Cu(II)-assisted Helicity Induction on a Poly(phenylacetylene) Derivative Bearing an Achiral Glycine Residue with Amino Acids in Water

Hiroaki Kawamura, Miki Ishikawa, Katsuhiro Maeda, and Eiji Yashima*
Department of Molecular Design and Engineering, Graduate School of Engineering, Nagoya University, Chikusa-ku, Nagoya 464-8603

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Poly(phenylacetylene) bearing an achiral glycine residue exhibits an induced circular dichroism in the UV–vis region upon complexation with free amino acids in water due to a predominantly one-handed helix formation and the Cotton effect intensity is amplified in the presence of a Cu(II) ion.

Amino acids are important chiral biomolecules not only as the components of proteins but also as active components in biological events. A number of synthetic receptor molecules for amino acids have been prepared.[1] However, most of these synthetic receptor molecules show molecular and chiral recognition for protected amino acids in only organic solvent. Host–guest systems capable of recognizing free amino acids in water are still rare.[2] We previously reported that optically inactive polyelectrolytes consisting of a poly(phenylacetylene) backbone and functional pendant groups such as a carboxylate[3] and a phosphonate group[4] exhibited an induced circular dichroism (ICD) in the polymer backbone region due to a predominantly one-handed helix formation upon complexation with various biomolecules including free amino acids, peptides, and aminosugars in water as well as in DMSO with chiral amines. The characteristic Cotton effect signs of the complexes can be used to predict the absolute configurations of optically active compounds. We report here that an optically inactive poly(phenylacetylene) bearing an achiral glycine residue, poly[*N*-(4-ethynylbenzyl)glycine sodium salt] (poly-**1**-Na), can also interact with free amino acids in water and the complexes exhibit ICDs. Furthermore, the ICD intensities of the complexes were found to be amplified in the presence of metal ions such as a Cu(II) ion. Amino acids are well known to form chelation complexes with Cu(II) ion and this complex formation has widely been used to separate amino acids in ligand-exchange chromatography[5] and also to recognize them in supramolecular systems.[6]

Figure 1 shows typical CD spectra of poly-**1**-Na[7] with a free amino acid, L-proline, in water in the presence and absence of Cu(II). Achiral poly-**1**-Na formed a predominantly one-handed helix and exhibited an ICD in the long wavelength region without Cu(II). The ICD results for the complexation of poly-**1**-Na with other optically active amino acids are summarized in Table 1. Among nineteen of the common free L-amino acids, poly-**1**-Na produced ICDs with seventeen amino acids, although the observed ICDs did not show clear relationship between the Cotton effect signs and the absolute configurations of the amino acids. This may be due to the flexible side chain of the pendant glycine residue of poly-**1**-Na, so that poly-**1**-Na can possess various conformations during the complexation with amino acids.

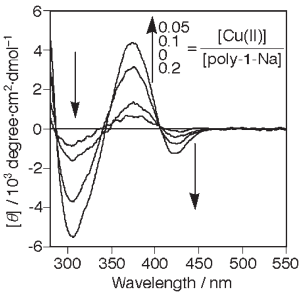

Figure 1. CD spectral changes of the poly-**1**-Na–L-Pro complex with Cu(II) ion in water at 0 °C; [poly-**1**-Na] = 1.0 mg/mL, [L-Pro]/[poly-**1**-Na] = 10 (mol/mol) (pH 8.8–9.0).

Interestingly, the Cotton effect intensity significantly increased by the addition of a small amount of Cu(II) to the poly-**1**-Na complexed with some amino acids including L-proline. The CD titration of the poly-**1**-Na–L-proline with Cu(II) (Figure 1) indicates that the ICD intensity reached a maximum value at [Cu(II)]/[poly-**1**-Na] = 0.05; the CD intensity was ca. four times larger than that in the absence of Cu(II). The ICD intensity gradually decreased by further addition of Cu(II). The poly-**1**-Na complexed with Cu(II) ion was finally precipitated at [Cu(II)]/[poly-**1**-Na] = 0.3. The complexes of L-amino acids and Cu(II) ions are known to form a ternary Cu(II) complex under equilibrium, resulting in a weak CD based on the metal ion d–d transition in the range from 450 to 900 nm[8] and such Cu-based ICD was observed at [poly-**1**-Na] = 10 mg/mL ([Pro]/[poly-**1**-Na] = 10) with 0.05 equiv. Cu(II), indicating that the Cu is in a chiral environment. Among ternary complexes, the poly-**1**–Cu(II)–Pro complex preferentially formed with 0.05 equiv. Cu(II) contributes to the effective helicity induction on the polymer. As shown in Table 1, some amino acids, particularly basic amino acids (L-arginine and L-histidine), exhibited more intense ICDs assisted by Cu(II) compared with those without Cu(II), whereas the ICD of poly-**1**-Na disappeared in alkaline solution for the amino acids having additional functional groups (cysteine, serine, and threonine) in the presence of Cu(II), probably because the Cu(II) also interacts with the functional groups away from the stereogenic center. Similar helicity induction on the polymer and amplification of ICDs by Cu(II) were also observed with chiral amino alcohols; for instance, the ICD intensity of the poly-**1**-Na complexed with (*R*)-phenylalaninol significant-

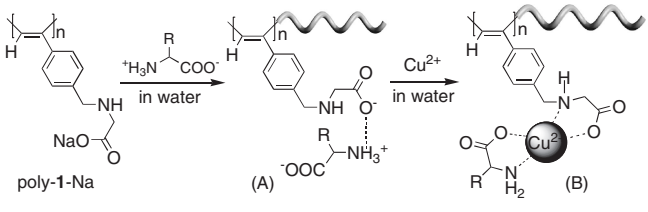

Figure 2. Possible models for helicity induction on poly-**1**-Na with amino acids in the absence (A) and presence of a Cu(II) ion (B).

ly increased in the presence of Cu(II) (Table 1).

Figure 2 schematically shows the possible models for the helicity induction on poly-**1**-Na with amino acids and the ternary complex system with a Cu(II) ion. A polyelectrolyte, poly-**1**-Na can bind to the oppositely charged ammonium ion of amino acids through electrostatic interaction in water due to the ion condensation effect of polyelectrolytes (Figure 2A).[4] In the presence of Cu(II), the pendant glycine residue of poly-**1** forms the ternary Cu(II) complex involving free optically active amino acids as a chelator (Figure 2B). In both models, the helix sense of the polymer appears to be governed by the configuration and binding geometry of the amino acids with or without Cu(II) (Figure 2), so that the Cotton effect signs of some ternary complexes were opposite to those of the corresponding poly-**1**-Na–amino acid complexes.

Since the binding affinity of Cu(II) to amino acids and the poly-**1**-Na's glycine residues is strongly influenced by pH,[5] we then investigated the effect of pH on ICDs in the ternary complexation system involving poly-**1**-Na, L-proline, and a Cu(II) ion ($7<pH<12$) (Figure 3). In the absence of Cu(II), the CD intensity was slightly influenced by pH ($8<pH<11$) and showed a maximum value at around pH 9. However, the ICD value of the ternary complex (Cu(II) = 0.05 equiv.) significantly increased with the increasing pH and exhibited a maximum value at pH 10.5 and decreased at higher pH range. On the other hand, the ICD value with 0.2 equiv. of Cu(II) monotonically increased in the pH range investigated. These results clearly indicate that the helicity induction efficiently occurred on poly-**1**-Na during the formation of a ternary chelate complex between a free amino acid and the glycine residue of the polymer side chain. It is worth noting that at higher pH range, only the ternary complex shows ICD. The poly-**1**-Na–L-proline complex exhibited no ICD at around pH 12, but an intense CD appeared in the presence of a Cu(II) ion.

Table 1. CD data of amino acids to poly-**1**-Na in the presence and absence of Cu(II) ion in water at 0 °C[a]

	Poly-**1**-Na		Poly-**1**-Na–Cu[b]	
Guest	pH	$[\theta]_{2nd} \times 10^{-3}(\lambda)$[c]	pH	$[\theta]_{2nd} \times 10^{-3}(\lambda)$[c]
L-Ala	8.7	−0.40 (375)	12.3	−1.14 (380)
L-Asn	7.8	−0.15 (365)	12.3	+0.17 (381)
L-Cys	7.5	+3.09 (372)		n. d.
L-Gln	8.4	−0.81 (372)	12.3	−0.62 (375)
L-Ile	8.8	−2.05 (378)	12.2	−3.14 (385)
L-Leu	8.6	−0.99 (375)	12.2	+1.06 (388)
L-Met	8.1	+1.30 (372)	12.4	+1.45 (387)
L-Phe	8.3	−2.00 (375)	12.1	+15.1 (381)
L-Pro	9.0	+1.37 (376)	12.3	+6.47 (383)
L-Pro[d]	9.0	+1.10 (376)	12.3	+6.82 (383)
			9.0	+4.41 (375)[e]
L-Ser	8.2	−0.18 (367)		n. d.
L-Thr	8.0	+0.33 (376)		n. d.
L-Trp	8.5	+32.9 (364)	12.3	+15.6 (371)
L-Tyr	8.9	+1.29 (376)	12.3	+0.45 (385)
L-Val	8.4	−1.38 (373)	12.3	+1.10 (385)
L-Asp		n. d.		n. d.
L-Glu		n. d.		n. d.
L-Arg	8.1	+2.72 (376)	12.3	−17.8 (375)
L-His	8.3	+1.35 (372)	12.3	+20.7 (374)[f]
L-Lys	8.3	−1.75 (377)	12.3	+2.61 (383)
(*R*)-Phenylalaninol	10.9	+6.38 (376)	12.0	−25.0 (363)

[a][poly-**1**-Na] = 1.0 mg/mL, [amino acid]/[poly-**1**-Na] = 10. The concentration of poly-**1**-Na is calculated based on the monomer unit. [b][Cu(II)]/[poly-**1**-Na] = 0.2. [c]λ (nm) and $[\theta]$ (degree·cm^2·dmol^{-1}) of the second Cotton. [d]At 25 °C. [e][Cu(II)]/[poly-**1**-Na] = 0.05. [f][amino acid]/[poly-**1**-Na]/[Cu(II)] = 10/1/4.

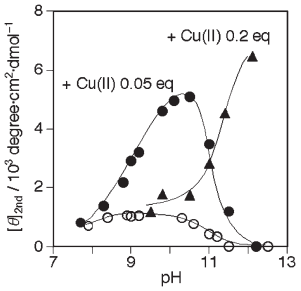

Figure 3. Plots of the $[\theta]_{2nd}$ for the poly-**1**-Na–L-Pro complex in the absence (○) and presence of 0.05 (●) and 0.2 equiv. (▲) Cu(II) in water at 0 °C against pH. [poly-**1**-Na] = 1.0 mg/mL, [L-Pro]/[poly-**1**-Na] = 10.

CD measurements were also carried out in the presence of other metal ions, such as Co(II), Ni(II), and Zn(II) in an alkali condition (pH 12.0) containing 10 equiv. of L-proline. The poly-**1**-Na ternary complexes exhibited ICDs ($[\theta]_{2nd} = 4.06 \times 10^3$ for Ni(II) and 6.13×10^3 for Co(II) ([M]/[poly-**1**-Na] = 0.2)), but the complex with Zn(II) showed a negligible ICD.

In conclusion, we found that poly-**1**-Na bearing an achiral glycine residue exhibited ICDs with free amino acids in water, and the ICD intensities of the complexes were enhanced by the addition of a Cu(II) ion. The method demonstrated here can be applied to the design and development of novel helical poly(phenylacetylene)s bearing optically active amino acid residues, which may possibly be utilized not only as chiral sensing materials for amino acids, but also as chiral stationary phases (CSPs) for HPLC separation of amino acid enantiomers, since amino acids-based CSPs have often been used in ligand-exchange chiral chromatography.[5] This work is now in progress.

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