

Conformational Analysis of α -Helical Polypeptides in Two Opposite Screw Forms. A Combined Use of ^2H NMR and MD Simulation

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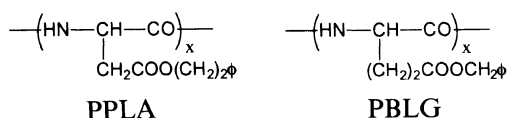
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ABSTRACT: In this work, we wish to report the results of conformational analysis of poly(β -phenethyl L-aspartate) (PPLA) and poly(γ -benzyl L-glutamate) (PBLG) in two opposite α -helical screw sense. Various deuterated PPLA samples were prepared, and ^2H NMR measurements were carried out in tetrachloroethane at two different temperatures: one for the right-handed and the other for the left-handed α -helical state. The rotational isomeric state (RIS) analysis of the ^2H NMR quadrupolar splitting data was carried out, and the sidechain conformations were estimated. The results of the analysis for the right-handed α -helical PBLG have been reported previously. In the right-handed α -helix regime, *i.e.*, *r*-PPLA and *r*-PBLG, the preferred form of the first two bonds was found to be $\chi_1\chi_2 = tt$, leading to an extended sidechain conformation in the direction perpendicular to the α -helical axis. The corresponding arrangements in the *l*-form (*l*-PPLA) are more or less evenly distributed among three states, g^-t , tt , and g^-g^+ . MD simulations were performed for the side chain flanking the right- and left-handed α -helical backbone by using Biosym's Discover program. An α -helix fragment consisting of 18 aminoacid residues, Ac- X_{18} -NHMe with $X = \text{Asp(OPhe)}$ or Glu(OBzl) , was adopted as a model for the polymers in the simulation. The preferred sidechain conformations were elucidated as an average over an interval 100—200 ps. The simulations were performed *in vacuo* as well as in the presence of solvent molecules (chloroform). The agreement was found to be quite reasonable in all three polymer systems for which relevant experimental data are available.

KEY WORDS Poly(γ -benzyl L-glutamate) / Poly(β -phenethyl L-aspartate) / Sidechain Conformation / ^2H NMR / RIS Analysis / MD Simulation / Helix-Sense Inversion /

Polypeptides such as poly(β -phenethyl L-aspartate) (PPLA) and poly(γ -benzyl L-glutamate) (PBLG) are man-made polymers having the poly(L- α -aminoacid) sequence along the backbone with an ester group in the side chain. PPLA and PBLG are mutually isomeric in their chemical structures:



i.e., PBLG can be converted into PPLA by

interchanging $\gamma\text{-CH}_2$ with the ester group in the side chain. Both PPLA and PBLG form an α -helix in various organic solvents, which by addition of denaturant acid, transforms to a random-coil.^{1,2} Yet the physical properties of these two polymers are drastically different. While the α -helical PBLG is known only in the right-handed form, PPLA can be either in the right- or left-handed arrangement depending on the solvent or temperature.³ (Hereafter we distinguish the handedness of the screw sense by prefixing *r*- or *l*- to PPLA or PBLG.) The latter behavior is widely known as a character-

istic of the poly(aspartic acid ester)s.⁴ The handedness of the screw sense also vary depending on the chemical constitution of the appended ester group. An inversion of the helical sense in a polyaspartate copolymer system comprising nitrobenzyl and benzyl residues at the ester terminal has been extensively investigated by Goodman and his coworkers⁵ as early as in 1960's. Scheraga and his group,⁶ in their pioneering energy calculation of these systems, have concluded that the dipole-dipole interactions between the side chain and the backbone play the key role in determining the preference of the screw sense of α -helix: while the dipole-dipole interaction favors the right-handed form in poly(γ -methyl L-glutamate), the same interaction tends to destabilize the right-handed form of the poly(β -methyl L-aspartate). Not much experimental work has been reported however regarding the spatial configuration of α -helical polypeptides because of the difficulty in estimating the conformation directly by conventional spectroscopic techniques.

More recently Yamazaki and one of the present authors⁷ have carried out ²H NMR studies on α -helical PBLG in the lyotropic liquid-crystalline state. Under the experimental condition (~ 12 T) employed in the conventional NMR measurements, anisotropic molecules capable of forming liquid crystals exhibit a nematic mono-domain with the director lying along the magnetic field. The orientational order parameter of α -helical axis S can then be defined as

$$S = 1 - (3/2)\langle \sin^2 \psi \rangle \quad (1)$$

where angle ψ designates the inclination of the molecular axis relative to the director of the domain. The deuterium atoms incorporated in the amide or methine groups provide the order parameter of the backbone by

$$S = (2/3)\Delta\nu/q_h \quad (2)$$

where $\Delta\nu$ represents the quadrupolar splittings observed for the N-D ($\Delta\nu_N$) or C $^\alpha$ -D bond

($\Delta\nu_\alpha$), and q_h is the component of quadrupolar interaction tensor along the α -helical axis. The quadrupolar splitting due to the i -th C-D bond of the side chain may be expressed as

$$\Delta\nu_i = (3/2) \left(\frac{e^2 q Q}{h} \right)_{\text{CD}} \left(\frac{3\langle \cos^2 \theta \rangle - 1}{2} \right) S \quad (3)$$

where $(e^2 q Q/h)_{\text{CD}}$ is the quadrupolar coupling constant of a given C-D bond, θ indicates the inclination of the C-D bond relative to the molecular axis, and $\langle \rangle$ designates an average taken over all conformations of the side chain. In other words, the quadrupolar splitting data observed for the individual CD bonds include information concerning the rotational characteristics of the constituent bonds, thus the conformation of the side chain. With the value of S obtained through eq 2, this expression (eq 3) permits an estimation of the orientational order $(3\langle \cos^2 \theta \rangle - 1)/2$ for a given C-D bond. The results of the rotational isomeric state (RIS) simulation of the deuterium quadrupolar splitting data indicate that the spatial configuration of the side chain is appreciably extended in the transverse direction to the α -helical axis due to steric interactions with the backbone and adjacent side chains. In an independent work,⁸ the molecular dynamic (MD) calculation has been performed by employing Biosym's Discover program equipped with the force field termed CVFF. The preferred conformations of the side chain thus estimated for a fragment Ac-Glu(OBzl)₃₆-NHMe were found to be reasonably consistent with those obtained above from the ²H NMR measurements. It has been thus demonstrated that the ²H NMR/RIS analysis and MD simulation could be used complementarily with each other.

In this work, we extended our investigation to include the conformation of PPLA in both right- and left-handed α -helices. The results of some preliminary observations have been previously reported.³ Various deuterated PPLA samples were prepared, and ²H NMR measurements were carried out for the two

opposite screw sense. Since the newly released version of Biosym's Discover program includes some revisions in the force field,⁹ the sidechain conformation of *r*-PBLG was first reexamined to confirm the previous results. MD simulations were then carried out for the side chain flanking the left-handed α -helical PBLG, and left- and right-handed PPLA systems.

SAMPLES AND MEASUREMENTS

Samples

N-Carboxy- β -phenethyl-L-aspartate anhydride was synthesized from triphosgene and β -phenethyl L-aspartate by Daly *et al.*'s prescription.¹⁰ Polymer samples were prepared by a standard *N*-carboxy-L-aminoacid anhydride (NCA) method. An NCA purified from dried tetrahydrofuran/*n*-hexane was polymerized in chloroform by using triethylamine as an initiator. The polypeptides thus obtained were purified by repeated precipitation from chloroform in a large volume of methanol. The molecular weights of PPLA samples were estimated from the intrinsic viscosities measured in dichloroacetic acid (2% v/v)/chloroform solution according to Teramoto *et al.*'s relation.¹¹

For the purpose of elucidating the conformation of side chains, we have prepared variously deuterated PPLA samples: PPLA-N-*d*, $-\alpha$, β_S -*d*₂, $-\beta_R$ -*d*, $-\epsilon$, ζ -*d*₄, $-\zeta$, Ph-*d*₇.

PPLA-N-*d*

PPLA was dissolved in trifluoroacetic acid-*d* (TFA-*d*) (38% v/v)/chloroform solution and kept under stirring at room temperature for 3 hours.¹² The sample was purified as above: $M_v = 78000$. The molecular weight of the sample was found to remain practically unaffected by this treatment.

PPLA- α , β_S -*d*₂, and PPLA- β_R -*d*

L-Aspartic acid- α , β_S -*d*₂, and $-\beta_R$ -*d* were synthesized according to the method described in literatures.^{13,14} The polymers were obtained

by the NCA method: $M_v = 43000$ (PPLA- α , β_S -*d*₂), 78000 (PPLA- β_R -*d*).

PPLA- ϵ , ζ -*d*₄

Phenethyl alcohol-*d*₄ was prepared as described by Zimmerman.¹⁵ PPLA- ϵ , ζ -*d*₄ was synthesized by the NCA method: $M_v = 49000$.

PPLA- ζ , Ph-*d*₇

PPLA- ζ , Ph-*d*₇ was prepared by using phenethyl alcohol-*d*₇ purchased from Merck Frosst Canada Inc.: $M_v = 33000$.

Measurements

The ²H NMR spectra of liquid-crystalline solutions were recorded on a JEOL JNM-GSX-500 spectrometer at 76.65 MHz under a complete proton decoupling and nonspinning mode. The volume fraction, V_x , was estimated from the density (1.33 g cm⁻³) of PPLA.¹⁶

RESULTS OF ²H NMR MEASUREMENTS AND ELUCIDATION OF SIDECCHAIN CONFORMATION

As has been reported previously,³ PPLA exhibits a helix sense inversion in 1,1,2,2-tetrachloroethane (TCE) around 80–100°C. While the polymer molecule exists in the right-handed α -helix regime at low temperature, it transforms to a left-handed form above the aforementioned transition range. The values of the deuterium quadrupolar splitting observed at 60 and 110°C are compiled in Table I, where the data associated with the main chain and the side chain are separately listed.

According to the definition of eq 2, the ratio of the splittings due to the N-D and C α -D bond should depend only on the geometry of the α -helix. The observed values of the ratio $\Delta\nu_\alpha/\Delta\nu_N$ were found to remain nearly constant over a certain concentration and temperature range (*cf.* Table I),⁷ indicating that the α -helices are quite rigid under the experimental condition. The corresponding value of *r*-PBLG has

been estimated to be 0.072 ± 0.001 .⁷ The geometries of the α -helix reported by X-ray measurements¹⁷ and adopted in molecular force field calculations¹⁸ were slightly adjusted so as to reproduce these experimental observations (Table II). The order parameters S of the α -helical backbone can be easily elucidated according to the procedure described in the previous work,³ and the results are included in Table I.

From eq 3, the ratio $\Delta v_i/S$ depends on the orientation of the C–D bond relative to the α -helical axis, and bears information regarding

Table I. Summary of the quadrupolar splittings Δv^{obs} and order parameters S observed for PPLA samples selectively deuterated^a

	60°C (Right)	110°C (Left)
Main chain		
$\Delta v_N/\text{kHz}$	247.8	235.5
$\Delta v_\alpha/\text{kHz}$	19.9	1.6
$\Delta v_\alpha/\Delta v_N$	0.08	0.007
S	0.93	0.88
Side chain ^b		
$\Delta v_{\beta S}/\text{kHz}$	19.9 (0.91)	1.3 (0.87)
$\Delta v_{\beta R}/\text{kHz}$	18.5 (0.92)	40.3 (0.88)
$\Delta v_\gamma/\text{kHz}$	29.8, 20.2 (0.91)	16.7, 4.4 (0.87)
$\Delta v_\delta/\text{kHz}$	9.7, 3.2 (0.91)	11.4, 2.1 (0.87)
$\Delta v_\rho/\text{kHz}$	9.5 (0.90)	18.6 (0.86)

^a The screw sense inversion of α -helix takes place in the range 80–100°C. ^b Values in parentheses are the order parameters (S) of given samples determined individually from the Δv_N data.

the sidechain conformation. The average orientation of the α -helix varies to some extent with the molecular weight of samples as well as the experimental condition.⁷ The order parameters (S) were therefore determined for the individual samples (Table I) by using the amide N–D bond: the values are included in parentheses. In a previous work,⁷ we have proposed a RIS simulation scheme to elucidate the conformation of side chain from the observed $\Delta v_i/S$ ratios. The underlying concept is briefly illustrated in Figure 1. Statistical weights σ_i assigned to the gauche states of every rotatable bond were treated as adjustable parameters. Simulations for the $\langle \cos^2 \theta \rangle$ term required in eq 3 were carried out according to the following expression:

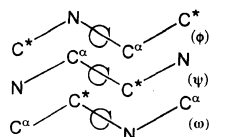
$$\langle \cos^2 \theta \rangle = Z^{-1} \sum_k \left[\cos^2 \theta \left(\prod_i s_i \right) \right]_k \quad (4)$$

and

$$Z = \sum_k \left(\prod_i s_i \right)_k \quad (5)$$

where Z represents the conformational partition function of the side chain and s_i denotes the weight for bond i , *i.e.*, 1 or σ_i , in the k -th configuration. The fraction of a given configuration can be deduced from the statistical weight parameter set thus defined. Comparison with the observed splittings requires only absolute values of Δv_i . The results of RIS

Table II. Geometrical parameters of the *r*- and *l*-PPLA backbones selected so as to reproduce the observed ratios of $\Delta v_\alpha/\Delta v_N$

Bond	Length/Å	Bond angle	Angle/deg.		Torsional angle	Angle/deg.		
			Right	Left		Right	Left	
C ^α –C*	1.530	∠ NC ^α C*		110.3				
C*–N	1.325	∠ C ^α C*N		115.0				
N–C ^α	1.453	∠ C*N C ^α		121.0				
C* = O	1.230	∠ C* C ^α C ^β		110.0				
C ^α –C ^β	1.530	∠ C ^α C*O		121.3				
C ^α –D ^α	1.100	∠ C*N D ^α		123.2				
N–D	1.000	∠ NC ^α D ^α	108.15	104.66				
						–62.36	62.36	
						–42.15	42.15	
						180.0	180.0	

been modified in consideration of the experimental data obtained from dimethyl succinate.²⁰ As for the rotational potentials of the terminal phenyl groups, the results of MO calculations and spectroscopic studies are available for relevant model compounds such as methyl benzyl ether²² and ethylbenzene.²³ The rotational minima of the phenyl rotation were adjusted in accord with these data for the respective polymers.

Following the previous treatment, the reliability of the PCFF force field expression was further examined by calculating the conformation of a cyclic dimer of γ -benzyl L-glutamate, cyclo[D-Glu(OBzl)-L-Glu(OBzl)].⁸ A satisfactory agreement between the calculation and experiment was achieved when the dispersion interactions involving aromatic rings were entirely ignored: *i.e.*, an unrealistic pairing between the diketopiperazine ring and the terminal phenyl group was suppressed. After these precautions, the PCFF package was adopted for the calculation of α -helical polypeptide systems. In the simulation, an integration of the equations of motion for all of the atoms was performed according to the "Leap Frog" variation of the Verlet method.²⁴ Nonbonded interactions greater than a given cut-off distance (r_c) were ignored.

MD simulations were first carried out at an elevated temperature (1000 K) for a period of 100 ps. After these equilibrium runs, the temperature was lowered to 500 K. The sidechain conformation was initially set equal to all-*trans*, and a Maxwell-Boltzmann distribution was assumed for the initial velocities of atoms in the system. During the simulation, the main chain was rigidly fixed in the α -helical conformation.²⁵ An α -helix fragment consisting of 18 aminoacid residues, Ac-X₁₈-NHMe with X = Asp(OPhe) or Glu(OBzl), was adopted as a model for PPLA or PBLG in the simulation. The preferred sidechain conformations were elucidated as an average over an interval 100–200 ps. In order to eliminate the end group effect, contributions from the six

terminal residues on either side were omitted in this averaging process. The rotational isomeric states were conventionally defined in terms of the domains of the dihedral angle: g^+ 0°/120°/t 120°/240°, g^- 240°/360°. Shown in Figure 2 are the representative examples (*r*-PPLA) of the rotational motion of the side chain monitored during a 200 ps run. The MD simulations were performed for the same polymer system under two different conditions. The cut-off distances (r_c) were set equal to 5 Å *in vacuo* (Figure 2a) and 7.5 Å in chloroform solution (Figure 2b). Bond rotations around the inside bonds (χ_1, χ_2) take place less frequently than those beyond the ester group. Although bond rotations tend to be enhanced by inclusion of solvent molecules, general feature of a given diagram is not much affected.²⁶ The results thus derived are summarized in Table IV, where bond conformations calculated *in vacuo* for a temperature of 500 K are compared with those estimated above from the ²H NMR spectra. The agreement is quite reasonable in all three polymer systems for which experimental data are available.

DISCUSSION

In the aforementioned study, the results of ²H NMR analysis obtained in the liquid-crystalline state have been compared with those of MD simulation in which an isolated perfectly-rigid α -helical chain is treated. Some comments may be needed in this context. (1) The concentration-dependence of the sidechain conformation has been previously examined on the basis of eq 3. The ratios $\Delta v_i/S$, which are sensitive to the sidechain conformation, were found to be practically invariant with the polymer concentration over the range $V_x = 0.15$ to 0.3.⁷ These observations are indicative of the fact that the average orientations, $\langle \cos^2 \theta \rangle$, of the C–D bonds are unaffected by steric interactions at given intermolecular distances. (2) To avoid a specific solvent effect affecting the conformation, experimental results ob-

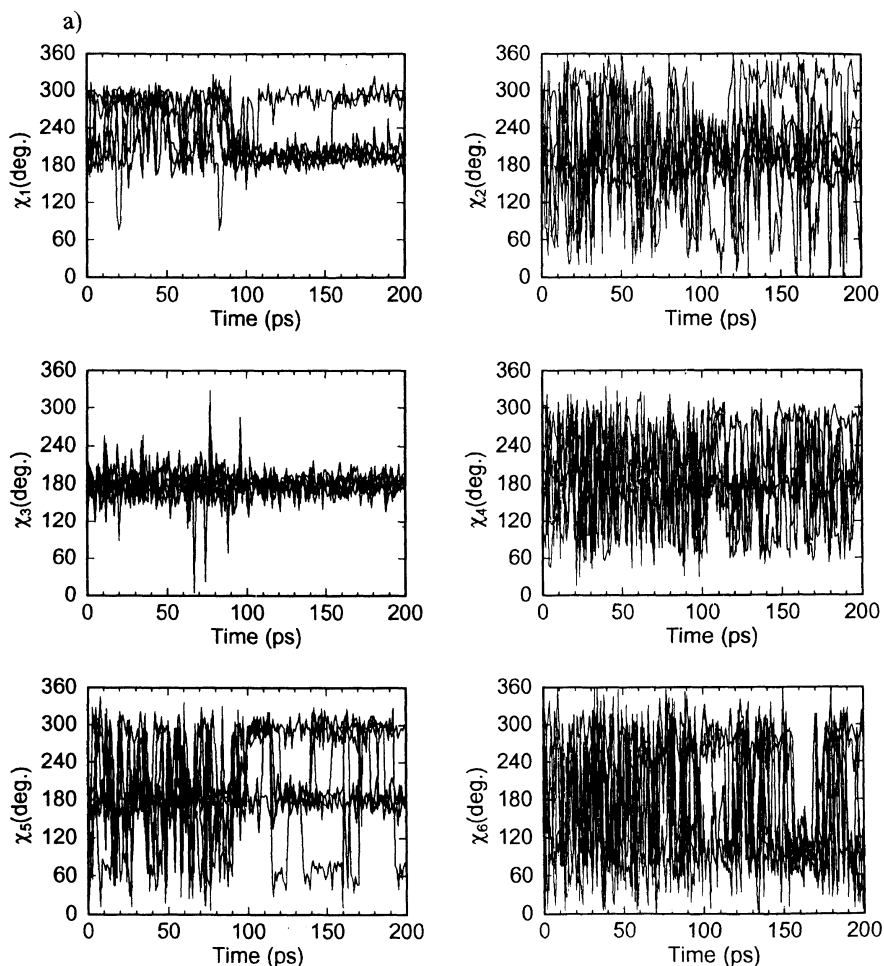


Fig. 2.

tained in less polar media were adopted for comparison. As an effort from the computation side, MD simulations were performed *in vacuo* as well as in the presence of solvent molecules (Figure 2). In brief, inclusion of solvent molecules apparently accelerates rotational transitions, but the average conformation remains more or less the same.²⁶ (3) Some experimental evidences can be found in the literatures concerning the stiffness of the α -helical backbone of the *r*-PBLG molecule in solution. The persistence length of *r*-PBLG has been estimated to be 700–1800 Å from the analysis of solution properties.²⁷ From the 2D

NMR measurements in solution, Mirau and Bovey²⁸ suggested that the hydrogen-bonded architecture of *r*-PBLG is consistent with those estimated in the solid state.¹⁷ In the present work, the ratio $\Delta\nu_\alpha/\Delta\nu_N$ has provided an information regarding the α -helical structure.

In Table IV, the results of MD calculation sampled during 100–200 ps runs at 500 K are summarized. The bond conformations deduced from the 0–100 ps runs at 1000 K were found to be nearly identical. The rotational transitions were substantially suppressed at 300 K. The extended runs (1 ns) did not appreciably affect the results.

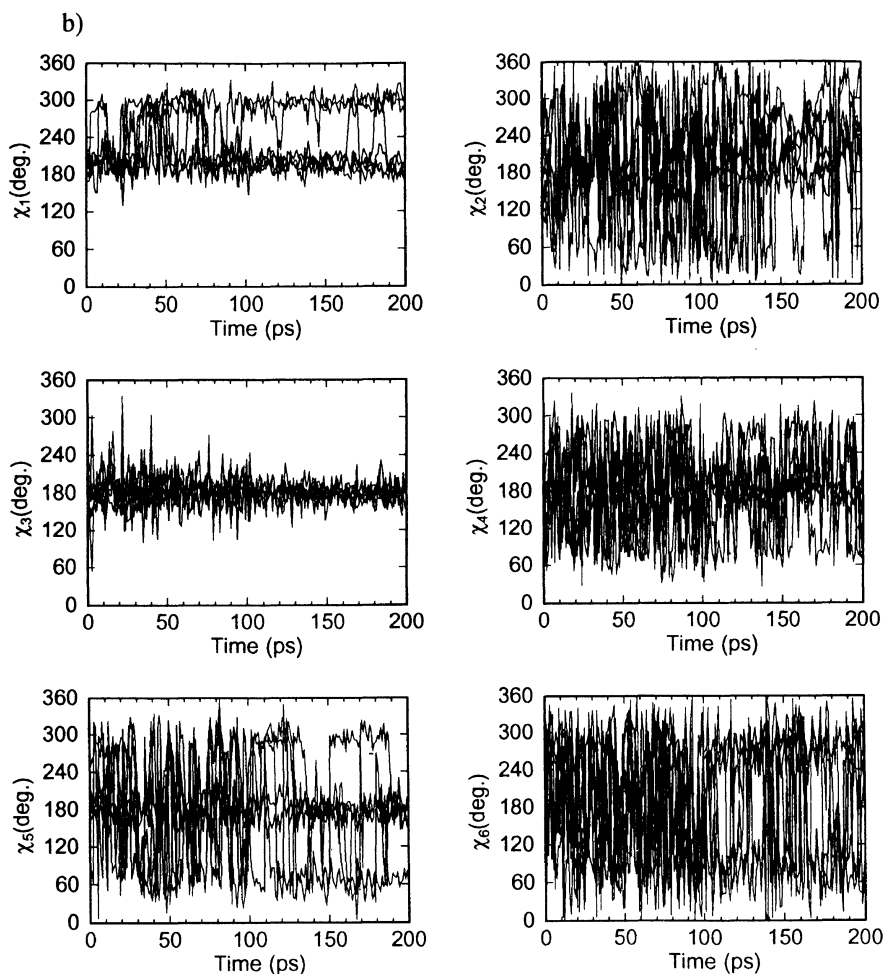


Figure 2. Dihedral fluctuations in PPLA during a 200 ps trajectory: a) *in vacuo*; b) in chloroform solution. (0–100 ps at 1000 K and 100–200 ps at 500 K.)

With a reasonable success in the computer simulation, we have further attempted to gain some insight into the conformational exclusion among side chains arranged along the backbone. Calculations were carried out for a hypothetical single-sidechain model in which an aspartate or glutamate residue is incorporated in a poly-L-alanine α -helix, e.g., Ac-(Ala)₉-(Asp(OPhe))₁-(Ala)₈-NHMe. The results of MD simulations carried out *in vacuo* at 500 K are summarized in Table V. The conformational transitions took place less frequently under these conditions. It is

interesting to note here that while the bond conformations defined for the aspartates (Table V) resemble those from the multi-sidechain model (Table IV), the glutamates exhibit a substantial deviation at the χ_1 and χ_2 level. The disparity noted above for the glutamates becomes smaller when calculations were performed at higher temperatures. The difference between the single- and multi-sidechain models should reflect the characteristics of the oscillating motion of lateral chains in a given hairy-rod system.

The results of the ²H NMR analysis indicate

Table IV. Bond conformations calculated for Ac- X_{18} -NHMe ($X = \text{Asp(OPhe)}$, Glu(OBzl)),^a and those observed^b

Bond	Calculated ^a			Observed ^b			
	f_t	f_{g^+}	f_{g^-}	f_t	f_{g^+}	f_{g^-}	
$X = \text{Asp(OPhe)}$							
Right	χ_1	0.76	0.00	0.24	0.72	0.00	0.29
	χ_2	0.67	0.10	0.23	0.80	0.01	0.20
	χ_3	1.00	0.00	0.00	1.00	0.00	0.00
	χ_4	0.56	0.15	0.30	0.38	0.28	0.34
	χ_5	0.49	0.09	0.42	0.50	0.30	0.20
Left	χ_1	0.36	0.00	0.64	0.36	0.00	0.64
	χ_2	0.68	0.18	0.14	0.72	0.25	0.03
	χ_3	1.00	0.00	0.00	1.00	0.00	0.00
	χ_4	0.57	0.26	0.17	0.85	0.08	0.08
	χ_5	0.57	0.34	0.10	0.77	0.11	0.11
$X = \text{Glu(OBzl)}$							
Right	χ_1	0.76	0.02	0.22	0.70	0.00	0.30
	χ_2	0.54	0.36	0.11	1.00	0.00	0.00
	χ_3	0.69	0.20	0.12	0.45	0.28	0.28
	χ_4	1.00	0.00	0.00	1.00	0.00	0.00
	χ_5	0.60	0.21	0.19	0.58	0.21	0.21
Left	χ_1	0.34	0.02	0.64			
	χ_2	0.61	0.13	0.27			
	χ_3	0.56	0.24	0.20			
	χ_4	1.00	0.00	0.00			
	χ_5	0.61	0.17	0.23			

^a Calculated with a cut-off distance $r_c = 5 \text{ \AA}$ and a dielectric constant $\epsilon = 3.5$ for the temperature of 500 K *in vacuo*. ^b For experimental conditions, see footnote to Table III.

that sidechain conformations are appreciably more proliferated when the backbone takes the left-handed α -helical form, suggesting that the conformational entropy of the side chain may play an important role in the helix-helix transition involved in the PPLA system. Since the α -helical backbone is stabilized by the hydrogen-bonds arranged in a highly cooperative manner, a reversible transformation between the two antipodes should occur abruptly, and may be regarded as a pseudo first-order type.³ The MD simulation however predicts a similar conformational free-energy difference between *r*- and *l*-PBLG, for which interconversion of

Table V. Bond conformations calculated for a single sidechain model^a: Ac-(Ala)₉- X -(Ala)₈-NHMe ($X = \text{Asp(OPhe)}$, Glu(OBzl))

Bond	f_t	f_{g^+}	f_{g^-}	
$X = \text{Asp(OPhe)}$				
Right	χ_1	1.00	0.00	0.00
	χ_2	0.74	0.09	0.17
	χ_3	1.00	0.00	0.00
	χ_4	0.56	0.12	0.32
	χ_5	0.99	0.00	0.01
Left	χ_1	0.07	0.00	0.93
	χ_2	0.71	0.15	0.14
	χ_3	1.00	0.00	0.00
	χ_4	0.60	0.11	0.29
	χ_5	0.84	0.00	0.16
$X = \text{Glu(OBzl)}$				
Right	χ_1	0.98	0.00	0.02
	χ_2	0.04	0.96	0.00
	χ_3	0.5 ^c	0.25	0.17
	χ_4	1.00	0.00	0.00
	χ_5	0.67	0.19	0.14
Left	χ_1	0.98	0.00	0.02
	χ_2	0.00	1.00	0.00
	χ_3	0.65	0.19	0.16
	χ_4	1.00	0.00	0.00
	χ_5	0.77	0.08	0.15

^a Calculated with a cut-off distance $r_c = 5 \text{ \AA}$ and a dielectric constant $\epsilon = 3.5$ for the temperature of 500 K *in vacuo*.

α -helices has never been observed. In order to investigate the origin of such discrepancy in the transition behaviors, energy calculations have been carried out with emphasis on the short-range interactions involving the C^α and C^β carbons in the side chain. In agreement with Scheraga *et al.*'s results,⁶ the energy difference between the left- and right-handed forms was found to be appreciably larger for PBLG than PPLA, suggesting that the transition would be more difficult to occur at ordinary temperatures in the former system. A detailed study of the helix-sense inversion phenomenon of PPLA will be reported elsewhere.

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- Discover ver. 2.95 program is available from Biosym Technologies, 9685 Scranton Road, San Diego, CA 92121-2777, U.S.A. In our previous study,⁸ we have used a forcefield called CVFF. Some of the energy expressions defined in CVFF are different from those of PCFF adopted in this work: e.g., the 6–12 potential of CVFF is replaced by the 6–9 expression in PCFF for the nonbonded interaction. PCFF is an extended version of the CFF forcefield.
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