Polymer Bulletin 60, 159–167 (2008)
DOI 10.1007/s00289-007-0849-7

Polymer Bulletin

Synthesis and Chiroptical Properties of Poly(phenylacetylene)s Carrying Two Amino Acid Moieties per Monomer Unit

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Received: 27 August 2007 / Revised version: 25 September 2007 / Accepted: 25 September 2007
Published online: 9 October 2007 –

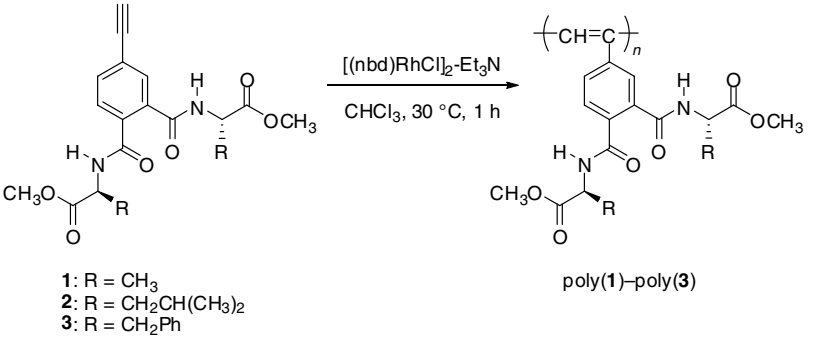
Summary

Novel phenylacetylenes carrying two amino acid moieties **1–3** were synthesized by the condensation of alanine, leucine, and phenylalanine with 4-ethynylphthalic anhydride. The corresponding polymers [poly(**1**)–poly(**3**)] with high molecular weights were obtained in 50–93% yields. The large specific rotations and intense CD signals indicated that poly(**1**)–poly(**3**) formed a helical structure with predominantly one-handed screw sense in $CHCl_3$. The helical conformation of the polymers was stable to heating but susceptible to MeOH.

Introduction

Amino acids are constituents of proteins and peptides, and not only are biologically important but also are useful substances for chiral auxiliaries and building blocks in organic synthesis [1–3]. Amino acid-based synthetic polymers are expected to show biocompatibility and biodegradability similarly to polypeptides. Among varieties of amino acid-containing synthetic polymers, amino acid-based polyacetylenes have interesting features such as formation of helical structure and responsiveness to external stimuli such as pH, photoirradiation, heating, and solvent. For example, poly(phenylacetylene) derivatives containing alanine residues with long alkyl pendants show liquid crystalline properties based on the helical structure [4,5]. Helical poly(phenylacetylene) derivatives carrying amino acid moieties with carboxy groups exhibit self-assembling properties to form superhelical fiber, and change the helicity by medium pH [6–10]. We have synthesized poly(phenylacetylene)s from tyrosine [11] and serine [12] to find that they take helical structures, which are mainly stabilized by steric repulsion between the side chains. We have also synthesized a series of amino acid-based helical poly(*N*-propargylamide)s. The helical structures are stabilized by intramolecular hydrogen bonding between the amide groups as well as steric repulsion, and some of these polymers transform the structure from a helix to a random coil, or from a helix to another helix with the opposite screw sense according to pH [13,14], photoirradiation [15,16], heating and solvent [17–25]. Consequently, introduction of amide moieties into amino acid-based

poly(phenylacetylene)s may lead to development of new type of stimuli-responsive helical polymers. In this article, we report the polymerization of novel phenylacetylenes carrying two amino acid residues (Scheme 1), chiroptical properties of the formed polymers, and responsiveness to heating and solvent.



Scheme 1. Polymerization of monomers **1**–**3**.

Experimental

Measurements

Melting points were measured on a Yanaco micro melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL EX-400 spectrometer. IR spectra were measured on a JASCO FTIR-4100 spectrophotometer. Elemental analysis was performed at the Microanalytical Center of Kyoto University. Specific rotations ($[\alpha]_D$) were measured on a JASCO DIP-1000 digital polarimeter. Number- and weight-average molecular weights (M_n and M_w) of polymers were determined by gel permeation chromatography (GPC) using $CHCl_3$ as an eluent calibrated by polystyrene standards at 40 °C. Thermal gravimetric analysis (TGA) was performed on a Shimadzu thermogravimetric analyzer TGA-50 under air. CD and UV-vis spectra were recorded on a JASCO J-820 spectropolarimeter.

Materials

$CHCl_3$ used for polymerization was distilled over CaH_2 prior to use. All other reagents were used as received without purification.

*Synthesis of Alanine-based Phenylacetylene (**1**)*

1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC•HCl, 3.84 g, 20 mmol) was added to a solution of L-alanine methyl ester hydrochloride (2.78 g, 20 mmol), 4-ethynylphthalic anhydride (1.72 g, 10 mmol), and Et_3N (2.22 g, 22 mmol) in CH_2Cl_2 (100 mL) at 0 °C. After the mixture was stirred at room temperature overnight, it was washed with saturated sodium hydrogen carbonate aqueous solution, 0.5 M HCl aqueous solution, and water. The organic phase was dried over anhydrous $MgSO_4$ and concentrated on a rotary evaporator. The residue was purified by silica gel column chromatography eluted with hexane/AcOEt (1/2, v/v) to obtain **1** as white powder (2.52 g, 70%). Mp 61.0–62.0 °C, $[\alpha]_D = -44.4°$

(c = 0.1 g/dL, $CHCl_3$, room temperature). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.47 (s, 6H, CH_3), 3.26 (s, 1H, HC≡), 3.76 (s, 6H, OCH_3), 4.68 (s, 2H, NHC*H*COO), 7.29 (s, 1H, CONH), 7.38 (s, 1H, CONH), 7.50 (s, 2H, Ar), 7.61 (s, 1H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 17.7, 48.7, 52.4, 80.0, 81.8, 124.4, 128.5, 131.6, 133.5, 134.1, 134.4, 167.5, 172.9. IR (cm^{-1}, KBr): 3255 (N–H), 2086 (C≡C), 1745, 1638, 1543, 1456, 1324, 1209, 1047, 846, 672. Anal. Calcd for $C_{18}H_{20}N_2O_6$: C, 59.99; H, 5.59; N, 7.77. Found: C, 59.71; H, 5.48; N, 7.69.

*Synthesis of Leucine-based Phenylacetylene (**2**)*

The title compound was synthesized from L-leucine methyl ester hydrochloride and 4-ethynylphthalic anhydride in a manner similar to **1**. Yield 74% (white powder). Mp 112.0–113.5 °C, $[\alpha]_D$ = +52.7° (c = 0.1 g/dL, $CHCl_3$, room temperature). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.97 [s, 12H, CH(CH_3)$_2$], 1.67–1.93 [m, 6H, CH_2CH(CH_3)$_2$], 3.23 (s, 1H, HC≡), 3.74 (s, 6H, OCH_3), 4.74 (s, 2H, NHC*H*COO), 7.09 (s, 1H, CONH), 7.24 (s, 1H, CONH), 7.82 (s, 2H, Ar), 7.94 (s, 1H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.7, 24.8, 41.2, 51.5, 52.3, 80.0, 81.9, 124.6, 129.0, 132.1, 133.7, 134.0, 134.4, 167.7, 172.9. IR (cm^{-1}, KBr): 3260 (N–H), 2107 (C≡C), 1746, 1637, 1561, 1201, 1153, 987, 840, 677. Anal. Calcd for $C_{24}H_{32}N_2O_6$: C, 64.85; H, 7.26; N, 6.30. Found: C, 64.76; H, 7.32; N, 6.28.

*Synthesis of Phenylalanine-based Phenylacetylene (**3**)*

The title compound was synthesized from L-phenylalanine hydrochloride and 4-ethynylphthalic anhydride in a manner similar to **1**. Yield 63% (white powder). Mp 81.5–82.5 °C, $[\alpha]_D$ = −31.8° (c = 0.1 g/dL, $CHCl_3$, room temperature). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.17–3.28 (m, 5H, HC≡, CH_2), 3.68 (s, 6H, OCH_3), 4.94 (s, 2H, NHC*H*COO), 7.09 (s, 1H, CONH), 7.24 (s, 1H, CONH), 7.15–7.31 (m, 10H, $CH_2C_6H_5$), 7.42–7.54 (m, 3H, Ar). ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.6, 52.1, 53.9, 80.0, 81.7, 124.4, 127.0, 128.4, 129.2, 131.7, 133.6, 134.1, 134.6, 135.7, 167.3, 171.5. IR (cm^{-1}, KBr): 3261 (N–H), 2100 (C≡C), 1741, 1642, 1558, 1201, 1150, 981, 853, 672. Anal. Calcd for $C_{30}H_{28}N_2O_6$: C, 70.32; H, 5.51; N, 5.47. Found: C, 69.82; H, 5.61; N, 5.31.

Polymerization

The polymerization was carried out in a glass tube equipped with a three-way stopcock under nitrogen. $[(nbd)RhCl]_2$ and Et_3N were added to a solution of a monomer in $CHCl_3$ under nitrogen, and the resulting solution ($[M]_0$ = 50 mM, [Rh] = 0.5 mM, $[Et_3N]$ = 5 mM) was kept at 30 °C for 1 h. Then, it was poured into a large mount of acetone to precipitate a polymer. The polymer was separated by filtration using a membrane filter (ADVANTEC H100A047A) and dried under reduced pressure.

Spectroscopic Data of the Polymers

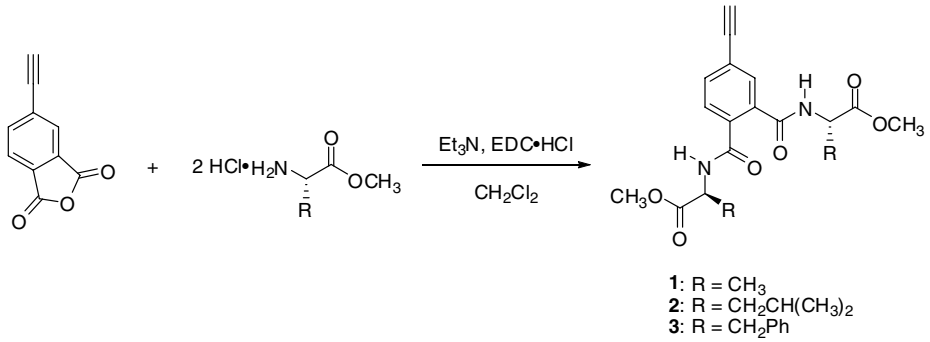
Poly(**1**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 6H, CH_3), 3.62 (s, 6H, OCH_3), 4.68–4.73 (m, 2H, NHC*H*COO), 5.41 (s, 1H, *Z* olefin proton), 6.92–7.08 (m, 2H, CONH), 7.31–7.52 (m, 3H, Ar). IR (cm^{-1}, KBr): 3263 (N–H), 2953, 1747, 1636, 1540, 1456, 1211, 1051, 983, 882, 662. Poly(**2**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.06–1.21 [m, 12H, CH(CH_3)$_2$], 1.60–1.74 [m, 6H, CH_2CH(CH_3)$_2$], 3.37–3.46 (m, 6H, $COOCH_3$),

4.59–4.69 (m, 2H, NHC*H*COO), 5.73 (s, 1H, *Z* olefin proton), 6.79–6.85 (m, 2H, CONH), 7.27–7.51 (m, 3H, Ar). IR (cm^{-1}, KBr): 3278 (N–H), 2956, 2360, 1748, 1637, 1541, 1202, 983, 669. Poly(**3**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.30–3.44 (m, 10H, $CH_2C_6H_5$, OCH_3), 4.81–4.92 (m, 2H, NHC*H*COO), 5.52 (s, *Z* olefin proton), 6.85–7.04 (m, 2H, 2CONH), 7.19–7.32 (m, 13H, $CH_2C_6H_5$, Ar). IR (cm^{-1}, KBr): 3264 (N–H), 3028, 2949, 2362, 1744, 1637, 1542, 1435, 1213, 981, 743, 699.

Results and discussion

Polymer Synthesis

Amino acid-based phenylacetylene monomers **1–3** were synthesized by the condensation of the corresponding amino acids with 4-ethynylphthalic acid anhydride using EDC•HCl as a condensation agent (Scheme 2). The structures of the monomers were confirmed by ^{1}H, ^{13}C NMR, and IR spectroscopies besides elemental analysis.



Scheme 2. Synthesis of monomers **1**–**3**.

The polymerization of **1–3** was conducted in $CHCl_3$ at 30°C for 1 h, catalyzed with $[(nbd)RhCl]_2$-Et_3N as summarized in Table 1. Monomers **1–3** underwent polymerization to afford the corresponding polymers [poly(**1**)–poly(**3**)] with high molecular weights in 50–93% yields.

Table 1. Polymerization of monomers **1–3** with $[(nbd)RhCl]_2$-Et_3N [a]

Monomer	Yield (%)	$M_w \times 10^{-6}$ [c]	M_w/M_n [c]	$[\alpha]_D$ [d]
1	93	Excluded	–	+2995
2	87	Excluded	–	+5256
3	50	1.5	11.3	+1314

[a] Carried out at 30 °C for 1 h; $[M]_0$ = 50 mM, [Rh] = 0.5 mM, $[Et_3N]$ = 5 mM.
[b] Acetone-insoluble part. [c] Determined by GPC (polystyrene, $CHCl_3$).
[d] Measured in $CHCl_3$ at room temperature (c = 0.10–0.11 g/dL).

The structures of the polymers were characterized spectroscopically. An example of the IR spectrum of poly(**1**) is shown in Figure 1 along with that of monomer **1**. The monomer exhibited an absorption band at 2086 cm^{-1} associated with the C≡C stretching vibration. This peak was not observed in the spectrum of poly(**1**), indicating

that the acetylene triple bond of **1** was consumed by the polymerization. The ^{1}H NMR spectra of the polymers exhibited signals reasonably assignable to the substituted polyacetylene structure as illustrated in Scheme 1. The *cis* content at the main chain was considered to be almost quantitative in every case judging from the integration ratio between the vinyl proton signal around 5.5 ppm and other proton signals. Poly(**1**)–poly(**3**) were soluble in $CHCl_3$, partly soluble in CH_2Cl_2, THF, and DMF.

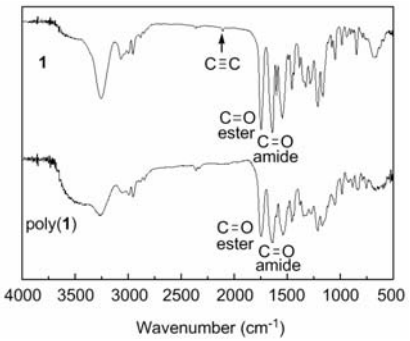


Figure 1. IR spectra of monomer **1** and poly(**1**).

Thermal Stability

The thermal stability of poly(**1**)–poly(**3**) was investigated by TGA. As shown in Figure 2, the polymers showed excellent thermal stability. They started losing weights around 250 °C under air. The temperatures for initial weight loss of leucine- and phenylalanine-based poly(**2**) and poly(**3**) were higher than that of alanine-based poly(**1**), which was possibly caused by the bulkier side chains of the former two polymers than those of the latter one, leading to suppression of thermal degradation. All the polymers completely lost the weights at 600 °C.

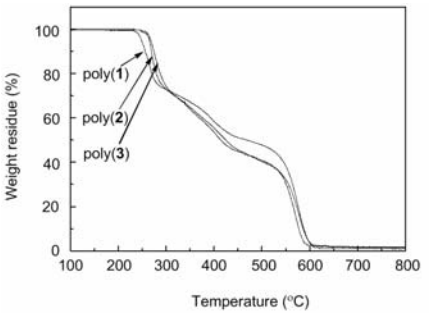


Figure 2. TGA curves of poly(**1**)–poly(**3**) (in air, heating rate 10 °C/min).

Secondary Structure

The secondary structure of poly(**1**)–poly(**3**) was examined by polarimetry, CD, and UV–vis spectroscopies. As listed in Table 1, all the polymers showed very large specific rotations (+1314–5256°) in $CHCl_3$ compared with those of the corresponding monomers (+52.7° and less), indicating that they took a secondary structure.

Figure 3 depicts the CD and UV–vis spectra of poly(**1**)–poly(**3**) measured in $CHCl_3$. Poly(**1**) and poly(**3**) exhibited an intense plus Cotton effect around 450 nm, and poly(**2**) did it around 455 nm. Since the polymers exhibited a UV–vis absorption peak at the same region as the CD signal, it is concluded that the Cotton effect originates from the conjugated polyacetylene backbone forming a helix with predominantly one-handed screw sense. The polymers also exhibited a bisignated CD signal at 250–320 nm.

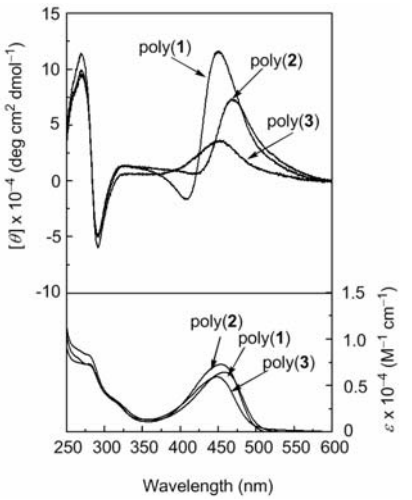


Figure 3. CD and UV–vis spectra of poly(**1**)–poly(**3**) measured in $CHCl_3$ ($c = 1.0 \times 10^{-4}$ M) at room temperature.

Left-handed helical poly(*N*-propargylamide)s exhibit a minus CD signal based on the polyacetylene backbone around 400 nm, and the side chain helical strands are right-handed, which are confirmed by the exciton chirality method [26] and molecular orbital calculations [27]. Considering that the CD signals of poly(**1**)–poly(**3**) around 450–455 nm and 250–320 nm come from the polyacetylene backbone and helical arrays of benzene rings, respectively, it is assumed that the helical sense of polyacetylene backbone of the present polymers is right-handed.

As described in the introduction, poly(*N*-propargylamide)s stabilize the helical conformation by intramolecular hydrogen bonding between the amide groups at the side chains as well as steric repulsion [13–25]. We measured the IR spectra of the present amino acid-based phenylacetylene monomers and polymers both in solid and

Table 2. Amide C=O absorption of the monomers and polymers

Compound	Wavenumber (cm^{-1})	
	Solid state [a]	Solution state [b]
1	1638	1664
Poly(**1**)	1636	1638
2	1637	1665
Poly(**2**)	1637	1636
3	1638	1666
Poly(**3**)	1637	1639

[a] KBr pellet. [b] Measured in $CHCl_3$ (c = 15 mM).

solution states to check the presence of intramolecular hydrogen bonding in the polymers. In solid state, there were little differences of amide $\nu_{C=O}$ between the monomers and the corresponding polymers as listed in Table 2. In contrary, poly(**1**)–poly(**3**) showed an amide absorption peak at 1636–1639 cm^{-1}, 26–29 cm^{-1} lower than that of the corresponding monomers. Judging from the low compound concentration (15 mM), it is concluded that the polymers form intramolecular hydrogen bonding between the amide groups.

Conformational Change on External Stimuli

Helical poly(phenylacetylene)s belong to dynamic helical polymers, similar to polyisocyanates and polysilanes [28], and their conformation is susceptible to external stimuli such as heating and solvent. We studied how temperature and solvent influence the secondary structure of poly(**1**)−poly(**3**). Figure 4 depicts the CD and UV-vis spectra of poly(**1**) measured in $CHCl_3$ at various temperatures. Poly(**1**) slightly changed the CD intensity accompanying a small change of the UV-vis absorption upon raising temperature from 0 to 50 °C. A similar tendency was observed in the temperature-variable CD and UV−vis spectra of poly(**2**) and poly(**3**). It was confirmed that the helical structure of poly(**1**)−poly(**3**) was stable to heating.

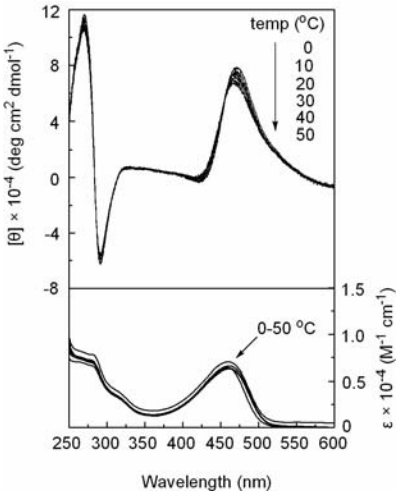


Figure 4. CD and UV-vis spectra of poly(**1**) measured in $CHCl_3$ 0–50 °C ($c = 1.0 \times 10^{-4}$ M).

MeOH breaks the hydrogen bonding strands and deforms the structure of poly(*N*-propargylamide)s as previously reported [13−25]. Figure 5 illustrates the CD and UV–vis spectra of poly(**1**) measured in $CHCl_3$/MeOH with various compositions. Poly(**1**) decreased the CD intensities upon raising MeOH content. During the transition of CD with MeOH addition, the UV–vis absorption was almost intact, suggesting that the decrease in the CD signal was not caused by the transition from a helix into a random coil but by decrease in the screw sense preference between right- and left-handed helices. The change of CD spectra of poly(**2**) and poly(**3**) upon MeOH addition was similar to that of poly(**1**). These results indicate that the helicity of poly(**1**)−poly(**3**) can be tunable by solvent.

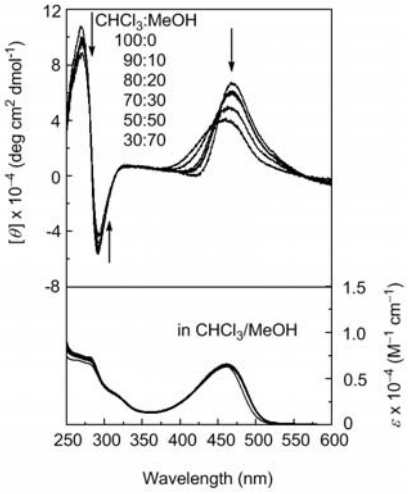


Figure 5. CD and UV-vis spectra of poly(**1**) measured in $CHCl_3$/MeOH ($c = 1.0 \times 10^{-4}$ M) at room temperature.

Conclusions

In this article, we have synthesized novel phenylacetylene monomers **1**–**3** carrying two amino acid moieties, and polymerized them using $[(nbd)RhCl]_2$-Et_3N as a catalyst in $CHCl_3$, and have obtained the corresponding polymers [poly(**1**)–poly(**3**)] with high molecular weights. The large specific rotations and intense CD signals indicated that the polymers formed a helical structure with predominantly one-handed screw sense. The presence of intramolecular hydrogen bonds between the amide groups of the polymers was confirmed. The hydrogen bonds presumably contributed to one-handedness of the helical conformation of the polymers, because the helix-based CD signals were susceptible to MeOH that disturbs the formation of hydrogen bonds between the amide groups.

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