2]



poly(MA-LA-M)

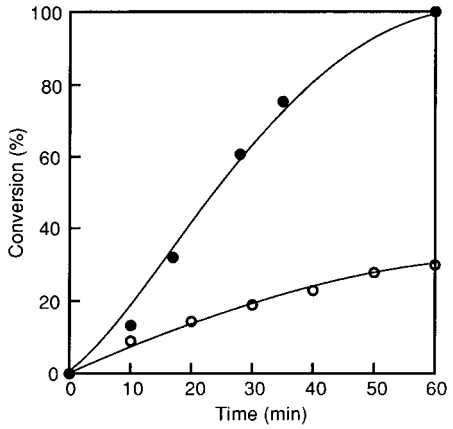


Figure 1. Time conversion relationships in the polymerizations of MA-LA-M and MA-L-M initiated by AIBN in benzene-d_6 at 60 °C: [M] = 1.0 mol/L; [AIBN] = 0.010 mol/L. (●) MA-LA-M, (○) MA-L-M.

Table 2. Polymerization Rate Constants (k) of MA-LA-M and MA-L-M[a]

temp (°C)	MA-LA-M	MA-L-M
80	13.80×10^{-3}	2.25×10^{-3}
70	8.32×10^{-3}	1.72×10^{-3}
60	4.83×10^{-3}	1.23×10^{-3}

[a] Conditions: [M] = 1.0 mol/L in benzene-d_6, [AIBN] = 0.010 mol/L.

Comparison of Radical Polymerizability of MA-LA-M and MA-L-M. Figure 1 depicts a comparison of the time conversion relationships of MA-LA-M and MA-L-M at 60 °C in benzene-d_6. It is clear that the polymerization rate of MA-LA-M is larger than that of MA-L-M. The polymerization rate constants (k) of MA-LA-M and MA-L-M at 60, 70, and 80 °C were estimated according to the following equation. The exponents of the monomer concentration (m) and initiator concentration (n) may be assumed to be 1 and 0.5, respectively.

$$k = R_p/[\mathrm{M}]^m[\mathrm{I}]^n \qquad (1)$$

The results obtained are summarized in Table 2, which show that the polymerization rate of MA-LA-M is 4−6 times larger than that of MA-L-M in benzene-d_6.

The activation energies (E_a) of radical polymerizations of MA-LA-M and MA-L-M in benzene-d_6 were calculated from the slope of the straight lines, for the relationship between log k and $1/T$ (Figure 2). The E_a of MA-LA-M (51.4 kJ/mol) was higher than that of MA-L-M (29.7 kJ/mol). The activation enthalpies ($\Delta H^{\ddagger}$) and entropies ($\Delta S^{\ddagger}$) of the both monomers at 60 °C were calculated from the k and E_a values (Table 3). The absolute value of $\Delta S^{\ddagger}$ of MA-LA-M (−144 J/(K·mol)) was smaller than that of MA-L-M (−221 J/(K·mol)). This result may suggest that MA-LA-M is more strongly aggregated each other by intermolecular hydrogen bonds in benzene than MA-L-M. The intermolecular hydrogen bond of MA-LA-M bearing dipeptide structure would be larger than that of MA-L-M. Consequently, MA-LA-M may polymerize faster than MA-L-M. Similar phenomena have been reported in the radical polymerizations of (meth)acrylic acids[6] and (meth)acrylamide derivatives,[7] namely, the rate of polymerization can be accelerated according to the association by hydrogen bond. The kinetic parameters of the radical polymerizations of MA-LA-M and MA-L-M in DMSO-d_6 were also determined to examine the solvent effect. The smaller polymerization rates of the both monomers in DMSO-d_6 than those in benzene-d_6 should be caused by the lower intermolecular interactions in DMSO-d_6 than those in benzene-d_6. The nearly equal values of E_a, $\Delta H^{\ddagger}$, and $\Delta S^{\ddagger}$ of the both monomers in DMSO-d_6 may suggest that the acceleration effect on the polymerization by aggregation is smaller in highly polar solvents such as DMSO-d_6 than in nonpolar solvents such as benzene-d_6.

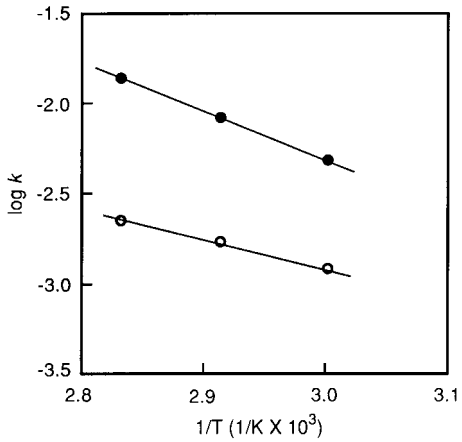


Figure 2. Relationships between log k and $1/T$ in the polymerizations of MA-LA-M and MA-L-M initiated by AIBN in benzene-d_6: [M] = 1.0 mol/L; [AIBN] = 0.010 mol/L. (●) MA-LA-M, (○) MA-L-M.

Table 3. Kinetic Parameters of MA-LA-M and MA-L-M in the Radical Polymerizations[a]

monomer	solvent	k (at 60 °C)	E_a (kJ/mol)	$\Delta H^{\ddagger}$ (kJ/mol)	$\Delta S^{\ddagger}$ (J/(K·mol))
MA-LA-M	benzene-d_6	4.83×10^{-3}	51.4	48.6	−144
MA-L-M		1.23×10^{-3}	29.7	26.9	−221
MA-LA-M	DMSO-d_6	1.19×10^{-3}	54.5	51.7	−147
MA-L-M		0.47×10^{-3}	55.5	52.8	−151

[a] Conditions: monomer concn 1 mol/L, initiator AIBN 1 mol % vs monomer. Activation enthalpies and entropies at 60 °C were calculated by the following equations. $\Delta H^{\ddagger}$: $E_a = \Delta H^{\ddagger} + RT$. $\Delta S^{\ddagger}$: $k = (\mathrm{k}T/h)\mathrm{e}^{\Delta S^{\ddagger}/R}\mathrm{e}^{-\Delta H^{\ddagger}/RT}$. R = gas constant, k = Boltzmann's constant, h = Planck's constant.

Table 4. IR Absorptions Based on Amide Moieties of MA-LA-M and MA-L-M

		wavenumber (cm^{-1})		
mononer		amide V	amide I	amide II
MA-LA-M	in benzene (1.0 mol/L)	3252	1657, 1652	1537
	in DMSO (1.0 mol/L)	3262	1662	1531
	KBr pellet	3262	1657, 1651	1537
MA-L-M	in benzene (1.0 mol/L)	3436	1672	1508
	in DMSO (1.0 mol/L)	3269	1662	1533
	KBr pellet	3260	1657	1535

IR and NMR Spectral Analyses of Hydrogen Bonds. To examine the aggregation of MA-LA-M by hydrogen bond, IR and ^{1}H NMR spectral analyses using the solvent titration method were carried out. The IR absorptions based on amide moiety of MA-LA-M and MA-L-M in benzene (1.0 mol/L) and KBr pellet measured at room temperature are summarized in Table 4. In benzene, MA-LA-M showed absorptions at 3252 (amide V region), 1657 and 1652 (amide I region), and 1537 cm^{-1} (amide II region). Since the IR absorptions of the amide group of MA-LA-M measured by the KBr pellet method (3261, 1657 and 1651, and 1537 cm^{-1} for amide V, I, and II reagions, respectively) were nearly the same as those measured in benzene, MA-LA-M should be strongly aggregated by hydrogen bonds in benzene similarly to the solid state.[8] On the other hand, MA-L-M in benzene showed IR absorptions at 3436,

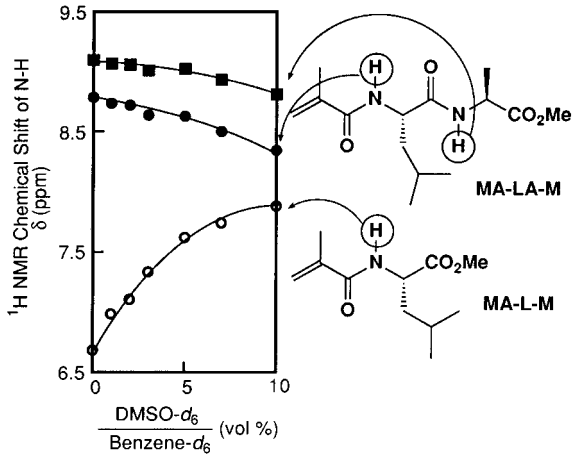


Figure 3. Solvent titration curves of NH signals of MA-LA-M and MA-L-M by ^{1}H NMR measurement in benzene-d_6 (1.0 mol/L) using DMSO-d_6 as a titrating solvent. (○) Leucine-NH (MA-L-M), (■) alanine-NH (MA-LA-M), (●) leucine-NH (MA-LA-M).

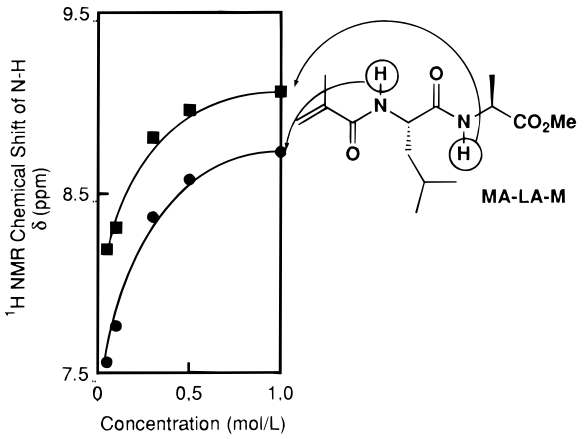


Figure 4. Concentration effect of NH signals of MA-LA-M by ^{1}H NMR measurement. (■) Alanine-NH (MA-LA-M), (●) leucine-NH (MA-LA-M).

1672, and 1508 cm^{-1}, which were much different from those measured by the KBr pellet method (3260, 1657, and 1535 cm^{-1}). These results may suggest that the hydrogen bonds of MA-LA-M in benzene are larger than that of MA-L-M. MA-LA-M has one more unit (alanine residue) capable of hydrogen bonding than MA-L-M; therefore, MA-LA-M might be able to be more aggregated by hydrogen bonds than MA-L-M in benzene. In DMSO, MA-LA-M showed IR absorptions at 3262, 1662, and 1531 cm^{-1}, and MA-L-M showed at 3259, 1662, and 1533 cm^{-1}. These results may suggest that NH of MA-LA-M or MA-L-M with S=O of DMSO form the hydrogen bonds.

Figure 3 shows solvent titration curves of NH signals of MA-LA-M and MA-L-M in benzene-d_6 (1.0 mol/L) using DMSO-d_6 as a titrating solvent. The NH signal of leucine of MA-L-M was remarkably shifted to lower magnetic field by titration with DMSO. On the other hand, both NH signals of leucine and alanine moieties of MA-LA-M were not appreciably shifted, indicating that those protons might be shielded from solvent by hydrogen bond.[9]

Next, the concentration effect on NH signals of MA-LA-M in benzene-d_6 was studied. Generally, peptides which form turn or helical structure do not show concentration effect on the NH signals of ^{1}H NMR, since each amino acid moiety forms intramolecular hydrogen bond. On the other hand, structure change of peptides from β-sheet to random coil causes a concentration effect on the NH signals of ^{1}H NMR. Namely, the signals of NH protons are shifted to higher magnetic field by increase of concentration due to intermolecular hydrogen bonds. Therefore, the remarkable shift of the NH signals of MA-LA-M to higher magnetic field in the ^{1}H NMR (Figure 4) may suggest that MA-LA-M is aggregated by intermolecular hydrogen bonds.

Conclusion

In this paper, the synthesis and the radical polymerization of methacrylamide having dipeptide structure, *N*-methacryloyl-L-leucyl-L-alanine methyl ester (MA-LA-M), were studied. MA-LA-M was prepared by the condensation of methacrylic acid with L-leucyl-L-alanine methyl ester using the EDC·HCl−HOBt method in quantitative yield. MA-LA-M showed larger radical polymerazability than methacrylamide having leucine structure, *N*-methacryloyl-L-leucine methyl ester (MA-L-M). Although the polymerization rate of MA-LA-M in benzene-d_6 was larger than that of MA-L-M, the former showed higher activation energy for polymerization than the latter. However, the absolute value of activation entropy for polymerization of MA-LA-M in benzene-d_6 was smaller than that of MA-L-M. From the IR and ^{1}H NMR spectral analyses, this was suggested to be caused by stronger aggregation of MA-LA-M than that of MA-L-M. The radical polymerizability in nonpolar solvents would be more influenced by the entropy factor, i.e., aggregation of monomers by intermolecular hydrogen bonds, rather than the activation energy.

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References and Notes

(1) (a) Maeda, M.; Inoue, S. *Makromol. Chem., Rapid Commun.* **1981**, *2*, 537. (b) Kiniwa, H.; Imanishi, Y.; Higashimura, T. *Polym. Commun.* **1983**, *24*, 188. (c) Imanishi, Y. *J. Macromol. Sci. Chem.* **1984**, *A24*, 1137. (d) Eckstein, H.; Hu, Z.; Schott, H. *Biopolymers* **1986**, *25*, 1055. (e) Komazawa, H.; Kojima, M.; Ono, M.; Saiki, I.; Azuma, I. **1993**, JP93-97699. (f) Methenitis, C.; Morcellet, J.; Pneumatikakis, G.; Morcellet, M. *Macromolecules* **1994**, *27*, 1455.

(2) Sanda, F.; Nakamura, M.; Endo, T.; Takata, T.; Handa, H. *Macromolecules* **1994**, *27*, 7928.

(3) (a) Katakai, R.; Nakayama, Y. *J. Chem. Soc., Chem. Commun.* **1977**, *22*, 805. (b) Katakai, R. *J. Chem. Soc., Perkin Trans. 1* **1979**, *4*, 905.

(4) Fujii, N.; Otaka, A.; Funakoshi, S.; Nomizu, M.; Akaji, K.; Yajima, H.; Kitagawa, K.; Akita, T.; Ando, K.; Kawamoto, T. *Chem. Pharm. Bull.* **1986**, *34*, 603.

(5) ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.6−2.3 (broad, 17 H, Leu$^{\beta,\gamma,\text{ and }\delta}$, Ala$^{\beta}$, -$CH_2$C-, and -$CCH_3$), 3.6−3.9 (broad s, 3 H, CO_2CH_3), 4.2−4.8 (broad, 2 H, Leu$^{\alpha}$ and Ala$^{\alpha}$), 6.0−6.7 (broad, 1 H, Leu-NH), 7.7−8.5 (broad, 1 H, Ala-NH).

(6) Chapiro, A. *Pure Appl. Chem.* **1972**, *30*, 77.

(7) (a) Saini, G.; Leoni, A.; Franco, S. *Makromol. Chem.* **1971**, *144*, 235. (b) Saini, G.; Leoni, A.; Franco, S. *Makromol. Chem.* **1971**, *146* 165. (c) Saini, G.; Leoni, A.; Franco, S. *Makromol. Chem.* **1971**, *147*, 213. (d) Saini, G.; Leoni, A.; Franco, S. *Makromol. Chem.* **1973**, *165*, 97.

(8) Baron, M. H.; de Lose, C.; Toniolo, C.; Fasman, C. D. *Biopolymers* **1978**, *17*, 2225.

(9) Pitner, T. P.; Urry, D. W. *J. Am. Chem. Soc.* **1972**, *94*, 1399.

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