Syntheses, Hydrogen-Bonding Interactions, Tunable Chain Helicities, and Cooperative Supramolecular Associations and Dissociations of Poly(Phenylacetylene)s Bearing L-Valine Pendants: Toward the Development of Proteomimetic Polyenes[†]

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ABSTRACT: 4-Ethynylbenzoyl-L-valine methyl ester (**1e**), an acetylene−valine adduct, is polymerized by organorhodium catalysts to the corresponding "polyester" (P**1e**) of high molecular weights (M_w up to 371 000) and high stereoregularities (Z content up to 100%) in high yields (up to ~95%). The amino acid residues form intrastrand and interstrand hydrogen bonds within and between the polymer chains. The ester groups of P**1e** are selectively deprotected by base-catalyzed hydrolysis, giving "polyacid" P**1a** with "free" valine pendants. While **1e** is CD-inactive at $\lambda > 300$ nm, both P**1e** and P**1a** exhibit intense Cotton effects in the long wavelength region where the polyacetylene backbone absorbs, confirming that the chiral valine pendants have induced the polymer chain to take a helical conformation with an excess in one handedness. The helicity of the chain segments is sensitive to the variations in their environmental surroundings. Utilizing this environmental susceptibility, the chain helicity of the polymers is tuned continuously by such external stimuli as solvent, temperature, pH, and additive, with cooperativity being observed in most systems. The manipulation of the chain helicity by solvent and pH is fully reversible.

Introduction

Amino acids are naturally occurring building blocks, from which polypeptide chains are constructed by protein-synthesizing machineries of cells.[1] The genetic blueprint determines the linear sequence of amino acids in a protein, and the balance of various forces such as hydrogen bonding and hydrophobic interaction dictates the folding of proteins into their native, active forms.[2] Because almost all the bonds involved in the higher-order bioassemblies are noncovalent, protein structures are intrinsically unstable. Solvent, temperature, pH, salt, soap, ion, hydrogen-bonding agent, etc. can readily denature proteins. The native conformations of proteins are often only marginally more stable than their denatured ones.[3] Such a small stability difference facilitates conformational shuttling, enabling proteins to respond to the variations in their surroundings and to adapt to the changed environments by swiftly switching between different conformations.[4] Some proteins can renature after denaturation, while some structures can refold faster than others. The α-helix seems to be the fastest folding, due to the involved cooperativity in the molecular association process: once a few hydrogen bonds of a helical segment are formed, subsequent amino acid residues are aligned to quickly form many more additional hydrogen bonds and to rapidly (re)fold many more additional segments, resulting in the fast formation of a long helical chain.[5]

Naturally occurring polyenes covalently linked or noncovalently bound to proteins play very important biological roles in the living kingdom.[6] The conformational change of 11-cis isomer of Schiff base of retinal, for example, is the primary event in the visual excitation.[7] Protein adducts of astaxanthin, a carotenoid, are ubiquitous in invertebrate marine animals. The combination of astaxanthin with protein via water-aided hydrogen bonding gives crustacyanin, a carotenoprotein.[8] The protein complexation induces astaxanthin to helically twist, which changes the color of the natural polyene chromophore from orange to blue. This conformational twisting provides the structural basis for the chromic shift that a living crustacean utilizes to produce dark pigment for camouflage.[9] Upon dehydration, crustacyanin is unfolded or denatured and astaxanthin reverts to its extended orange form. Rehydration may renature crustacyanin through reversible hydrogen bonding and helical twisting of the astaxanthin chromophore. In other words, the denaturation−renaturation process of the carotenoprotein is reversibly accompanied by a polyene chain extending-twisting process.

Polyacetylenes are synthetic polyenes. We have embarked upon a research program of combining polyacetylenes with amino acids at molecular level.[10,11] In our previous work, we have found that the polyacetylenes containing amino acid residues can self-assemble into biomimetic nanostructures such as micelles, vesicles, globules, and helical cables and have demonstrated that the organizational structures of the amphiphilic polyenes can be modulated by changing external conditions such as solvent and pH in the morphological assembling processes.[10−12] The manipulability of the higher-order structures suggests that the chain conformations of the synthetic polyenes is tunable by external stimuli, as briefly discussed in our previous publications.[10−12] Careful scrutiny of the stereostructures of a chiral polyene

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[†] Parts of the results described in this paper were reported at the ACS National Meetings in 2000.[11]

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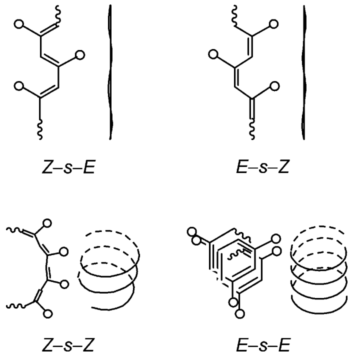
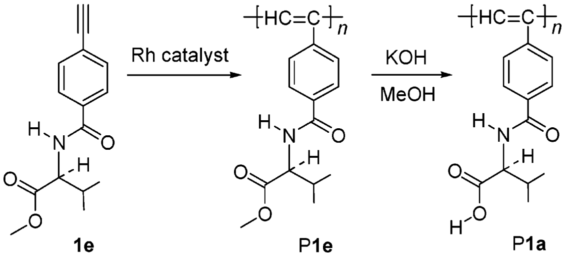
Chart 1



Scheme 1



segment reveals that the chain helicity is labile: a simple single-bond rotation can readily alter the handedness and pitch of a helical chain segment (Chart 1). Indeed, our theoretic calculation indicates that the energy differences between the *Z*-*s*-*E*, *E*-*s*-*Z*, and *Z*-*s*-*Z* conformers are marginally small.[13] The conformational change induced by the single bond rotation is, however, difficult, if not impossible, to follow by NMR spectroscopy. In this work, we used circular dichroism (CD) spectroscopy to systematically investigate the helicity changes of two valine-containing polyacetylenes, namely, poly(4-ethynylbenzoyl-L-valine methyl ester) (P**1e**) and poly(4-ethynylbenzoyl-L-valine) (P**1a**; Scheme 1), under different environmental conditions. In this paper, we present the synthetic details of the nonbiological polyenes and demonstrate the continuous and reversible tunability of their chain helicity by external stimuli.

Experimental Section

Full details about materials, instrumentation, polymer synthesis (including polyester hydrolysis), and spectroscopic analysis (including the lists of numerical spectral data) are given in the Supporting Information. Part of the experimental details can also be found in our previous publications of this series.[12] The phenylacetylene−valine adduct of 4-ethynylbenzoyl-L-valine methyl ester (**1e**) and the organorhodium complexes of Rh(cod)(NH_3)Cl (cod = 1,5-cyclooctadiene), Rh(cod)(tos)(H_2O) (tos = *p*-toluenesulfonate) and Rh(nbd)(tos)(H_2O) (nbd = 2,5-norbornadiene) were prepared according to our previously reported experimental procedures.[12,14]

Results and Discussion

Polymerization Behaviors and Thermal Properties. Rhodium complexes such as $[Rh(cod)Cl]_2$ and $[Rh(nbd)Cl]_2$ are known as effective, functionality-tolerant catalysts for acetylene polymerizations. We tried to use the rhodium complexes to polymerize the acetylene monomer containing functional L-valine residue (**1e**). To our surprise, the attempted polymerizations of **1e** in the presence of $[Rh(cod)Cl]_2$ in THF, DCM, and dioxane all failed, with almost no polymeric products obtained after the reaction mixtures had been stirred at room temperature for 24 h (Table 1, nos. 1−3). Clearly, a well-known "catalyst" does not automatically guarantee the occurrence of polymerization of **1e**. We tried to change the reaction parameters, with an aim of identifying optimal polymerization conditions for the preparation of high molecular weight polymers in high yields. Gratefully, in toluene, the rhodium complex showed some catalytic activity in polymerizing **1e**, though both M_w and yield of the isolated polymer (P**1e**) were relatively low. When a drop of triethylamine was added into THF, the polymerization proceeded well, giving a polymer with a high M_w (158 000) in high yield (68%). Addition of triethylamine into DCM also helped, yielding a polymer with an M_w of over 2×10^5.

Table 1. Polymerization of Valine-Containing Acetylene Monomer 1e[a]

no.	catalyst[b]	solvent[c]	yield (%)	M_w[d]	M_w/M_n[d]	*Z*, %[e]
1	$[Rh(cod)Cl]_2$	THF	trace			
2	$[Rh(cod)Cl]_2$	DCM	trace			
3	$[Rh(cod)Cl]_2$	dioxane	trace			
4	$[Rh(cod)Cl]_2$	toluene	37.5	31 000	3.43	81.3
5	$[Rh(cod)Cl]_2$	THF/Et_3N	68.1	158 000	7.15	100.0
6	$[Rh(cod)Cl]_2$	DCM/Et_3N	37.8	213 000	5.24	89.8
7	Rh(cod)(NH_3)Cl	THF	46.6	150 000	6.13	83.1
8	Rh(cod)(tos)(H_2O)	THF	17.6	150 000	4.67	80.2
9	Rh(cod)(tos)(H_2O)	THF/Et_3N	18.1	205 000	5.63	80.3
10	$[Rh(nbd)Cl]_2$	THF	88.6	279 000	5.95	94.1
11	$[Rh(nbd)Cl]_2$	THF/Et_3N	93.2	168 000	4.84	87.4
12	$[Rh(nbd)Cl]_2$[f]	THF/Et_3N	95.3	371 000	7.93	93.4

[a] Carried out at room temperature under nitrogen for 24 h; $[M]_0$ = 0.1 M, [cat.] = 5 mM. [b] Abbreviations: nbd = 2,5-norbornadiene, cod = 1,5-cyclooctadiene, tos = *p*-toluenesulfonate, THF = tetrahydrofuran, and DCM = dichloromethane. [c] Volume of solvent used: 2 mL. Volume of Et_3N added: 1 drop. [d] Estimated by GPC in THF on the basis of a polystyrene calibration. [e] Determined by ^1H NMR analysis. [f] [cat.] = 1 mM.[12c]

Not only the externally added amine cocatalyst but also the internally coordinated amine ligand helped improve the performance of the organorhodium catalyst. Thus, Rh(cod)(NH_3)Cl, a rhodium complex with an amine ligand, catalyzed well the polymerization of **1e** in THF, giving P**1e** of high M_w in good yield (Table 1, no. 7). The rhodium complex Rh(cod)(tos)(H_2O) produced polymers with high M_w's but in low yields. The rhodium complex with an nbd ligand initiated the polymerization of **1e** in both THF and THF/Et_3N, leading to the formation of polymers with high molecular weights (M_w up to 371 000) in high yields (up to ~95%). These results demonstrate that the catalytic activity of the rhodium complexes in the polymerization of **1e** is sensitively affected by the structures of their ligands.

A chain segment of a substituted polyacetylene can take four theoretically possible conformations: *Z*-*s*-*E*, *E*-*s*-*Z*, *Z*-*s*-*Z*, and *E*-*s*-*E* (cf., Chart 1).[13,15,16] P**1e** shows sharp, resolved NMR spectra (panels A and B of Figure s1, Supporting Information), suggestive of a high stereoregularity. The singlet centered at δ ~6.0 in the spectrum of P**1e** is assignable to the resonance of the olefinic proton of its chain segment with a *Z*-*s*-*E* conformation.[15,16] Using an equation similar to those we published before,[15,17] the *Z* content of P**1e** is estimated to be ~93% (Table 1, no. 12). The *Z* contents of other polymers prepared under different conditions are estimated by the same method and tabulated in Table 1. All the polymers show high *Z* contents, in agreement with the general observation that Rh-catalyzed poly-

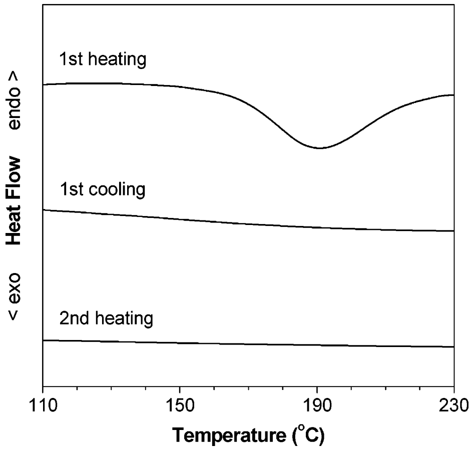


Figure 1. DSC thermograms of P**1e** (sample from Table 1, no. 11) recorded under nitrogen at a heating rate of 10 °C/min.

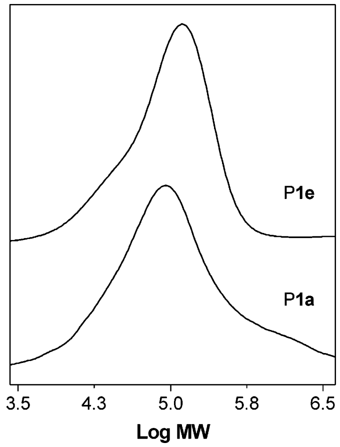


Figure 2. GPC chromatograms of P**1e** (sample from Table 1, no. 12) and P**1a** (prepared by ~2 h hydrolysis of P**1e**) calibrated by polystyrene standards in THF.

merizations produce polyacetylenes with *Z*-rich conformations.[15,17,18] The polymer prepared by $[Rh(cod)Cl]_2$ in THF/Et_3N has a *Z* content of 100% (Table 1, no. 5), that is, the polymer possesses a perfectly stereoregular chain conformation.

(Unsubstituted) polyacetylene chain undergoes thermally induced cis−trans isomerization.[19] P**1e** is a polyacetylene derivative, whose chain segments of *Z* conformation may also isomerize into their *E* conformational counterparts when a sufficient amount of energy is supplied. Figure 1 shows DSC thermograms of P**1e**. In the first heating scan, P**1e** starts to release heat from ~165 °C. Because P**1e** is thermally stable below ~300 °C (Figure s2; Supporting Information), the exothermic valley bottomed at ~190 °C should be associated with its thermal *Z*−*E* isomerization. Similar to that of its polyacetylene parent, the isomerization process of P**1e** is thermally irreversible: the successive first cooling and second heating scans detect no any peaks at ~190 °C, giving almost flat lines parallel to the abscissa over the whole scanned temperature region. These results also support that the exothermic valley at ~190 °C is not due to chain scission because the thermolysis process should reoccur when the polymer is reheated to the high temperatures.

After the success in converting **1e** to P**1e**, we tried to cleave the methyl ester-protecting groups and transform the “polyester” to its “polyacid” form P**1a** (Scheme 1). Under the basic condition using KOH as cleaving reagent,[20] the deprotection reactions went smoothly and the polyacids were all obtained in high yields (>90%) under different hydrolysis conditions. GPC analysis reveals that a polyacid obtained by, e.g., ~2 h hydrolysis possesses a high molecular weight (M_w ~4.1×10^5), parallel to that of its polyester parent (M_w ~3.7×10^5; Figure 2). The profiles of the GPC curves of P**1e** and P**1a** are similar, indicating that the polymer has not experienced disastrous degradation during the hydrolysis reaction. The reaction condition is likely mild enough to be harmless to other functional groups of the polymer.

We used spectroscopic methods to further examine the structural integrity of the hydrolysis product of P**1a** (see Experimental Section in the Supporting Information for detailed spectral analysis data). Figure s1 (Supporting Information) compares the ^1H NMR spectra of P**1a** with those of its polyester parent P**1e**. The spectrum of P**1e** in deuterioacetone is well resolved, with the protons of its ester (CO_2CH_3), vinyl ($HC=$), and amide ($HNCO$) groups resonating at δ ~3.6, ~6.0, and ~7.7, respectively (Figure s1A). Its resonance peaks in methanol-d_4 are also sharp, but due to the exchange between the active proton of the polymer and the protic residue of the solvent,[21] the amide peak disappears (Figure s1B). Its hydrolysis product P**1a**, however, shows no resonance signal of methyl ester at δ ~3.6; a new acid peak instead appears at δ ~12.6 (Figure s1D), though this peak is not observed in the methanol solution (Figure s1C) due to the involved proton exchange process.[21] The spectroscopic analysis confirms that the methyl ester group has been completely cleaved and that the acid group has been generated accordingly. In addition, the spectrum shows that other functional groups like vinyl and amide have remained intact during the ester hydrolysis reaction. In other words, the double bonds in the main chain and the amide bonds in the side chain have been undamaged by the base-catalyzed ester-deprotection reaction. The integration of the areas of the resonance peaks also supports the molecular structure of P**1a**. The highly selective feature of the ester deprotection reaction enabled us to prepare the polyacid with high structural homogeneity. From the NMR spectrum of P**1a**, it is estimated that its *Z* content is ~97%, verifying that the stereoregularity of the polymer chains is also virtually unaffected by the hydrolysis reaction.

Hydrogen-Bond Interaction and Chain Helicity. Noncovalent molecular interactions play critical roles in protein folding. The α-helix, for example, is a cylindrical structure maintained by hydrogen bonds, where every carbonyl oxygen atom is hydrogen bonded to an amide hydrogen atom four residues ahead in the polypeptide chain. In our previous study, we have found that the L-leucine residue of the leucine−acetylene adduct readily forms intermolecular hydrogen bonds.[22] The L-valine residue of **1e** may also experience hydrogen-bond interaction, and we thus investigated its hydrogen bonding behaviors. Figure 3 shows the ^1H NMR spectra of **1e** solutions in deuteriochloroform with different concentrations at room temperature. In a dilute solution (50 mg/mL), **1e** shows resonance signals of amide proton at δ ~6.7 (marked with a downward arrow in Figure 3A). When the solution concentration is gradually increased, the amide signals are progressively downfield shifted. At a concentration of 300 mg/mL, the amide signals of **1e** are downfield shifted to as far as δ ~7.2 (Figure 3F). Noticing that chloroform is an aprotic

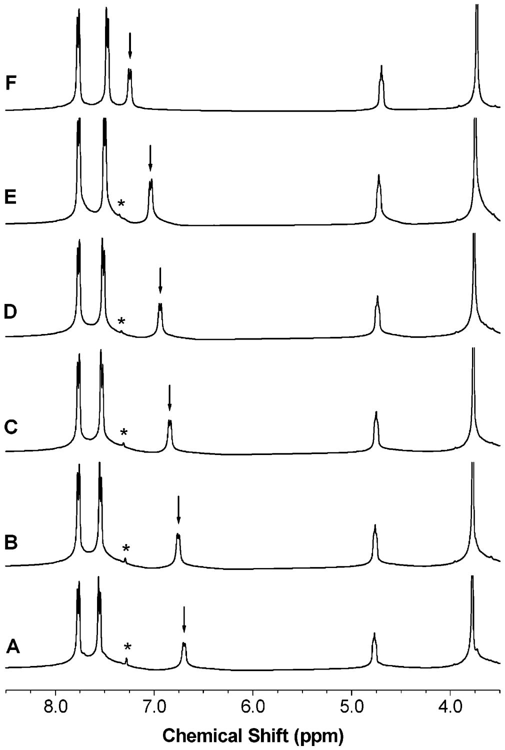


Figure 3. ^{1}H NMR spectra of chloroform-*d* solutions of **1e** with concentrations of (A) 50, (B) 75, (C) 100, (D) 150, (E) 200, and (F) 300 mg/mL. The resonance peaks of the amide proton are marked with downward arrows (↓), while those of the solvent are marked with asterisks (∗).

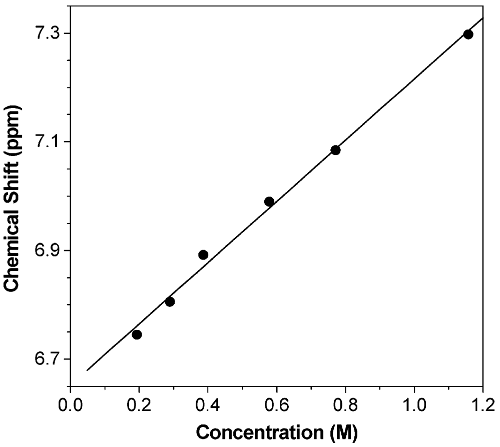
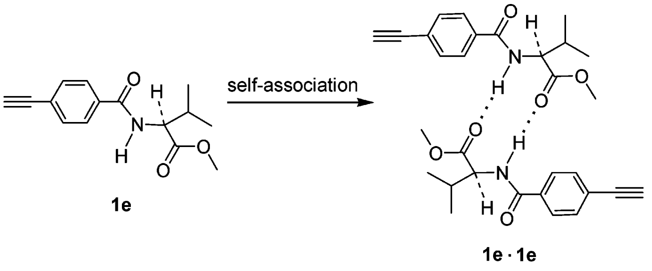


Figure 4. Concentration dependence of chemical shift of amide proton resonance of the chloroform-*d* solutions of **1e**.

Scheme 2



solvent, the downfield shift of the amide peak thus should be due to the formation of intermolecular hydrogen bond. When a proton is involved in hydrogen bonding, its electron is shared by two electronegative elements and its electron density is decreased. As a result, the proton is deshielded and comes into resonance at a lower field.[21]

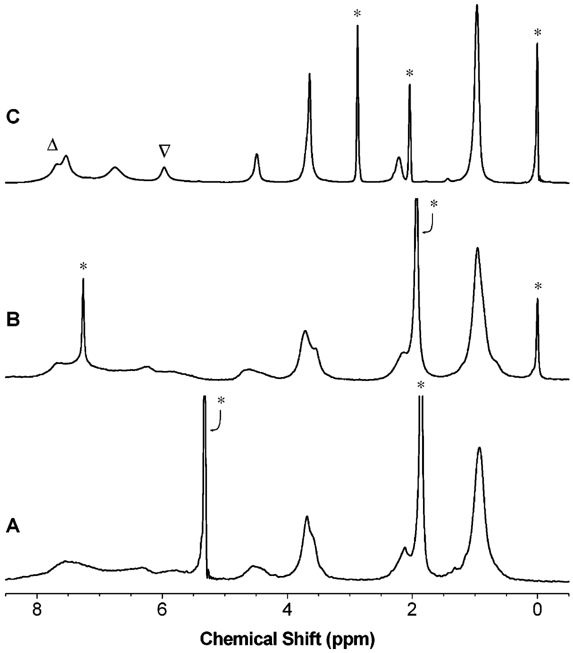


Figure 5. ^{1}H NMR spectra of (A) DCM-d_2, (B) chloroform-*d*, and (C) acetone-d_6 solutions of P**1e** (sample from Table 1, no. 11). Polymer concentration: (A and B) ~20; (C) ~8 mg/mL. The resonance peaks of the amide (*H*NCO) and vinyl (*H*C=) protons are respectively marked with up (△) and down triangles (▽), while those of the solvents, water, and TMS are marked with asterisks (∗).

Plotting the resonance data of the amide proton reveals a linear relationship between the peak position (δ) and the solution concentration (c); that is to say, the population of the hydrogen-bond complexes of **1e** increases linearly with concentration (Figure 4). The δ–c relationship observed here for the valine–acetylene adduct is in agreement with that observed previously for its congener of leucine–acetylene adduct.[22] The deshielding effect is arisen from the molecular interaction involved in the self-association of the adduct molecules through the formation of multiple hydrogen bonds between the N–*H* group of one molecule and the C=*O* group of another (Scheme 2).

How will the amino acid residues or the L-valine pendants interact in the polymer system? It can be imagined that when the valine residues are covalently bound to every repeat unit of the polyene chains, the closely located amide groups in the same and/or different chains may readily form hydrogen bonds in nonpolar environments. To learn the molecular interactions in the P**1e** system, we measured its NMR spectra in different solvents. (The limited solubility of the polymer in common deuterated solvents has prevented us from checking the concentration effect on its NMR spectra in the same solvents.)

The ^{1}H NMR spectrum of P**1e** in DCM, a nonpolar solvent, is poorly resolved, making it difficult to elucidate the resonance signals (Figure 5A). The broad peaks of the proton resonance are probably due to the existence of intra- and interchain hydrogen bonds in the polymer system.[23] The hydrogen bonds may stiffen the polymer chains and restrict their movements, thus broadening the resonance peaks.[21] The chloroform solution of P**1e** displays a similar spectrum. However, the polymer solution in acetone, a polar solvent, gives a

Table 2. Specific Optical Rotations of P1 in Different Solvents[a]

		$[\alpha]^{20}_{\mathrm{D}}$, degree (c, g/dL)	
no.	solvent	P**1e**	P**1a**[b]
1	chloroform	−244.4 (0.126)	−423.3 (0.030)[c]
2	DCM	−67.3 (0.088)	
3	methanol	+210.9 (0.064)	+67.6 (0.034)
4	THF	+326.7 (0.164)	+126.5 (0.034)
5	acetone	+355.4 (0.065)	
6	DMF	+502.9 (0.035)	+534.4 (0.032)

[a] $[\alpha]^{20}_{\mathrm{D}}$ of **1e** (monomer) in chloroform: +54.2° (0.038 g/dL). [b] Prepared by ∼1 h hydrolysis of P**1e**. [c] A mixture of chloroform and THF (50:50 by volume) was used in this measurement.

better-resolved spectrum, where the amide resonance is seen at δ ∼7.8 (Figure 5C). This implies that the intra- and interstrand hydrogen bonds of P**1e** chains have been partially broken. Other than the intra- and interstrand interactions between the polymer chains, intermolecular hydrogen bonds can also be formed between the carbonyl groups of the molecules of acetone solvent and the amide groups of the valine pendants of the polymer solute. Such hydrogen bonding contributes to the solvation of the macromolecular chains and to the partial disassembling of the associated polymer clusters,[23b] thus making the polymer better dissolved and the spectrum better resolved.

In the biological system, folding structures of proteins can be varied or denatured by the changes in their environmental surroundings. We examined how the environmental conditions such as dissolving media would affect the chain conformations of our valine-containing polyacetylenes. We measured the specific optical rotations of the polymers at 20 °C ($[\alpha]_{\mathrm{D}}^{20}$) in different solvents, with the aim of gathering information on their chain conformations. In chloroform, P**1e** shows an $[\alpha]_{\mathrm{D}}^{20}$ value of −244.4° (Table 2, no. 1), which is opposite in sign and larger in magnitude when compared to that of its monomer (**1e**) in the same solvent (+54.2°). It is known that a polymer chain with a helical conformation can show very high optical activity.[24−26] The high $[\alpha]_{\mathrm{D}}^{20}$ value of P**1e** suggests that the polymer chain is helically rotating. When the solvent is changed from chloroform to DCM, methanol, ..., and DMF, the $[\alpha]_{\mathrm{D}}^{20}$ value of P**1e** varies drastically from −244.4° to −67.3, +210.9, ..., and +502.9° (Table 2, nos. 1−6). Similarly, the $[\alpha]_{\mathrm{D}}^{20}$ value of P**1a** greatly changes with solvent. In a nonpolar medium such as a mixture of chloroform and THF (50 vol %),[27] P**1a** exhibits an $[\alpha]_{\mathrm{D}}^{20}$ value of −423.3°, whereas in a polar solvent like DMF, its $[\alpha]_{\mathrm{D}}^{20}$ jumps to a large positive value (+534.4°). There seemly exists some correlation between the solvent polarity and the optical rotation: the polymers exhibit the highest negative $[\alpha]_{\mathrm{D}}^{20}$ values in a less polar chlorinated solvent[28] and the highest positive $[\alpha]_{\mathrm{D}}^{20}$ values in a more polar non-chlorinated solvent.[29]

As discussed above, the high optical activities of the polymers imply that their chain segments take helical conformations. To confirm this, we used CD spectroscopy, a powerful tool for investigating helical structures.[30] As can be seen from the upper panel of Figure 6, P**1e** gives intense CD signals in the long wavelength region where its monomer does not absorb at all or is completely CD-inactive. The strong Cotton effects of P**1e** in the long wavelength region thus must be due to the absorption of its polyene backbone, confirming that the polymer chains are indeed helically rotating. The chain helicity changes with solvent. In DMF and acetone, P**1e** shows strong CD spectra with their first, second, and third Cotton effects at ∼375, ∼320, and ∼270 nm being positive (+), negative (−), and positive (+), respectively. The high CD intensities suggest that the polymer chain takes a helical conformation with a large excess of one handedness. In THF and methanol, the spectral profiles of P**1e** remain almost unchanged but the peak intensities are weakened, implying that a fraction of the helical chain segments has reversed its screw sense. In a less polar chlorinated solvent of DCM, the CD pattern is completely inverted in sign, indicating that the relative population of the right- and left-handed helical chain segments is reversed. In chloroform, the preference for one handedness further prevails over another. Interestingly, the signs and the relative strengths of the first Cotton effects of the polymer in the solvents well coincide with those of its specific optical rotations in the same solvents (cf., Table 2).

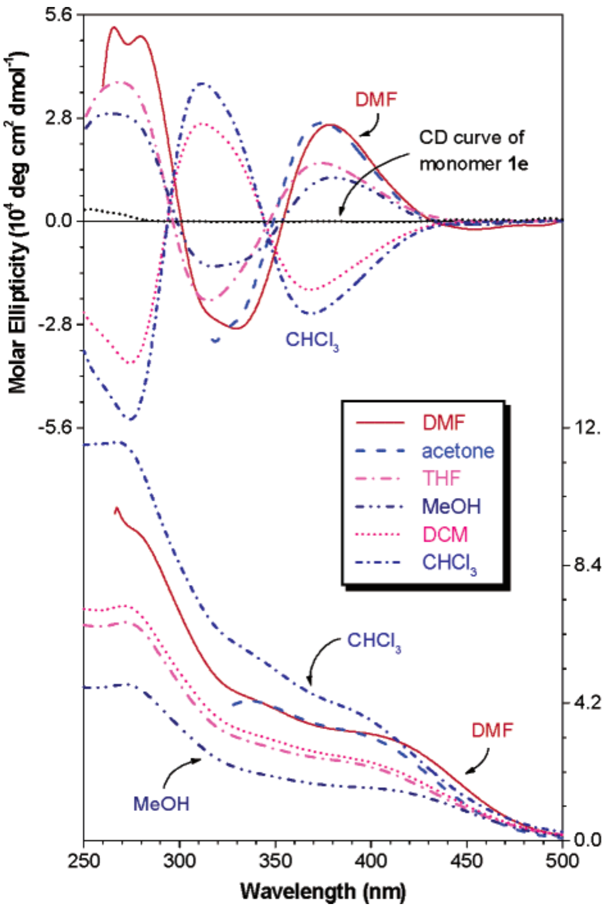


Figure 6. CD and UV spectra of P**1e** (sample from Table 1, no. 11) in different solvents. Polymer concentration (mM): ∼1.5 (CD); ∼0.1−0.2 (UV). The CD spectrum of a chloroform solution of monomer **1e** with a similar concentration is shown for comparison. The spectral data in DMF below 260 nm and in acetone below ∼325 nm were not taken to avoid the complications caused by the solvent absorptions.

The lower part of Figure 6 shows the UV spectra of P**1e** in different solvents. In methanol, its polyene backbone absorbs at ∼420 nm. In DMF, this backbone absorption locates at about the same wavelength but its molar absorptivity is nearly doubled. The absorption spectrum of P**1e** progressively blue shifts when the solvent is changed from THF to DCM, acetone, and chloroform, with the molar absorptivity of its backbone varied from ∼2000 to ∼4000 mol^{-1} L cm^{-1}. This solvatochromic effect is probably due to the conformational

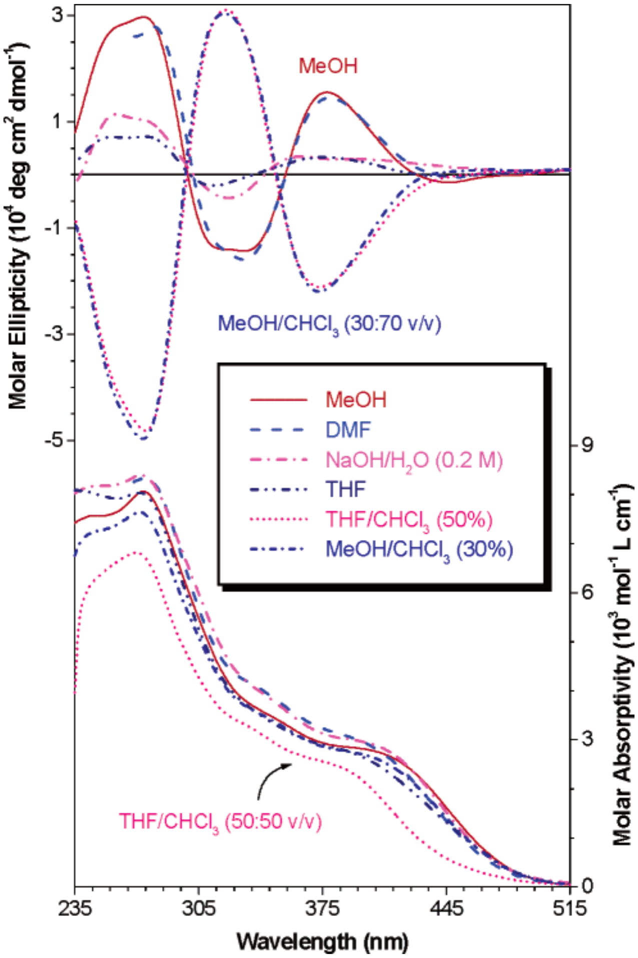


Figure 7. CD and UV spectra of P**1a** (sample prepared by ~2 h hydrolysis of P**1e**) in different solvents. Polymer concentration (mM): ~1.5 (CD); ~0.1 (UV). The spectral data in DMF below 260 nm were not taken to avoid the interference by the solvent absorption.

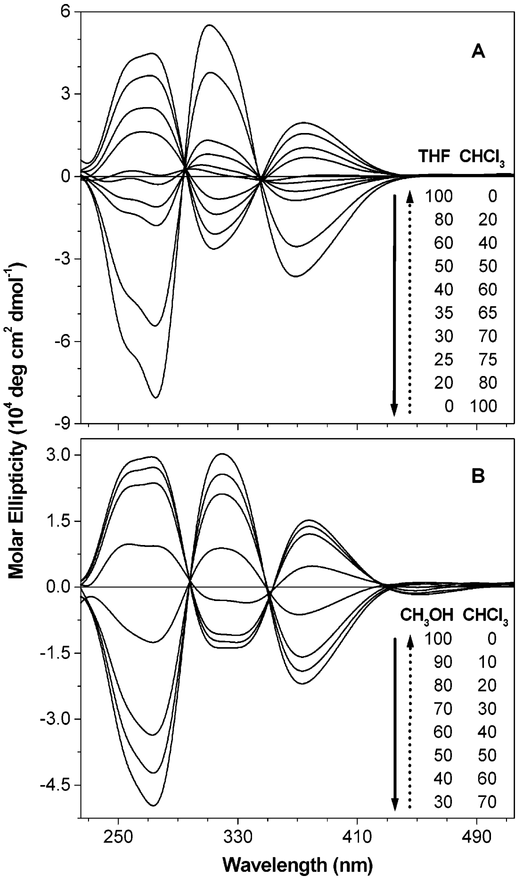


Figure 8. Tuning CD spectra of (A) P**1e** (sample from Table 1, no. 11) and (B) P**1a** (sample prepared by ~2 h hydrolysis of P**1e**) by solvent composition. Polymer concentration (mM): (A) ~1.5 (in THF/chloroform mixtures); (B) ~1.6 (in methanol/chloroform mixtures).

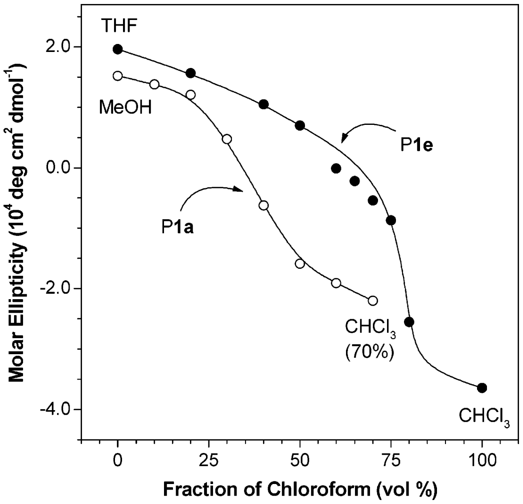


Figure 9. Solvent dependence of the first Cotton effects of THF/chloroform solutions of P**1e** (~1.5 mM; sample from Table 1, no. 11) and methanol/chloroform solutions of P**1a** (~1.6 mM; sample prepared by ~2 h hydrolysis of P**1e**) at ~370 and ~375 nm, respectively.

change of polymer chain in the solvents. In a solvent with a high solvating power like DMF, the well-solvated polymer chains may take an extended conformation, in which the polyene backbone is better conjugated, hence the observed high absorptivity in the long wavelength region.

Polyacid P**1a** is only soluble in polar solvents, which greatly restricted our choice of solvents in the study of the solvent effect on its chiroptical properties. Because the solvents we can use all have fairly similar polarities, no profound solvent effect on the UV spectra of the polyacid solutions are observed (lower panel of Figure 7). Whereas the chain conjugation of P**1a** seems insensitive to the change in the solvent, its chain helicity is inclined to vary with solvent (upper panel of Figure 7). Compared to that of its P**1e** parent, the Cotton effect of P**1a** changes with solvent in a different way. This is understandable because the polyacid possesses an additional polar acid group capable of hydrogen bonding in each of its repeat units. The two polymers, however, also share some similarity: like its P**1e** congener, P**1a** always exhibits positive first Cotton effects in the polar non-chlorinated solvents but negative ones in less polar solvent mixtures containing large amounts of chloroform, a chlorinated solvent. Noting that chloroform is a nonsolvent of the polyacid,[27] superhelixes[31] with regularly interwounded chains or chain segments of preferred handedness may have formed in the solvent mixtures, accounting for the strong Cotton effects of the polymer in the mixtures.

Tuning Chain Helicity by External Stimuli. It now becomes clear that the solvent environment can affect the helical conformations of the amino acid containing polyacetylenes to a great extent. The next natural question is: can the chain helicity be manipulated continuously or reversibly by external stimuli? To

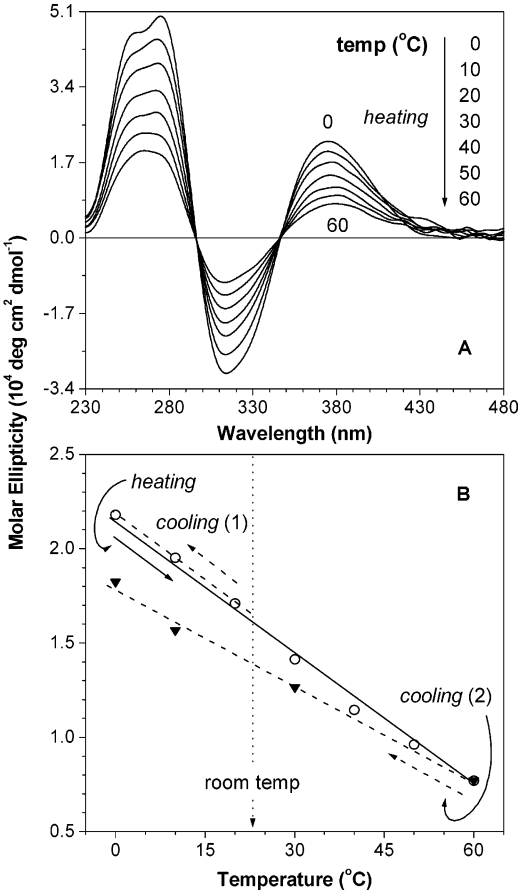


Figure 10. (A) CD spectra of a THF solution (1.3 mM) of P**1e** (sample from Table 1, no. 11) at different temperatures and (B) temperature dependence of its first Cotton effect at ~375 nm.

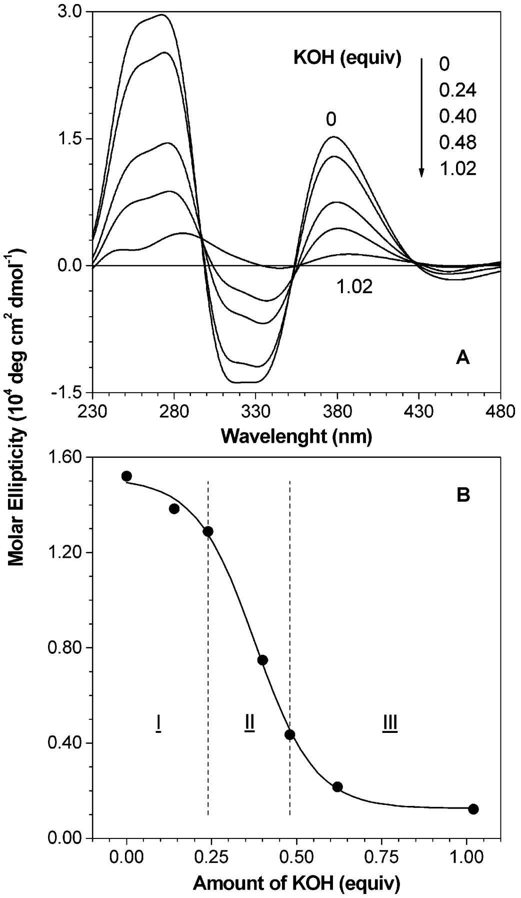


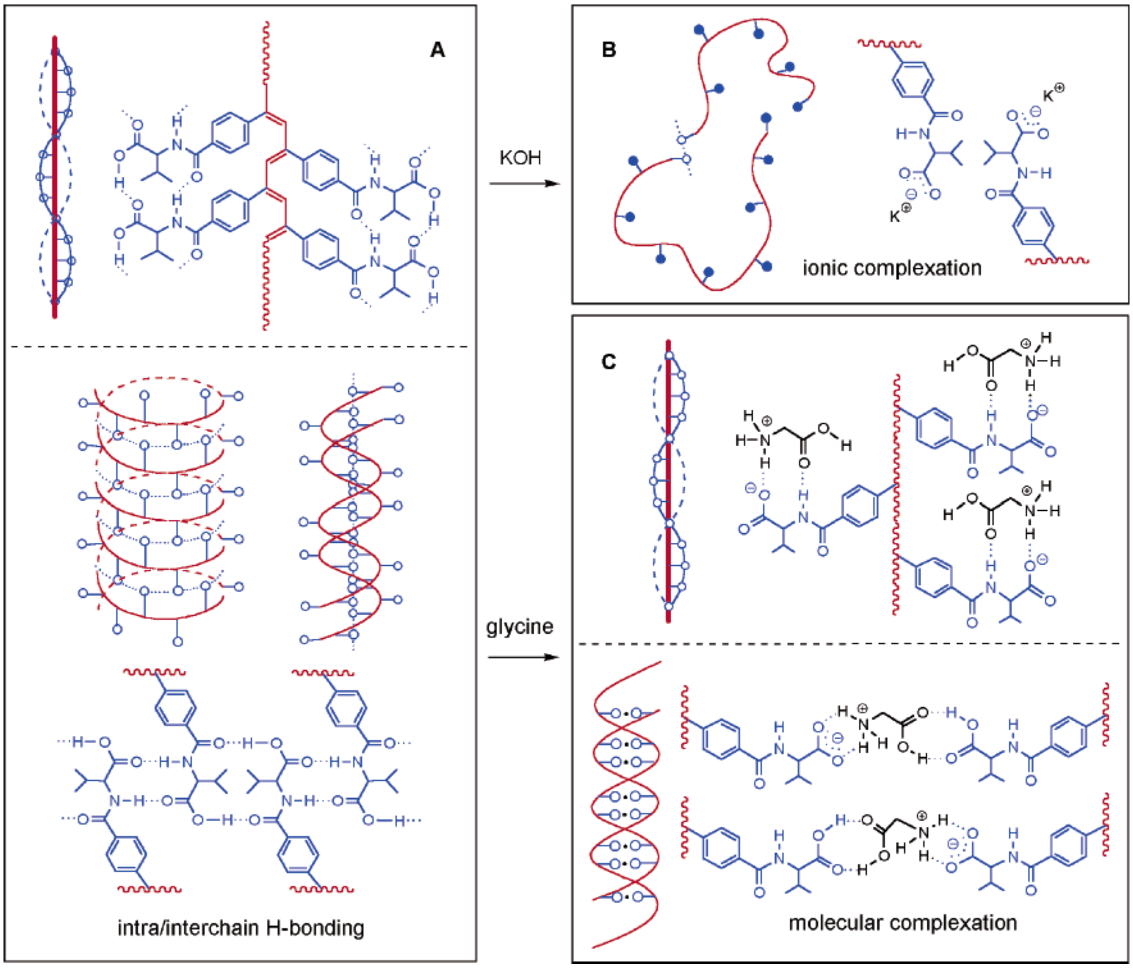
Figure 11. (A) CD spectra of P**1a** solutions (~1.6 mM; sample prepared by ~2 h hydrolysis of P**1e**) in potassium hydroxide/methanol and (B) dependence of its first Cotton effect at ~375 nm on the amount of potassium hydroxide.

answer this question, we systematically studied the effects of environmental conditions on the helical chirality of the polymer chains, using CD as a spectroscopic probe.[32]

We first checked the tunability of the chain helicity by solvent composition. When a small amount of chloroform (20%) is admixed with THF, the absolute molar ellipticity (positively or negatively signed) of P**1e** in the chloroform/THF mixture decreases (e.g., the first Cotton effect moves downward), in comparison to that of the polymer solution in pure THF solvent with the same concentration (Figure 8A). The helical chain segments with the handedness opposite to that predominated in the pure THF may have formed in the chloroform/THF mixture. The chain segments with this opposite handedness progressively populate with further mixing of chloroform with THF and eventually become dominant, as evidenced by the sign inversion of the CD pattern in the solvent mixtures with high chloroform volume fractions. This spectral change is completely reversible, as shown by the dotted upward arrow in the figure: the CD spectrum changes in exactly opposite direction with an increase in THF fraction in the THF/chloroform mixture. This indicates that the polymer chains remember their helical conformations under particular sets of environmental conditions.[25e] Similarly, as can be seen from Figure 8B, the chain helicity of P**1a** changes continuously and reversibly when chloroform (or methanol) is admixed with methanol (or chloroform), although only 70 vol % of chloroform can be admixed with methanol due to the insolubility of the polyacid in the solvent mixtures with higher fractions of the nonpolar solvent of chloroform.[33]

The dependence of the first Cotton effect of P**1e** on the solvent composition follows an arc-cotangent curve rather than a linear line (Figure 9). With an increase in the fraction of chloroform in the THF/chloroform mixture, the Cotton effect of P**1e** decreases steadily when its molar ellipticity is positive in sign and then swiftly moves downward when a large amount of chloroform is admixed with THF. In a narrow window of solvent composition of 5 vol % (from 75% to 80%), the molar ellipticity changes from ca. -8700 to ca. -25500 deg cm^2 dmol^{-1}, with a net change as large as $\sim|16800|$ deg cm^2 dmol^{-1}. This is indicative of a cooperative process: once some chain segments are supramolecularly associated in a solvent mixture with an appropriate amount of chloroform, the rest of the polymer chains are rapidly zipped up through the formation of complementary interchain hydrogen bonds. Similarly, cooperativity is also at play in the formation of superhelix of the P**1a** chains in the methanol/chloroform mixtures. In this case, however, the helical transition from one predominant handedness to another spans a wider composition range, possibly due to the competitive interactions of the molecules of the two solvents with the polyacid chains. Polar methanol may facilitate the formation of isolated helical chains of one preferred handedness by hydrogen bonding with the valine residues of the polyacid chains, whereas nonpolar chloroform may allow the polyacid chains to self-assemble into superhelical strands of the opposite

Scheme 3



handedness. The balance of the two effects is the observed dependence of the molar ellipticity of P**1a** on the composition of the mixture of the two solvents.

Biopolymers such as proteins can be thermally denatured.[34] A moderately cooled or warmed protein may be renatured, but an overheated or cooked one will not.[2−4] The blue color of the lobster carapace, for example, changes to orange upon cooking, which cannot be renatured to the blue state because the helical structure of the carotenoprotein is irreversibly unfolded by the overheating process.[8] How will our synthetic polymers respond to thermal perturbation? When a THF solution of P**1e** is heated from 0 to 60 °C, its absolute molar ellipticity monotonically decreases (Figure 10A), similar to that occurred in the helical poly(phenylpropiolate) system.[26a,b] Chain helicity generally decreases with an increase in temperature because the thermal perturbation activates the randomization of chain conformations. The decrease in the chain helicity of P**1e** is probably also associated with the thermally induced partial cleavage of hydrogen bonds of the polymer chains, which contributes to the instability of the helical segments.

The temperature dependence of the first Cotton effect of P**1e** follows a linear line (Figure 10B), similar to the temperature-helicity relationship in the poly(phenylpropiolate) system.[26a,b] Cooperativity is not observed here, possibly because the temperatures used are not high enough. (Further heating P**1e** to higher temperatures was not attempted, because of the concern over polymer thermolysis). When the polymer solution is stepwise cooled from room temperature (23 °C) to 20, 10, and 0 °C (cooling route 1), the ellipticity of P**1e** is progressively intensified and its CD spectra perfectly matches those measured at the same temperatures during the heating process. The reinstallation of the original CD spectra indicates that the moderately warmed or cooled polymer can be completely renatured. However, when the polymer heated to 60 °C is cooled (cooling route 2), it does not give original but weaker spectrum with lower ellipticity. Clearly, some helical chains or chain segments of P**1e** cannot be renatured when the polymer was heated to a “high” temperature of 60 °C.

Structures and properties of proteins vary with pH. RNase A, for example, shows maximum activity ($k_{\mathrm{cat,max}}$) in a neutral medium (pH ∼ 7), which sharply drops even when the pH is only slightly increased (e.g., at pH 7.9, $k_{\mathrm{cat}} \approx 0.3\ k_{\mathrm{cat,max}}$), because of the change in the active-site structure caused by the basic medium.[35] The conformational structure of P**1a** is also susceptible to pH change. Addition of a small amount of potassium hydroxide (0.2 equiv or ∼0.32 mM) into methanol immediately weakens the CD signals of the polymer in the KOH/methanol mixture (Figure 11A). The CD spectrum decreases with an increase in the molar equivalent of potassium hydroxide (relative to the molar concentration of P**1a** in methanol), with its first Cotton effect almost vanished when ∼1 equiv of potassium hydroxide is added to methanol. The original CD spectrum is, however, completely reinstalled when the alkaline solution is neutralized by an acid of hydrochloride. Thus, similar to the manipulation by solvent composition (cf., Figures 9 and 10), the modulation of the chain helicity of P**1a** by pH is also continuous and reversible. In this case again, the polymer chains remember their folding structures at a specific pH.[25e] Figure 11B depicts the change of the first Cotton effect of P**1a** with the amount of potassium hydroxide added into methanol. The pH effect once again follows a curve similar to those in the solvent composition systems (cf., Figure 9). The Cotton effect initially moderately decreases when less than 0.24 equiv of potassium hydroxide is added (stage I). It then quickly falls in a narrow range of KOH concentrations from 0.24 to 0.48 equiv (stage II), after which, its change becomes moderate again, with the ellipticity approaching the minimum at ~1 equiv of potassium hydroxide (stage III).

The formation of regular structures of helical chain segments is obviously entropically unfavorable. This entropic expense, however, may be compensated by the multiple intra- and interchain hydrogen bonds formed between the valine residues, as diagrammatically illustrated in panel A of Scheme 3. The helical structure is thus a consequence of the subtle balance between the two antagonistic effects; any external perturbation that disrupts the hydrogen bond formation will break the balance and may partially or fully randomize the polymer chains. The KOH molecules in methanol will ionize the carboxylic acid groups in the P**1a** chains and hence cleave the hydrogen bonds (panel B of Scheme 3). The negatively charged carboxylate ions will be solvated by the polar molecules of methanol solvent, which blocks the access of the amide hydrogen for hydrogen bond formation.

A small amount of potassium hydroxide breaks a proportionally small fraction of hydrogen bonds, resulting in the moderate decrease in the molar ellipticity of the polymer (cf., stage I of Figure 11B). The helical conformation catastrophically collapses when the KOH amount reaches a threshold value, causing rapid unfolding or unzipping of the helical chains accelerated by entropy-driven randomization (stage II). The molar ellipticity drops to almost minimum when only 0.62 equiv of potassium hydroxide is added into methanol, further confirming the important contribution of the entropic effect to the chain randomization. The second stage is obviously a cooperative process: when some fractions of hydrogen bonds are broken, the entropy-driven randomization separates the chain segments apart and tears down many more hydrogen bonds. In the third stage, the increase in KOH amount increases the solution pH but causes little change to the chain conformation because most of the polymer chains have already been randomized. Complete ionization of all the carboxy groups, however, may be hampered by the well-known steric effect in a polymer reaction or macromolecular complexation process.[36]

Natural polymers are in constant contact with achiral species in their surrounding environments, and investigation of the effects of achiral species on helical conformations of nonnatural polymers may help advance our understanding on the molecular interactions of biopolymers with their foreign guests. We studied different inorganic and organic species (lithium chloride, sodium carbonate, triethylamine, etc.) and found that the effect of glycine, the only achiral amino acid commonly found in proteins, on the CD spectra of P**1a** was most intriguing. With continuous addition of glycine to a 50 vol % methanol/water mixture, the absolute molar ellipticities of the polymer solution continuously increase (Figure 12A). The glycine concentration−molar ellipticity plot again reveals a cooperative process: a fast increase in the first Cotton effect is seen in the concentration range of 0.1−0.2 M (Figure 12B). The intensification of CD signals by the addition of glycine is probably the result of the formation of glycine−P**1a** helical complexes, where glycine molecules bind with the valine residues in the polyacid chain via salt bridges (panel C of Scheme 3). The glycine complexation effectively increases the bulkiness of the pendant, and the increased steric effect may induce the chain segments to further twist in a single chain event. In a multiple chain event, double helices or even superhelices may be formed, where the glycine molecules serve as the chain “glues”. Both of the events will increase the chain helicity of the polymer system. Cooperativity may come into play in the multiple chain events: formation of a few interchain hydrogen bonds via the glycine bridges will bring the polymer chain segments to close vicinity, making it easier for additional hydrogen bonds to form. At present time, we are unable to confirm the reversibility of the chain helicity tuning by glycine removal or decomplexation because of the involved technical difficulty in completely stripping off all the glycine molecules complexed to the polymer chains.

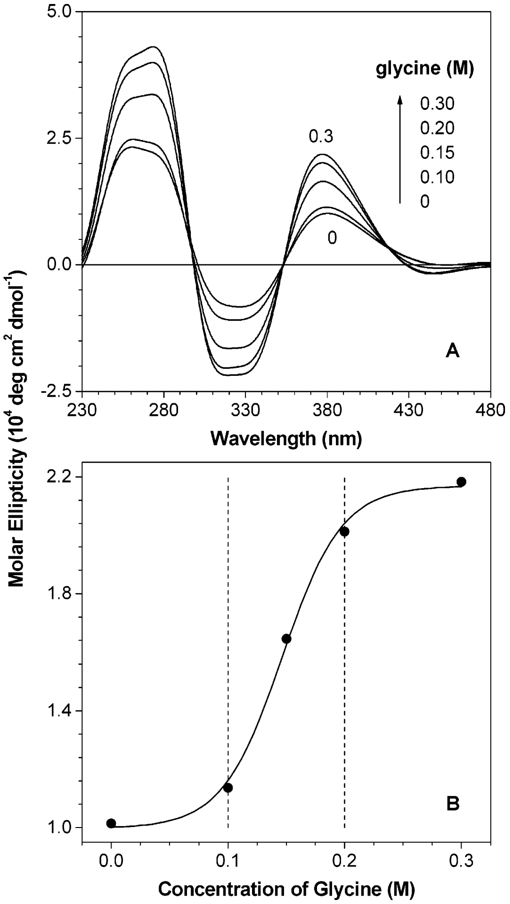


Figure 12. (A) Change of CD spectra of P**1a** (sample prepared by ~1 h hydrolysis of P**1e**) with the addition of glycine into a mixture of methanol and water (50:50 by volume) and (B) dependence of the first Cotton effect at ~375 nm on glycine concentration. Polymer concentration: ~1.6 mM.

Concluding Remarks

In this work, the polymerization behaviors of the valine−acetylene adduct (**1e**) are investigated. Under optimal polymerization conditions, high molecular weight polymers (P**1e**) are obtained in high yields. Polyester P**1e** is selectively hydrolyzed to polyacid P**1a** without harming other functional groups and damaging the macromolecular structural integrity. The molecular interaction of hydrogen bonding between the amino acid residues in the polymer chains is verified by the NMR studies through both the indirect spectral measurement using the monomer as a model compound and the direct measurement of the polymer solutions in various solvents. The helical chirality of the chain segments is confirmed and the continuous and sometime reversible manipulability of the chain helicity is demonstrated by the CD spectral analyses.

The conformational structures of the polymer chains enjoy both static stability and dynamic mobility. The intra- and interchain hydrogen bonds between the valine residues help stabilize the helical structures and the energy minimization enables the chain segments to remember their "native" conformations under a particular set of external conditions. The single bond rotation of the backbone segments, on the other hand, offers the polymers with structural flexibility or plasticity,[37] allowing them to dynamically change their chain conformations in response to environmental variations. Such behaviors are obviously proteomimetic.[38] The biomimetism of the helical polymers, coupled with their photoconductivity,[39,40] self-assembling capability,[10−12] and cytocompatibility,[10,41] makes them promising candidate materials for biotechnology applications, especially for bioelectronics and nanoinformatics innovations.[42]

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Supporting Information Available: Text giving experimental details and Figures s1 and s2 showing ^{1}H NMR spectra of P**1e** and P**1a** in different solvents and their TGA thermograms under nitrogen. This material is available free of charge via the Internet at http://pubs.acs.org.

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