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Synthesis and Chiroptical Property of Helical Conjugated Poly(isocyanide) derived from L-Valine

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Abstract: Moderately bulky isocyanide monomer synthesized from L-valine, *i.e.*, (S)-1-ethoxycarbonyl-2-methylpropylisocyanide, was polymerized with $NiCl_2$ catalyst at various temperatures to afford poly(isocyanide)s with various helical conformation along the conjugated main chain. The polymers obtained by the polymerization at < 40 °C showed both much larger negative values of specific rotation than that of the monomer and appreciable negative Cotton effect on the n-π* and π-π* transitions (300-500 nm) of the imino groups conjugated through the tilted sp^2-carbons to form the main chain, indicating predominantly one-handed helical conformation along the main chain. On the contrary, the polymers obtained at > 55 °C showed little circular dichroism and only 16 % of the specific rotation of the polymer obtained at 5 °C, suggesting serious disorder of the helical conformation. The present result is consistent with thermal stability of the helical conformation of poly(isocyanide) derived from phenylalanine in our previous report (*J. Polym. Sci., A: Polym. Chem.*, **40**, 399-408 (2002)).

Keyword: helical conformation, poly(isocyanide), amino acid, conformational control.

1. INTRODUCTION

Helical structures have drawn attention widely as a three dimensional asymmetric molecular architecture which reminds us of natural polymer's motif found in DNA, protein, and so on.[1] As chirality resulted from the secondary conformation of the polymer, remarkable progress has been made recently on studies of helical polymers, *i.e.* the screw sense polymerization,[2] helical structure,[3] and chiral recognition[4] for the last three decades. Why such helical structures are assembled in natural organism could be interpreted by not only skeletal reinforcement as rod-like supports but also "smart" framework in which the helical conformation can be varied continuously and delicately toward the environmental stimuli. In recent years, considerable attention has been drawn to studies on the stimuli-induced changes in helical conformation, either helix-helix inversion or helix induction demonstrated by responses of functional moieties in the side chain. These conformational controls have been achieved by introducing the stimuli-responsible molecular units to the side chain, such as *E-Z* photo-isomerization of azobenzene[5] or acid-base interaction.[6] On the other hands, thermal stability of these helical conformations have been also discussed so far. Helical conformation of poly(isocyanate), [7] poly(acetylene), [8] and poly(isocyanide) can be varied reversibly by heating and cooling their solutions.

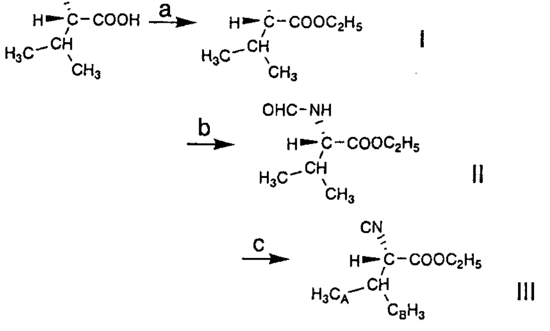
We have reported that poly(isocyanide) composed of the π-conjugated main chain, derived from chiral amino acids, can be controlled thermodynamically.[9] Helical conformation can be reversibly changed between tightly coiled and loosely coiled helical conformation while heating and cooling the solution. Helical conformation of poly(isocyanide) bearing the azobenzene unit in the side chain are also controlled by using the geometrical photo-isomerization of azobenzene.[10] *Trans* to *cis* isomerization of azobenzene under UV irradiation would cause disorder of the helical conformation and *cis* to *trans* isomerization under visible irradiation would recover the disordered helical conformation to the original tightly coiled helical conformation. On the other hands, these poly(isocyanide)s derived from amino acids exhibit another irreversible process of the decreasing Cotton effect, in which the helical conformation of the resulting polymers could be determined by polymerization temperature. By finely tuning the bulkiness of the side chain with respect to the kind of the amino acid and the ester group, poly(isocyanide)s were prepared systematically to take various helical conformation. When the side chain was small enough like the alanine ethylester residue, the resulting poly(isocyanide) showed little Cotton effect, suggesting a more planar conformation. When the side chain was bulky like phenylalanine *t*-butylester residue, the resulting poly(isocyanide) took thermally stable helical conformation. Especially, in the case of poly(isocyanide) bearing phenylalanine ethylester, middle size between the last two residues, the helical conformation of the main chain could be thermally changed between the tightly coiled and the loosely coiled conformation as we mentioned above.

2. EXPERIMENTAL

Measurement: Specific rotation was measured on a JASCO polarimeter. Elemental analyses were performed on a Leco CHNS-932 and VTF-900 Elemental Analyzer.

CD spectra were measured with a JASCO J-720 spectrometer. UV-vis spectra were taken on a Shimadzu UV-3100S. Chloroform for spectrometry (Wako) was used as solvent for CD and UV spectral measurements. ^{1}H NMR spectra were taken on a JEOL JNM-LA500 spectrometer with tetramethylsilane (TMS) as the internal standard in $CDCl_3$ at room temperature. IR spectra were recorded on a JASCO Herschel FT/IR-660 Plus V spectrometer. The molecular weight of the polymer was determined by GPC measurement on a JASCO equipped with an ELMER UV detector and serially connecting GPC columns of a Shodex KF-802 and a JAIGEL 3H-AF, using THF as the eluent at 30 °C. The molecular weight of the polymer was determined using a calibration curve obtained with standard polystyrenes (Tosoh).

Chemicals: L-Valine in the synthetic route shown in Scheme 1, L-valine was obtained from Wako. $NiCl_2{\cdot}6H_2O$ as the polymerization catalyst was purchased from Kojundo Chemical laboratory. Unless otherwise indicated, other chemicals were commercially available and used without further purification.



Scheme 1. Synthetic route of isocyanide monomer derived from L-valine. (a) ethanol, $SOCl_2$, r.t. (b) acetic formic anhydride in formic acid, r.t. (c) bis(trichloromethyl)carbonate, triethylamine in CH_2Cl_2, -10 °C.

L-Valine ethylester hydrochloride (I): L-Valine ethylester hydrochloride was synthesized as general esterification procedure[11] with ethanol. Yield, 92%; $[\alpha]_D^{20}$ +18.4 (*c* 1.14, EtOH), IR (KBr, cm^{-1}) $\nu_{C=O}$ 1741 (in ester) ^{1}H NMR (500MHz, $CDCl_3$) δ 1.16 (d, 3H, $^3J_{HH}$ = 6.76Hz, $C_A\mathit{H}_3$), 1.17 (d, 3H, $^3J_{HH}$ = 6.76Hz, $C_B\mathit{H}_3$), 1.32 (t, 3H, $^3J_{HH}$ = 7.29 Hz, $CH_2C\mathit{H}_3$), 2.47 (m, 1H, $C\mathit{H}(CH_3)_2$), 3.94 (d, 1H, $^3J_{HH}$ = 4.05Hz, $C^*\mathit{H}$), 4.28 (m, 2H, $C\mathit{H}_2CH_3$), 8.83 (br, 3H, $N\mathit{H}_3^+Cl^-$) ^{13}C NMR (126MHz, $CDCl_3$) δ 14.15 ($CH_2\mathit{C}H_3$), 18.26 ($CH\mathit{C}_AH_3C_BH_3$), 18.43 ($CHC_AH_3\mathit{C}_BH_3$), 29.91 ($\mathit{C}HC_AH_3C_BH_3$), 58.57 (C^*H), 62.35 ($\mathit{C}H_2CH_3$), 168.33 (C=O). Anal. Calcd. for $C_7H_{16}NO_2Cl$: C, 46.28; H, 8.88; N, 7.71; O, 17.61; Cl, 19.52. Found: C, 46.17; H, 8.93. N, 7.69; O, 17.51; C, 19.05.

***N*-Formyl-L-valine ethylester(II)**[12]: The *N*-formylation of **I** with acetic formic anhydride afforded **II** as a colorless liquid, followed by distillation under reduced pressure (110 °C at 3 mmHg). Yield, 65%; $[\alpha]_D^{20}$ -26.5 (*c* 1.05, EtOH), IR (KBr, cm^{-1}) $\nu_{C=O}$ 1740 (in ester), $\nu_{C=O}$ 1688 (in formamide), ν_{NH} 3297. ^{1}H NMR (500MHz, $CDCl_3$) δ 0.92 (d, 3H, $^3J_{HH}$ = 6.75 Hz, $CH(C_A\mathit{H}_3C_BCH_3)$), 0.97 (d, 3H, $^3J_{HH}$ = 6.75 Hz, $CH(C_AH_3C_B\mathit{H}_3)$), 1.30 (t, 3H, $^3J_{HH}$ = 7.08 Hz, $CH_2C\mathit{H}_3$), 2.20 (m, 1H, $C\mathit{H}(CH_3)_2$)), 4.22 (m, 2H, $C\mathit{H}_2CH_3$), 4.65 (m, 1H, $C^*\mathit{H}$), 6.12 (br, 1H, $N\mathit{H}CHO$), 8.27 (s, 1H, $NHC\mathit{H}O$). ^{13}C NMR (126MHz, $CDCl_3$) δ 14.21($CH_2\mathit{C}H_3$), 17.61 ($CH\mathit{C}_AH_3C_BH_3$), 18.93 ($CHC_AH_3\mathit{C}_BH_3$), 31.39 ($\mathit{C}HC_AH_3C_BH_3$), 55.60 (C^*H), 61.50 ($\mathit{C}H_2CH_3$), 160.8 ($NH\mathit{C}HO$), 171.6 (C=O). Calcd. for $C_8H_{15}NO_3$: C, 55.47; H, 8.73; N, 8.09; O, 27.71. Found: C, 55.18; H, 8.65; N, 8.12; O, 27.47.

(S)-1-Ethoxycarbonyl-2-methylpropylisocyanide(III): The isocyanide was synthesized by dehydration of the *N*-formamide according to the method of Nolte and Drenth.[13] At 0 °C, bis(trichloromethyl)carbonate (Wako, 1.65 g, 5.6 mmol) in 12 ml of dry CH_2Cl_2 was introduced into a 22 ml of dry CH_2Cl_2 containing 3.0 g (17 mmol) of formamide over a period of 2 h with stirring. Just after the reaction was completed for 3 h, 50 ml of water was added to the mixture. The organic layer was quickly washed with 150 ml of a 7.5 % $NaHCO_3$ aqueous solution and dried over $MgSO_4$. The crude product was purified by column chromatography on silica gel using CH_2Cl_2 as the eluent. Yield, 46%; $[\alpha]_D^{20}$ +6.73 (*c* 1.02, EtOH), IR (KBr, cm^{-1}) $\nu_{C=O}$ 1752 (in ester), $\nu_{C\equiv N}$ 2149. ^{1}H NMR (500MHz, $CDCl_3$) δ 1.02 (d, 3H, $^3J_{HH}$ = 6.75 Hz, $CH(C_A\mathit{H}_3C_BH_3)$), 1.10 (d, 3H, $^3J_{HH}$ = 6.75 Hz, $CH(C_AH_3C_B\mathit{H}_3)$, 1.31 (t, 3H, $^3J_{HH}$ = 3.78 Hz, $CH_2C\mathit{H}_3$), 2.34 (m, 1H, $C\mathit{H}(CH_3)_2$)), 4.17 (d, 1H, 3JHH = 4.32 Hz, $C^*\mathit{H}$), 4.28 (q, 2H, $^3J_{HH}$ = 3.78 Hz, $C\mathit{H}_2CH_3$). ^{13}C NMR (126MHz, $CDCl_3$) δ 14.10 ($CH_2\mathit{C}H_3$), 16.62 ($CH\mathit{C}_AH_3C_BH_3$), 19.39 ($CHC_AH_3\mathit{C}_BH_3$), 31.21 ($\mathit{C}HC_AH_3C_BH_3$), 62.48 ($\mathit{C}H_2CH_3$), 62.99 (C^*H), 166.4 (C=O), 195.5 ($\mathit{C}\equiv$N).

Polymerization. Methanol for polymerization solvent was dried with $CuSO_4$ (2g/L) under dry N_2 stream, and then distilled before use. Just prior to the polymerization, the isocyanide monomer (III) was derived from precursor (II) and purified by column chromatography. An aliquot of methanol containing appropriate amount of $NiCl_2{\cdot}6H_2O$ (0.5 mol % for monomer) was loaded to a reaction vessel and the solvent was flushed up. The polymerization started by the addition of the chloroform solution containing the isocyanide monomer with stirring at room temperatures. After 1.5 day, the reaction solution became viscous and turned brown. After solvent evaporation, the concentrated reaction mixture was added dropwise to an excess amount of vigorously stirred methanol/water (1:4 (v/v)). The dark brown precipitate was collected by filtration and dried *in vacuo* at ambient temperature.

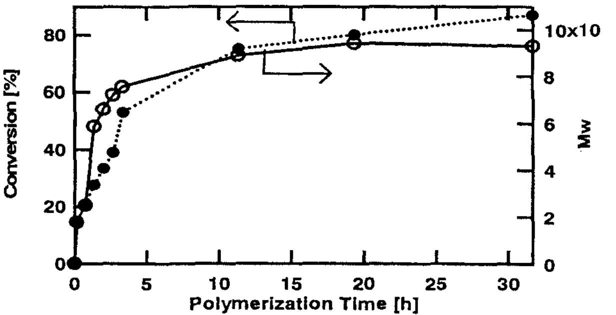


Figure 1. Time courses of the monomer conversion (dotted line) and the MW of the polymerization (solid line) of the isocyanide monomer III in methanol at room temperature. [III] = 1.0 mol / l. [III] / [Ni(II)] = 100. Both conversion and MW were determined by GPC (polystyrene standard).

Table 1. Temperature Dependence on Polymerization of Chiral Isocyanide derived from L-Valine in MeOH with $NiCl_2 \cdot 6H_2O^a$.

Polymer	Temperature °C	Conversion^b %	Yield^c %	Mw^b	# of unit	Mw / Mn^b	$[\alpha]_D^{20d}$
poly05	5	75	66	8320	54	1.1	-384
poly25	25	87	83	9220	59	1.1	-294
poly40	40	86	80	8230	53	1.1	-173
poly55	55	83	61	6870	44	1.1	-72
poly68	68	81	63	6740	43	1.1	-63

[a] Condition: [III] / [Ni(II)] = 100, [III] = 1 mol/l. Reaction time; 1.5 day. [b] Detemined by GPC (polystyrene standard). [c] Isolated polymers were reprecipitated in $MeOH-H_2O$(1:4 (v/v)). [d] Specific rotation in units of $deg \cdot cm^3 \cdot g^{-1}$ were measured in a 1cm cell at concentrations(*c* in g/cm^{-3}) of 0.1-0.3 g / dl in $CHCl_3$.

3. RESULT AND DISCUSSION

3-1. Polymerization of (S)-1-Ethoxycarbonyl-2-methylpropylisocyanide

Polymerization of the chiral monomers (III) gave the poly(isocyanide) bearing L-valine residue. Figure 1 shows typical time courses of the monomer conversion and the weight-averaged molecular weight (MW) of the polymer obtained by the polymerization at 5 °C in methanol. The polymerization underwent within 36 h to reach 83 % of the monomer conversion and to give brown powder in about 72 % of the isolated yield by reprecipitation with $MeOH/H_2O$ (1:4(v/v)). The gel permeation chromatography showed 9,220 of MW and 1.12 of polydispersity, based on a calibration with polystyrene standards.

3-2 Secondary Conformation of poly05

The polymer **poly05** showed -384° (*c* 0.1, $CHCl_3$) of specific rotation, of which absolute value is hundred times larger than the value of the isocyanide monomer (+6.73° (c 1.02, $CHCl_3$)) with the opposite sign. Similar increases in the specific rotations, ranging the hundreds or even the thousands of degrees, have been reported for several helical polymers prepared via screw-sense polymerization techniques, such as poly(isocyanate),[14] poly(silane),[2(c)] and poly(methacrylate).[2(a)] The UV-vis and CD spectra of **poly05** and monomer **III** are shown in Figure 2. The **poly05** showed a very broad absorption band extended to 600 nm, which may be assigned to π-conjugated main chain consisting of sp^2 carbons of the imino groups, while the absorption bands of the monomer appeared in a < 300 nm region. Over a near UV region up to 380 nm a negative Cotton effect was observed in **poly05**. This CD spectrum indicates that the **poly05** should adopt predominantly a one-handed helical conformation along with the π-conjugated main chain, similar to poly(isocyanide) reported previously.[15] The spectral feature of **poly05** is that the broad absorption tail is still extended over 400nm around which the circular dichroism vanished. The polymer conformation might involve some contribution of a relatively loosen helical conformation, *e.g.*, partly planar conformation.

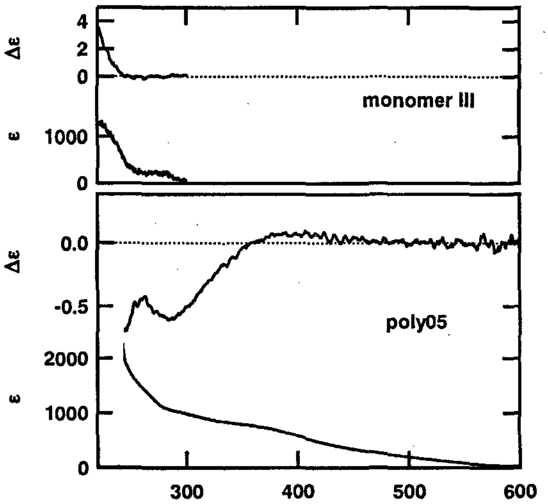


Figure 2. UV-vis and CD spectra (a) monomer III and (b) **poly05** in $CHCl_3$.

3-3. Polymerization Temperature Effect

The polymerization temperature effect on the secondary conformation was examined. Table 1 shows the characterization of **poly05**, **poly25**, **poly40**, **poly55**, and **poly68** polymerized under 5, 25, 40, 55, and 68 °C, respectively. Through the temperature range from 5 °C to 68 °C, the monomer was polymerized to give about 75% of the conversion, 6700-9300 of MW with 1.1 of polydispersity. Some differences in the monomer conversion and the MW of the obtained polymer may be interpreted by temperature dependence of the polymerization kinetics and the technical allowance on the reprecipitation procedure.

Here, it should be noticed that the specific rotation of the resulting polymers strongly depended on the polymerization temperature as Table 1 shows. The

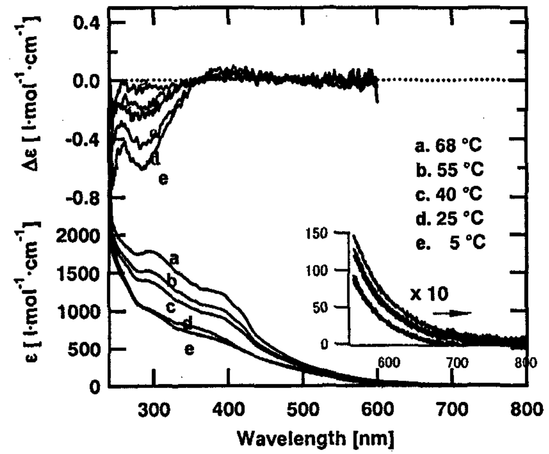


Figure 3. UV-vis and CD spectra of **poly05**, **poly25**, **poly40**, **poly55**, and **poly68** in $CHCl_3$, which were obtained by polymerization at 5, 25, 40, 55, and 68 °C, respectively. The measurements were carried out at room temperature. The details on the isolation procedure and the sample preparation are described in the text.

specific rotation of **poly68** is only one sixth of that of **poly05** but its absolute value is still sufficiently larger than that of the monomer. This implies that the helical conformation of the polymer prepared at high temperature should be disordered, in other words, the helix would become loosen, in comparison with that of the polymer prepared at low temperature.

UV-vis and CD spectra showed more clearly the difference of the polymer conformation. The **poly05, 25** and **40** showed the large negative Cotton effect in the wavelength region up to 380 nm corresponding to the absorption band of the main chain. On the contrary, **poly55** and **68** showed almost no Cotton effect in the same region. The broad absorption in the long wavelength region, corresponding to the effective conjugation length, increases with the elevated temperature on the polymerization. These results suggest that the resulting polymers, of which polymerization underwent at up to 40 °C, prefer the one-handed helical conformation. In the case of high polymerization temperature (>55 °C), the polymers prefer rather the disordered conformation. Our previous study clarified that the bulkiness of the side chain strongly determines thermal stability of the helical conformation of poly(isocyanide) derived from amino acid. Helical conformation of *t*-butylester was thermally stable in 5-68 °C of temperature range. On the contrary, poly(isocyanide) bearing optically active alanine ethylester as the smallest side chain had no indication of the helical conformation even though the polymerization underwent at 5 °C. Poly(isocyanide) bearing phenylalanine ethylester as a moderately sized side chain, compared with the other two, took the various conformations depending on the polymerization temperature, similar to the case of valine-based polymer in this study. It is consistent with the result of the difference in the conformation of valine-based poly(isocyanide) as a function of polymerization temperature. In other words, the energy barrier between the two states, helical conformation and disordered conformation, can be tuned by the size of the side chain. Thermal stability of the helical conformation after polymerization should be also interesting so as to evaluate the energy barrier between the helical conformation and the disordered one. Further analysis is now under investigation.

4. CONCLUSIONS.

Poly(isocyanide) derived from L-valine derivative was prepared in the presence of $NiCl_2$ catalyst. The polymer showed very large specific rotation in comparison with the corresponding **III** monomer, predominantly indicating a one-handed helical conformation. Polymerization temperature effects strongly to the resulting polymer conformation. Poly(isocyanide) obtained at lower than 40 °C prefer the helical conformation. On the contrary, poly(isocyanide) prepared at higher than 55 °C prefer the disordered helical conformation. It is suggested that the helical conformation of the resulting poly(isocyanide) bearing L-valine residue can be controlled by the polymerization temperature.

5. ACKNOWLEDGEMENT

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