RAPID COMMUNICATION

Optically Active Polyacetylene: Synthesis and Helical Conformation of a Poly(phenylacetylene) Carrying L-Alanyl-L-alanine Pendants

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INTRODUCTION

The development of biomimetic helical polymers is a topic of current interest. Studies of these simple unnatural systems may help us to understand complex natural systems and to explore efficient strategies for assembling molecular components into hierarchical architectures. Helical polymers with π conjugation along the main chain are of particular interest because of their high-tech applications as chiral stationary phases, optical polarizing films, asymmetric electrodes, and so forth. Polyacetylene is the best known conjugated polymer and exists in an excess of one-handed helical conformation when appropriate chiral pendants are attached.[1–4] Yashima et al.[5] prepared helical polyacetylenes bearing poly(γ-benzyl-L-glutamate) and poly(L-glutamic acid) moieties. Masuda et al.[6] synthesized chiral copolymers with amino acid side groups and found that the helix content could be controlled through the variation of the concentrations of the chiral monomers. Attracted by the academic and practical aspects, we have also worked on the synthesis of optically active polyacetylenes with naturally occurring building blocks of amino acids, saccharides, and nucleobases.[7–10] The chain helicity of the polymers can be continuously and reversibly tuned by simple external stimuli such as the solvent and pH. Amphiphilic polyacetylenes, in response to changes in their environments, spontaneously assemble into a variety of morphological structures, such as helices, vesicles, honeycomb patterns, and mollusk shapes.[11–13] To enrich the research field of helical polyacetylenes, in this communication, we report the first synthesis of a chiral poly(phenylacetylene) containing dipeptide appendages, and we present its chiroptical properties.

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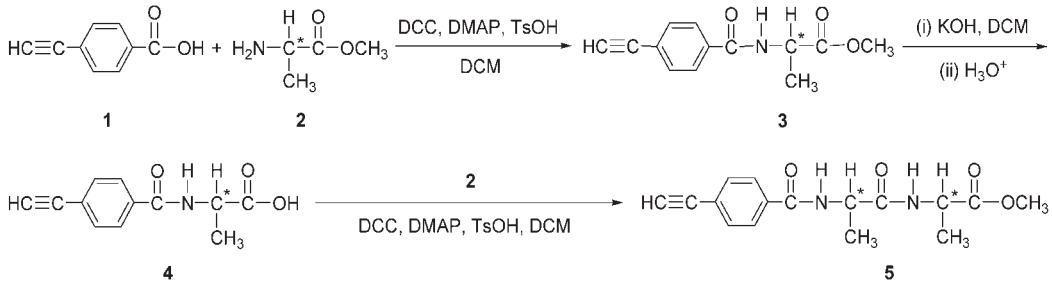
RESULTS AND DISCUSSION

We designed the molecular structure of a phenylacetylene containing a dipeptide pendant and elaborated a multistep reaction route for its synthesis (Scheme 1). We first reacted 4-ethynylbenzoic acid (**1**) with L-alanine methyl ester hydrochloride (**2**), with 1,3-dicyclohexylcarbodiimide (DCC), 4-(dimethylamino)pyridine (DMAP), and *p*-toluenesulfonic acid (TsOH) as the condensation reagents. The ester bond in **3** was cleaved in a strong basic medium, the acidification of which gave **4**. Further amidation of **4** with **2** produced the desirable product **5** in an approximately 35% yield, based on the amount of **2** used. The monomer was further purified by recrystallization in an ethanol/water mixture. A large, white single crystal was obtained and characterized with an X-ray diffractometer. An Oak Ridge thermal ellipsoid plot (ORTEP) drawing is shown in Figure 1. The crystal



Scheme 1

data and analysis parameters are summarized in Table 1.

Monomer **5** crystallizes in the monoclinic system space group $P2_1$. The two alanine moieties have the same *S* configuration, representing a phenylacetylene carrying L-alanine dipeptide. The polymerization of the monomer is effected by $[Rh(nbd)Cl]_2$ (nbd = 2,5-norbornadiene), a well-known catalyst for the polymerization of phenylacetylenes,[3–10] in a $CHCl_3/Et_3N$ mixture (10:1 v/v) at room temperature; polymer **P5** is obtained in a 94.8% yield. Although **P5** is insoluble in nonpolar solvents such as $CHCl_3$, dichloromethane (DCM), and tetrahydrofuran, it readily dissolves in polar solvents such as methanol, dimethyl sulfoxide (DMSO), and dimethylformamide (DMF). The polymer is fibrous in nature, and analysis by gel permeation chromatography (GPC) in DMF at room temperature with monodisperse polystyrene as a calibration standard gives an estimated weight-average molecular weight of 3 billion. The polymer chains may physically link together via hydrogen bonds, and this leads to such an abnormal high molecular weight.

We characterized the molecular structure of the polymer by IR and NMR spectroscopy, and satisfactory analysis data corresponding to its molecular structure were obtained (see the Experimental section for details). The absorption peaks measured in DMSO-d_6 are broad. The introduction of substituents into the poly(phenylacetylene) structure may increase the rotational barrier of **P5**. The polymer chains are thus stiffened, and subsequently the relaxation time is changed.[14] The main chains may also aggregate together through hydrogen bonding, and this leads to such broad NMR signals. The resonance of the *cis*-(*Z*)-olefin proton is found at $\delta = 5.8$. With Percec's equation,[15–23] the *Z* content of **P5** is calculated to be 80.1%, and this is demonstrative of its high stereoregularity.

Polymers with chiral pendants often show high optical rotations ($[\alpha]_D^{20}$) because of the helicity of the polymer segments. This also holds true for **P5**. In DMF, the $[\alpha]_D^{20}$ value (+232.8°; concentration = 5 mg/dL) is four times higher than those of **3** (+16.7°; concentration = 150 mg/dL) and **5** (+53.0°; concentration = 50 mg/dL), and this is suggestive of the chirality contribution from the polymer backbone, which may take an excess of helical screw sense. The $[\alpha]_D^{20}$ value changes in DMSO (+288.2°) and methanol (+1.6°) at the same concentration, but the direction remains unchanged, in contrast to our previous observations that the optical rotations of poly(phenylacetylene)s containing amino acid pendants reverse their signs even when the polarity of the solvents is similar.[7–9] The steric crowdedness of the dipeptide appendages of **P5** may impose an energy barrier, which is high enough to endow the polymer with a resistance to the solvent-induced inversion in the helical sense preference. The low value in methanol may also be related to the hydrogen-bonding capability of

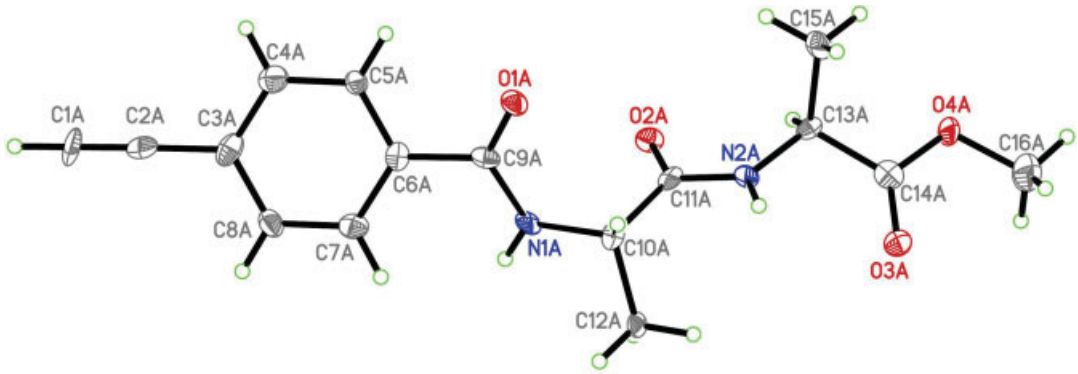


Figure 1. ORTEP drawing of monomer **5** with an atom labeling scheme. The C and O atoms are drawn as 50% thermal ellipsoids. The H atoms are shown but are not labeled.

Table 1. Summary of the Crystal Data and Intensity Collection Parameters of **5**[a]

Color/shape	White/plate
Crystal dimension (mm^3)	$0.30 \times 0.10 \times 0.08$
Chemical formula	$C_{16}H_{18}N_2O_4$
Formula weight	302.32
Temperature (K)	100(2)
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	$a = 6.4628(11)$ Å $b = 31.170(5)$ Å $c = 7.5950(13)$ Å $\beta = 94.300(4)^\circ$
Volume ($Å^3$)	1525.7(5)
Z	4
Density (Mg/m^3)	1.316
Absorption coefficient (mm^{-1})	0.096
$F(000)$	640
θ range for data collection	$1.31–24.99^\circ$
Index ranges	$-6 \le h \le 7$, $-34 \le k \le 37$, $-9 \le l \le 9$
Reflections collected	7781
Independent reflections	4407 [R(int) = 0.0508]
Completeness to θ	24.99°, 98.4%
Absorption correction	Semiempirical from equivalents
Maximum and minimum transmissions	1.00 and 0.89
Refinement method	Full-matrix least squares on F^2
Data/restraints/parameters	4407/1/397
Goodness of fit on F^2	1.028
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0651$, $wR2 = 0.0978$
R indices (all data)	$R1 = 0.0970$, $wR2 = 0.1062$
Absolute structure parameter	0.8(14)
Largest diffraction peak and hole	0.265 and -0.204 e.$Å^{-3}$

[a] Abbreviations: Z = number of asymmetric unit in a unit cell, F = scattering factor, θ = angle of incidence, I = intensity, σ = standard deviation, and w = weighting scale.

the solvent, which competes with the N—H protons for the carbonyl oxygen atoms in the polymer.

To confirm whether the L-dipeptide pendants induce the polymer backbone to helically rotate, we carried out circular dichroism (CD) analysis. As shown in the upper part of Figure 2, monomer **5** is CD-inactive at wavelengths longer than 300 nm. Its polymer, however, shows strong absorptions at 330 and 370 nm with high molar ellipticities ($[\theta] = -19{,}700$ and $+15{,}300$ deg cm^2 $dmol^{-1}$, respectively) in DMF, and this proves that the polymer backbone indeed takes a predominantly one-handed helical conformation. The spectral patterns are similar in DMSO and methanol, but the peak intensity varies, and this suggests that some parts of the chain segments have changed their handedness or helicity with the solvent change.

The lower part of Figure 2 depicts the UV spectra of **P5** in different solvents. The broad absorption at approximately 400 nm has been assigned to the π–π^* transitions of the helical polymer backbones. Unlike the results obtained from the specific rotation and CD measurements, the absorbance is less sensitive to the solvent change, with the spectral profiles being practically the same in different solvents.

In our previous work,[7] we found that the chain helicity of poly(phenylacetylene) bearing L-valine pendants decreases with increasing temperature because randomization of chain conformation is promoted by the thermal agitation. It is of interest to learn whether **P5** shows the same response to thermal perturbation. When a DMF solution is heated

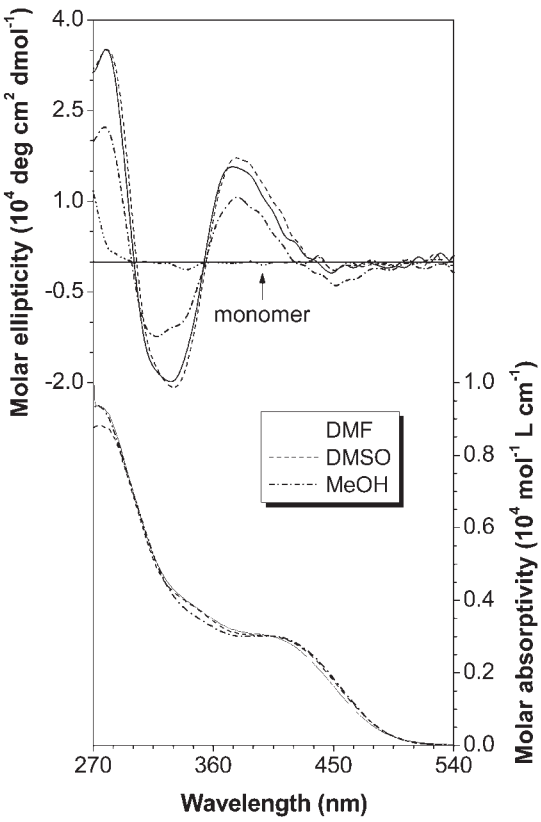


Figure 2. CD and UV spectra of **P5** in different solvents at room temperature (~23 °C). The CD spectrum of monomer **5** in a DMF solution is shown for comparison. Spectral data in DMF and DMSO below 270 nm were not taken to avoid interference by solvent absorption. The concentrations were approximately 1.65 mM (CD) and approximately 0.07 mM (UV).

from 10 to 80 °C, the intensities of the peaks are progressively lowered [Fig. 3(A)]. The helical conformation of **P5** is thermally quite stable because the chain conformation is not completely randomized at temperatures up to 80 °C. When the solution is cooled back to room temperature (23 °C), the CD spectrum is not fully reinstalled. Degradation of *Z*-poly(phenylacetylene)s via intramolecular cyclization is a well-established reaction taking place even at room temperature.[14–23] No peaks related to the absorptions of the degradative products, however, appear in the ^{1}H NMR spectrum of **P5** after its DMSO solution has been heated at 80 °C in air for 30 min [Fig. 3(B), inset], and this indicates that the change, if any, in the molecular structure of **P5** after the thermal treatment is negligibly small. This is further proved by the UV spectra of the polymer solutions measured at different temperatures. The UV spectrum changes little even when the temperature is raised to 80 °C, although it fails to return to its original intensity after the solution is cooled back to 30 °C. The NMR and UV experiments thus confirm that the polymer has not suffered from thermal degradation during the heating process and suggest that the change in the CD absorption is probably due to irreversible conformational changes of the chain segments.

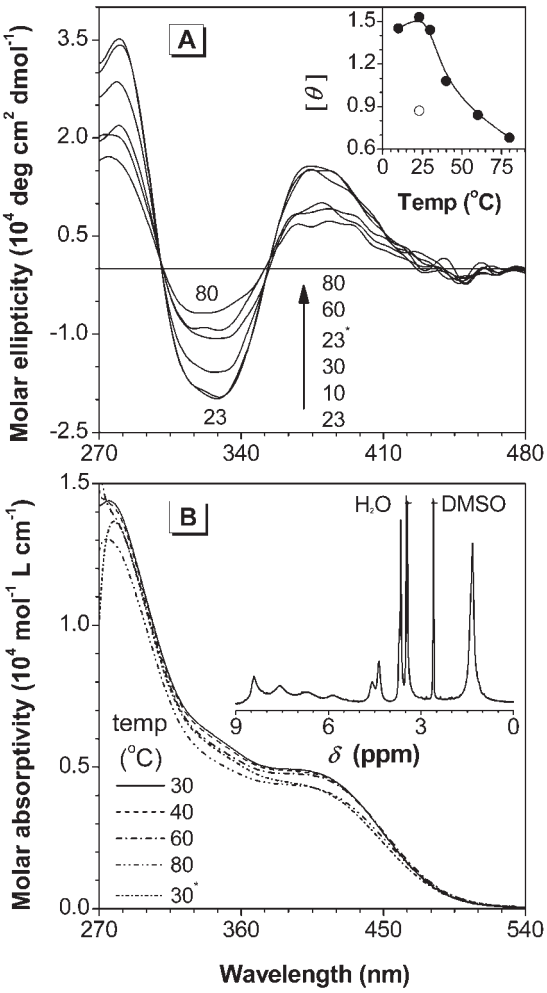


Figure 3. (A) CD and (B) UV spectra of **P5** in DMF at different temperatures. The polymer concentrations were approximately 1.65 mM (CD) and approximately 0.07 mM (UV). The spectra for the samples heated at 80 °C are marked with asterisks. The insets show the variation of the molar ellipticity at 370 nm with the temperature and the ^{1}H NMR spectrum of **P5** after its DMSO-d_6 solution was heated at 80 °C for 30 min.

CONCLUSIONS

In this work, we have synthesized a new phenylacetylene with L-alanine dipeptides by multistep reactions and confirmed its structure by X-ray crystal structure analysis. The monomer is polymerized by $[Rh(nbd)Cl]_2$, and this produces a yellow, fibrous polymer in a high yield. The polymer shows high specific rotation and backbone CD absorptions because of an excess of one-handed helical conformation. The backbone helicity can be tuned by the solvent and temperature, and a change by the latter is partially irreversible. Dipeptides are useful small biomolecules in medicinal and food science. Dipeptides such as Phe-Phe-OMe, Leu-Ala-OMe, and Leu-Gly-OMe have been found to exhibit antileishmanial activity on *leishmania amazonensis* amastigotes.[24] The polymer bearing the dipeptide pendants may thus show some unique biological properties such as biomimetic environmental adaptability and cell-growth-stimulating capability.

EXPERIMENTAL

Materials

1 was synthesized according to previous publications[7,8,25] and stored in a dry, cool place. All other chemicals were purchased from Aldrich or Acros and used without further purification.

Instrumentation

The IR spectra were measured on a PerkinElmer 16 PC Fourier transform infrared spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker ARX 300 NMR spectrometer with DMSO-d_6 as a solvent and tetramethylsilane (TMS; $\delta = 0$) or DMSO (2.6) as an internal reference. The UV spectra were measured on a Milton Roy Spectronic 3000 array spectrophotometer, and the molar absorptivity of the polymers was calculated on the basis of their

monomer repeat units. The mass spectra were recorded on a Finnigan TSQ 7000 triple quadrupole mass spectrometer operating in a chemical ionization (CI) mode with methane as the carrier gas. The molecular weights of the polymers were estimated with a Waters Associates GPC system at room temperature. Degassed DMF was used as an eluent at a flow rate of 1.0 mL/min. A set of monodisperse polystyrene standards covering the molecular weight range of 10^3–10^7 was used for the molecular weight calibration. The $[\alpha]_D^{20}$ values were measured on a PerkinElmer 241 polarimeter at 20 °C with a beam of plane-polarized light of the D line of a sodium lamp (589.3 nm) as a monochromatic source. The CD measurements were recorded on a Jasco J-720 spectropolarimeter in 1-mm quartz curettes with a step resolution of 0.2 nm, a scan speed of 50 nm/min, a sensitivity of 0.1 °, and a response time of 0.5 s. Each spectrum was the average of 5–10 scans.

Synthesis

The phenylacetylene containing an L-alanine dipeptide pendant was synthesized by the following procedure. In a 500-mL, round-bottom flask were dissolved 1.5 g of 4-ethynylbenzonic acid (10.3 mmol), 1.2 g of **2** (8.6 mmol), 2.6 g of DCC (12.6 mmol), 0.4 g of TsOH (2.1 mmol), and 0.6 g of DMAP (4.9 mmol) in 250 mL of dry CH_2Cl_2. The reaction mixture was stirred overnight. The product **3** was purified by a silica-gel column with chloroform/ethyl acetate (15:1 v/v) as an eluent. The methyl ester group in **3** was cleaved in a KOH/DCM mixture for 30 min. The mixture was then neutralized by dilute HCl. The precipitate was dissolved in $CHCl_3$ and washed with brine twice. The crude product **4** (1.5 g; 6.9 mmol) was then reacted with 1.1 g of **2** (7.9 mmol) in $CHCl_2$ in the presence of 1.7 g of DCC (8.2 mmol), 0.4 g of DMAP (3.3 mmol), and 0.3 g of TsOH (1.6 mmol). The solution was stirred at room temperature for 24 h. After filtration, the filtrate was evaporated by a rotary evaporator. The product was purified by silica gel chromatography with chloroform/ethyl acetate (5:1 v/v) as an eluent, and this yielded a white solid (33.3%, 0.6 g).

IR (KBr, v, cm^{-1}): 1741 (s, C=O), 1666 and 1644 (s, N—H). ^1H NMR (300 MHz, DMSO-d_6, δ, TMS, ppm): 8.7 (d, 1H, PhCONH), 8.5 (d, 1H, NH), 8.0 (d, 2H, Ph—H ortho to C=O), 7.7 (d, 2H, Ph—H meta to C=O), 4.6 (m, 1H, PhCONHC*H*), 4.5 (s, 1H, CH) 4.4 (m, 1H, C*H*CO_2CH_3), 3.7 (s, 3H, CO_2CH_3), 1.2 [m, 6H, NHCH(C*H*$_3$)CO]. ^{13}C NMR (75 MHz, DMSO-d_6, δ, TMS, ppm): 173.0 (CO_2), 172.3 (NHCH*C*ONH), 165.2 (Ph*C*ONH), 134.1 (aromatic carbon attached to C=O), 131.5 (aromatic carbons meta to C=O), 127.8 (aromatic carbons ortho to C=O), 124.4 (aromatic carbons para to C=O), 82.9 (Ph*C*), 82.8 (HC), 51.8 (NHCH), 48.57 (CO_2CH_3), 47.569 (CH), 17.767 and 16.85 ($CHCH_3$). Mass spectrometry (CI): *m/e* 303.3 [$(M + 1)^+$, calcd. 303.3].

Polymerization

The monomer was polymerized by $[Rh(nbd)Cl]_2$ in a $CHCl_3/Et_3N$ mixture (10:1 v/v). Into a 20-mL test tube with a septum were added 179 mg (0.6 mmol) of **5** and 71 mg (0.015 mmol) of $[Rh(nbd)Cl]_2$. A 10:1 (v/v) mixture of $CHCl_3/Et_3N$ (6 mL) was added. The reaction mixture was stirred at room temperature for 24 h. The mixture was then diluted with 5 mL of $CHCl_3$ and added dropwise to a diethyl ether solution with stirring. The precipitate was collected by filtration and dried *in vacuo* at room temperature to a constant weight. The polymeric product was isolated as a yellow, fibrous solid in a high yield (96.8%).

IR (KBr, v, cm^{-1}): 1743 (s, C=O), 1640 (s, N—H). ^1H NMR (300 MHz, DMSO-d_6, δ, TMS, ppm): 8.7 (NH), 7.6 (Ph—H ortho to C=O), 6.7 (Ph—H meta to C=O), 4.6 (PhCONHC*H*), 4.4 (C*H*CO_2CH_3), 3.7 (CO_2CH_3), 1.3 [NHCH (C*H*$_3$)CO]. ^{13}C NMR (75 MHz, DMSO-d_6, δ, TMS, ppm): 172.9 (CO_2), 172.5 (NHCH*C*ONH), 165.3 (Ph*C*ONH), 143.85 (aromatic carbon attached to C=O), 138.46 (aromatic carbons meta to C=O), 132.31 (aromatic carbons ortho to C=O), 126.9 (aromatic carbons para to C=O), 51.77 (NHCH), 48.619 (CO_2CH_3), 47.58 (CH), 17.798 and 16.794 ($CHCH_3$).

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