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Tune of the helix sense of amino acid-containing poly(*N*-propargylamides) by temperature and solvent. Control by competition between structurally different units with the same chirality

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Abstract

Homo- and copolymerizations of chiral amino acid-based *N*-propargylamides, i.e., *N*-(*tert*-butoxycarbonyl)-L-alanine *N*′-propargylamide (LA) and *N*-(trifluoroacetyl)-L-valine *N*′-propargylamide (FLV), were conducted with (nbd)$Rh^+[\eta^6\text{-}C_6H_5B^-(C_6H_5)_3]$ as a catalyst to afford the corresponding copolymers with moderate molecular weights in good yields. The CD and UV–Vis spectra showed that poly(LA) and poly(FLV) take helical structures with predominantly one-handed helices, whose CD signs are opposite. The helices of the homopolymers could be tuned by temperature and solvent. The specific rotation, CD and UV–Vis spectra showed that some of the copolymers underwent temperature- and solvent-induced helix inversion.

Keywords: Polypropargylamide; Amino acid; Helix

1. Introduction

Synthesis of polymers containing amino acid and peptide moieties is a subject of much interest, since a high degree of amino acid functionality and chirality can lead to polymers with enhanced biocompatibitity, biodegradability, and the ability to form secondary structures such as α-helices and β-sheets [1]. On the other hand, the helix inversion of synthetic polymers by external stimuli has gained much attention, because such helical polymers are applicable to stimuli-responsive materials such as data storage and optical devices [2].

Polyacetylenes possess alternating double bonds in the main-chain, which endows them with special optical, electrical, and magnetic properties. Appropriately substituted polyacetylenes can take helical structures [3]. We have reported that poly(*N*-propargylamides) bearing alanine in the side-chain form a helical structure, which is stabilized by intramolecular hydrogen bonds between the amide groups in the side chains [4]. We have also found that the copolymers of *N*-(*tert*-butoxycarbonyl)-L-valine *N*′-propargylamide and *N*-(*tert*-butoxycarbonyl)-D-alanine *N*′-propargylamide undergo inversion of helix sense upon temperature change [5]. This phenomenon is based on the competition between structurally different enantiomeric amino acid moieties, whose concept has been reported in the copolymerization of chiral isocyanates by Green et al. [6].

In the course of our study concerning amino acid-derived poly(*N*-propargylamides), we have found that the combination of *N*-(*tert*-butoxycarbonyl)-L-alanine *N*′-propargylamide (LA) and *N*-(trifluoroacetyl)-L-valine *N*′-propargylamide (FLV) (the same chirality) is also operative to achieve this helix inversion (Scheme 1). Here, we report that the homopolymers carrying the above chiral units form helices with opposite sense, and the helix sense can be tuned by solvent and temperature. The chiral units of the copolymers have different dependence on the external stimuli and compete each other to control the conformation of the copolymer, which allows some copolymers to interconvert between left- and right-handed conformations dynamically.

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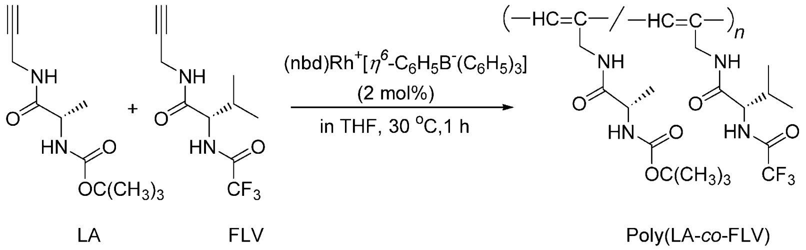

Scheme 1. Copolymerization of LA with FLV.

2. Experiment

2.1. Measurements

^{1}H and ^{13}C NMR spectra were recorded in chloroform-*d* ($CDCl_3$) and DMSO-*d* on a JEOL EX-400 spectrometer. IR spectra were performed on a Shimadzu FTIR-8100 spectrophotometer. Elemental analysis was carried out at the Kyoto University Elemental Analysis Center. The number- and weight-average molecular weights of the polymers were determined by GPC (Shodex KF-850 column) calibrated by polystyrene standards and THF as an eluent. Melting points (mp) were measured on a Yanaco micro melting point apparatus. Specific rotations ($[\alpha]_D$) were measured on a Jasco DIP-1000 digital polarimeter with a sodium lamp as a light source. CD and UV–Vis spectra were recorded in a quartz cell (thickness: 1 cm) using a Jasco J-820 spectropolarimeter.

2.2. Materials

All the reagents in monomer synthesis were used as purchased without purification. LA and *N*-(*tert*-butoxycarbonyl)-L-valine *N*′-propargylamide were synthesized according to our previous method [4,5]. 4-[4,6-Dimethoxy-1,3,5-triazine-2-yl]-4-methylmorpholinium chloride (TRIAZIMOCH) was supplied by TOKUYAMA Co. (nbd)Rh$^+$[η^6-$C_6H_5B^-(C_6H_5)_3$] was prepared as reported [7]. Tetrahydrofuran (THF) was distilled by the usual method before use.

2.3. Synthesis of FLV

Trifluoroacetic acid (15 mL, 45 mmol) was added to a solution of *N*-(*tert*-butoxycarbonyl)-L-valine *N*′-propargylamide (5.1 g, 20 mmol) in dichloromethane (100 mL) at 0 °C, and the resulting mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated by rotary evaporation and dried in vacuo. The residual compound was dissolved in CH_2Cl_2 (100 mL). Triethylamine (3.7 mL, 20 mmol), trifluoroacetic acid (5 mL 9 mmol), and TRIAZIMOCH (6.0 g) were added to the solution, and it was stirred at room temperature for 3 h. The reaction mixture was subsequently washed with 1 M HCl (50 mL), saturated aqueous solution of $NaHCO_3$ (50 mL), and saturated aqueous solution of NaCl (50 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation. The residue was purified by silica gel column chromatography eluted with *n*-hexane/AcOEt = 1:1 (volume ratio)) to afford the product in 68% yield. Mp: 166.0–166.5 °C. $[\alpha]_D$ −24.8° ($c=0.1$ g/dL in THF at room temperature), −5.4° ($c=0.1$ g/dL in $CHCl_3$ at room temperature). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.00 [s, 6H, $(CH_3)_2$], 1.72 [s, 1H, $CH(CH_3)_2$] 2.16 [1H, s, $CH{\equiv}C$], 4.11 [2H, d, CH_2NH], 4.33 [1H, t $J=3.9$ Hz, CHN*H*], 6.36 [1H, s, CH_2NHCO]. ^{13}C NMR (100 MHz, DMSO): δ 18.72 $(CH_3)_2$, 27.86 ($CH(CH_3)_2$), 29.81 (CH_2NH), 59.00 (*C*HNH), 73.10 (H*C*≡), 81.09 (HC≡*C*), 119.88, ($COCF_3$), 169.13 ($COCF_3$), 184.61 (*C*ONH). IR (cm^{-1}, KBr): 3360 (H–C≡), 2320, 1735, 1685 (C=O), 1559, 1372, 1189, 1165, 715, 689). Anal. Calcd for $C_{10}H_{13}F_3N_2O_2$: C, 48.00, H, 5.24, N, 11.20. Found: C 48.06, H, 5.16, N, 11.18.

2.4. Polymerization

All the polymerizations were carried out in a glass tube equipped with a three-way stopcock under nitrogen. (nbd)Rh$^+$[η^6-$C_6H_5B^-(C_6H_5)_3$] was added to a THF solution of monomers under dry nitrogen, and the resulting solution ($[M]_{total}=1.0$ M, $[M]_{total}/[cat]=50$) was kept at 30 °C for 1 h. The polymer was obtained by precipitation with a large amount of *n*-hexane.

2.5. Spectroscopic data of poly(FLV)

^{1}H NMR (400 MHz, DMSO-d_6)(δ 1.10 [s, 6H, $(CH_3)_2$], 3.70 [broad, s, 3H, *CH*, CH_2], 5.98 [broad, s, 1H, $NHCH_2$], 6.76 [broad, s, 2H, N*H*CO, –C*H*=]. IR (cm^{-1}, KBr)(3330 (N=H), 1648 (C=O), 1540 (N=H, C=N), 1214, 1029.

3. Results and discussion

3.1. Synthesis of homo- and copolymers

Table 1 summarizes the conditions and results of the (co)polymerization of LA and FLV catalyzed with (nbd)Rh$^+$[η^6-$C_6H_5B^-(C_6H_5)_3$] in THF under N_2 atmosphere at 30 °C for 1 h. Monomers LA and FLV satisfactorily

Table 1
Copolymerization of LA with FLV

Run	Monomer feed ratio LA:FLV	Yield[a] (%)	M_n[b]	M_w/M_n[b]	$[\alpha]_D$[c] (deg)	
					in THF	in $CHCl_3$
1	100:0	98	10300	2.17	−981	−1059
2	75:25	93	14100	1.90	−483	−617
3	60:40	95	11800	1.79	−218	−556
4	50:50	92	13400	2.00	−185	−461
5	47:53	85	13000	2.00	−108	−443
6	45:55	76	12500	1.96	−15	−431
7	40:60	81	13200	1.89	+288	−334
8	25:75	86	10600	1.80	+504	−102
9	0:100	76	7700	1.73	+628	–[d]

Polymerization time: 1 h, temperature 30 °C. $[M]_{total}/[Cat]=50$ in THF. Catalyst: $(nbd)Rh^+[\eta^6\text{-}C_6H_5B^-(C_6H_5)_3]$.

[a] n-Hexane-insoulble part.

[b] Determined by GPC, polystyrene standards, eluent THF.

[c] Measured by polarimetry at room temperature, $c=0.10$–0.11 g/dL.

[d] Unstable.

underwent (co)polymerization to afford the corresponding (co)polymers with moderate molecular weights (M_n in the range from 7700 to 14,100) in good yields. The copolymer compositions, which were determined by ^{1}H NMR spectroscopy, were almost the same as the monomer feed ratios. All the (co)polymers were completely soluble in THF and $CHCl_3$, in contrast to the poor solubility of the homopolymer of *N*-(*tert*-butoxycarbonyl)-L-valine *N*′-propargylamide in these solvents [5]. The solubility was improved by substitution of *tert*-butoxycarbonyl group with trifluoroacetyl group.

3.2. Secondary structure of the homopolymers

The secondary structure of poly(LA) and poly(FLV) was examined by specific rotation, CD and UV–Vis spectroscopic methods. Poly(LA) and poly(FLV) displayed very large specific rotations in THF as shown in Table 1, which should be based on the helical structure with predominantly one-handed screw sense. In THF, the $[\alpha]_D$ of FLV was negative (−24.8°), while that of poly(FLV) was positive (+628°). This is noteworthy because *N*-propargylamides prepared from *N*-(*tert*-butoxycarbonyl)-L-alanine and *N*-(*tert*-butoxycarbonyl)-L-valine showed $[\alpha]_D$ with negative value in THF (−9.0° ($c=0.1$ g/dL) and −9.5° ($c=0.1$ g/dL), respectively), and the polymers obtained from them also showed $[\alpha]_D$ with negative sign in THF. The opposite sign of specific rotations of poly(LA) and poly(FLV) indicates that the helix sense is opposite each other in THF. Fig. 1 shows the CD and UV–Vis spectra of poly(LA) and poly(FLV) measured at various temperatures. Poly(LA) exhibited large minus molar ellipticity $[\theta]$ around 390 nm in THF, corresponding to the UV–Vis absorption of the main chain. On the other hand, poly(FLV) exhibited a positive CD signal and UV–Vis absorption around 420 nm. Compared to the UV–Vis spectra of poly(LA), the red-shifted absorption of the UV–Vis spectra suggests that poly(FLV) takes a looser helix than poly(LA) does [8]. It should be noted that the λ_{max} of poly(FLV) is positioned at the longest wavelength region among poly(*N*-propargylamides) reported so far. The fluorine-containing substituent should play a significant role for this result, but its concrete reason is unclear.

The helical structure of poly(*N*-propargylamides) is stabilized by intramolecular hydrogen bonding, and the stability depends on temperature and solvent [4]. It is considered that changing the environments of the polymers by means of external stimuli results in the change of strength of hydrogen bonding in conjunction with the

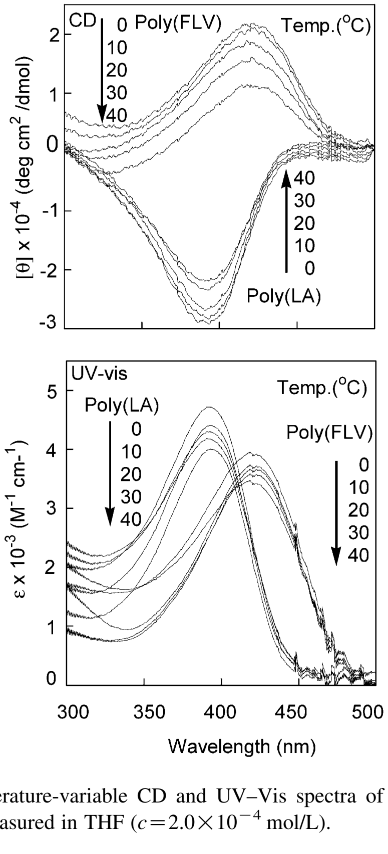

Fig. 1. Temperature-variable CD and UV–Vis spectra of poly(LA) and poly(FLV) measured in THF ($c=2.0\times10^{-4}$ mol/L).

secondary structure of the polymer. As shown in Fig. 1, the CD and UV–Vis intensities gradually decreased by raising temperature, which confirms that lower temperature is favorable to form the helical structure.

Addition of MeOH, a protic solvent that destroys the hydrogen bond, clearly decreased the intensities of the CD sign and UV–Vis absorption of poly(LA) and poly(FLV). Fig. 2 shows CD and UV–Vis spectra for poly(LA) in mixtures of THF and MeOH. The CD and UV–Vis intensities at 400 nm decreased with the increase of the MeOH content. When the MeOH content reached 60%, the intensities of CD signal and UV–Vis absorption became about a half of those in THF. Fig. 3 showed the CD and UV–Vis spectra of poly(FLV) measured in a similar manner to Fig. 2. The CD and UV–Vis signals of poly(FLV) at 420 nm gradually decreased with increasing the MeOH content, and almost disappeared when the MeOH content reached 60%. This result indicates that poly(FLV) underwent helix-to-random coil transition upon addition of 60% MeOH into THF. The helical structure of poly(FLV) was more easily broken by MeOH than that of poly(LA).

We have also found an interesting phenomenon that the helices of poly(LA) and poly(FLV) show quite different responses in THF/$CHCl_3$ mixed solvent. The CD and UV–Vis spectra of poly(LA) scarcely depended on the THF/$CHCl_3$ composition (Fig. 4), which is consistent with the slight variation in $[\alpha]_D$ with the solvent composition. These results indicate that the composition of THF/$CHCl_3$ mixture has little influence on the helical structure of

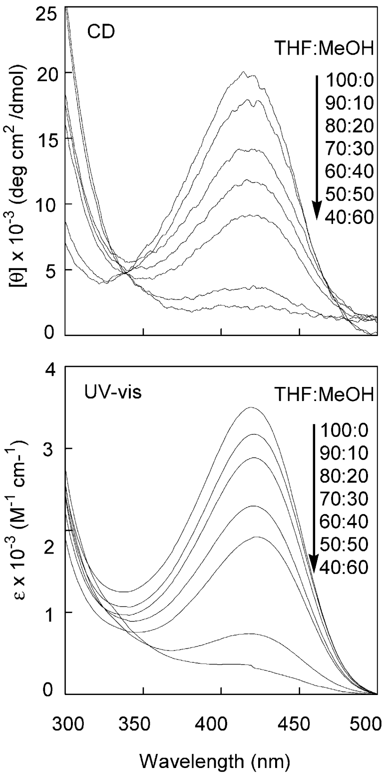

Fig. 3. CD and UV–Vis spectra of poly(FLV) measured in mixtures of THF and MeOH at room temperature ($c = 2.0 \times 10^{-4}$ mol/L).

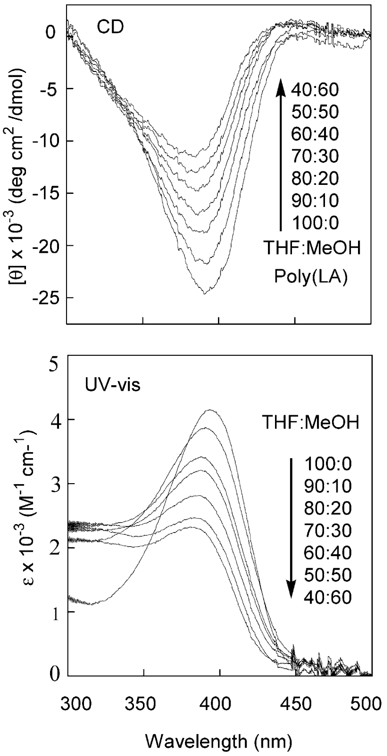

Fig. 2. CD and UV–Vis spectra of poly(LA) measured in mixtures of THF and MeOH at room temperature ($c = 2.20 \times 10^{-4}$ mol/L).

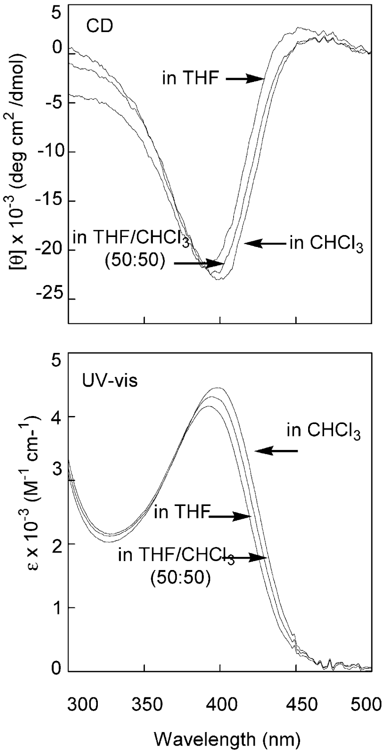

Fig. 4. CD and UV–Vis spectra of poly(LA) measured in mixtures of THF and $CHCl_3$ at room temperature ($c = 2.0 \times 10^{-4}$ mol/L).

poly(LA). On the other hand, the secondary structure of poly(FLV) largely depended on the THF/$CHCl_3$ compositions as shown in Fig. 5. Namely, increase of $CHCl_3$ content obviously weakened the CD signal and UV–Vis absorption at 420 nm, similarly to the case of MeOH addition in Fig. 3. The addition of 50% $CHCl_3$ led to the disappearance of the CD and UV–Vis peaks at 420 nm, indicating that the helical structure transformed into a random coil at this composition.

3.3. Transformation of the helix sense of the copolymers by temperature

Green et al. have demonstrated that a small amount of enantiomeric excess decides the helix sense of the copolymers of L- and D-isocyanates, which is called 'the majority rule' [9]. We have recently found that the copolymerization of LA and its enantiomer obeys this rule [10]. In the present case, poly(LA) and poly(FLV) have the same chirality, but take the opposite helix sense to each other in THF as shown in Table 1 and Fig. 1. The specific rotations of the copolymers varied in the range of −483 to +504° in THF depending on the composition of the chiral units; i.e. the copolymers formed predominantly either left- or right-handed helix according to the composition. On the other hand, the two homopolymers exhibited different dependences on temperature and solvent as described above. It is hence expected that the helical sense of the copolymers is reversibly controlled by the external stimuli.

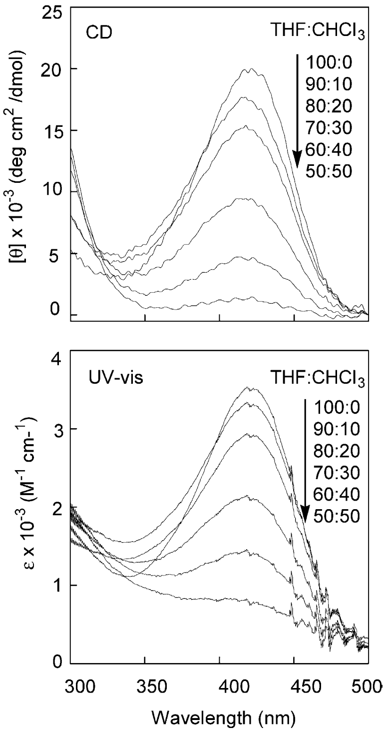

Fig. 5. CD and UV–Vis spectra of poly(FLV) measured in mixtures of THF and $CHCl_3$ at room temperature ($c=2.0\times10^{-4}$ mol/L).

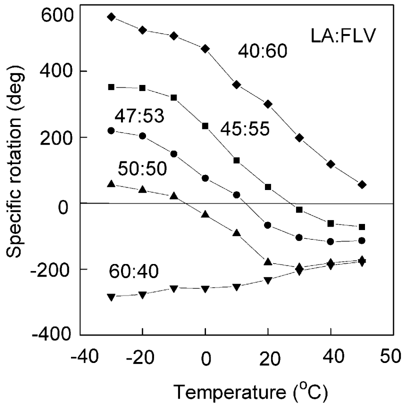

Fig. 6. Temperature dependence of the specific rotation of poly(LA-*co*-FLV) measured in THF ($c=0.11$–0.12 g/dL).

Fig. 6 shows the temperature dependence of the specific rotation of the LA/FLV copolymers. Poly(LA_{45}-*co*-FLV_{55}), poly(LA_{47}-*co*-FLV_{53}) and poly(LA_{50}-*co*-FLV_{50}) exhibited switching points of specific rotations, which demonstrates that the predominant helix sense of the copolymers with certain compositions can be transformed by temperature. This switching reversibly occurred from low to high temperature, and high to low temperature. We can say that this phenomenon is brought about by competition of the two optically active monomer units, as has been explained by Green et al. [6]. Our finding confirms that this conflict can be established not only by a pair of structurally different enantiomers with the opposite chiralities as in Green's report, but also by a pair of structurally different monomers with the same chirality.

3.4. Transformation of the helix sense of copolymers by solvents

As shown in runs 7 and 8 in Table 1, the two copolymers showed opposite specific rotations in THF and $CHCl_3$, which indicates that the copolymers take helical conformations of reversed senses in the two solvents. We further examined solvent effects on the CD and UV–Vis spectroscopic patterns of poly(LA_{40}-*co*-FLV_{60}). The copolymer exhibited a large CD signal and an intense UV–Vis absorption peak at 400 nm in $CHCl_3$ (Fig. 7). With increasing the THF content up to 50%, the intensities of CD signals and UV–Vis absorption gradually decreased. When THF amounted to 60%, the CD signal took a positive value. By further increasing the THF content, the CD and UV–Vis signals became larger accordingly. The CD signal turned to a largest positive value when THF was 100%. From these results, we can conclude that the copolymer transformed from a helix with predominantly one-handed screw sense into another helix with the opposite screw sense via random coil structure with the change of the THF/$CHCl_3$ composition [11]. THF is a solvent with strong Lewis basicity, while $CHCl_3$ is not. It is likely that the way of

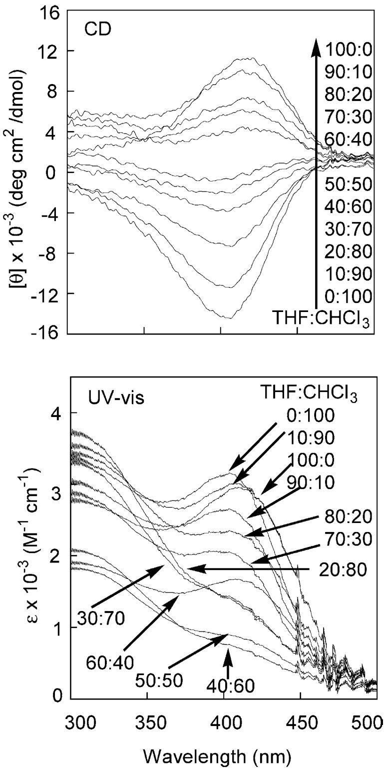

Fig. 7. CD and UV(vis spectra of poly(LA_{40}-*co*-FLV_{60}) measured in mixtures of THF and $CHCl_3$ at room temperature ($c=2.0\times10^{-4}$ mol/L).

interaction between the strongly polarized trifluoroacetyl groups of the copolymers and solvent molecules is very different in THF and $CHCl_3$ each other, resulting in the difference of conformation of the side chains in these solvents. It is considered that the conformations of the side chains of the copolymers in THF and $CHCl_3$ are energetically favorable to take one-handed helices showing plus and minus CD signals, respectively.

4. Summary

We synthesized and characterized the higher order structures of *N*-(*tert*-butoxycarbonyl)-L-alanine- and *N*-(trifluoroacetyl)-L-valine-based polyacetylenes. The homopolymers took predominately one-handed helical structures, whose contents could be tuned by external stimuli such as temperature and solvents. The helix sense of some copolymers could be inverted by temperature and solvent. The present study has presented a new method for designing helical polymers, whose screw sense can be switched by external stimuli by means of the copolymerization of structurally different amino acid-based monomers.

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[11] Poly(FLV) was not dissolved enough in $CHCl_3$, presumably due to aggregation. In fact, we could not obtain a reliable specific rotational data of the polymer in $CHCl_3$ as mentioned in. On the other hand, all the copolymers of LA and FLV were easily dissolved in $CHCl_3$ and THF. We measured the CD spectrum of poly(LA_{40}-*co*-FLV_{60}) in $CHCl_3$ after filtration with a membrane filter (pore size: 0.45 μm to find no difference from that before filtration. When poly(*N*-propargylamides) aggregate, the CD spectroscopic pattern of a filtered sample solution becomes significantly different [See Sanda F, Araki H, Masuda T. Macromolecules 2004; 37, 8510–6]. Consequently, we can exclude the possibility of formation of aggregate whose size is larger than 0.45 μm.