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Random-coiled conformation of polypeptide chains

3. Theoretical conformational analysis of poly(L-leucine)

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SUMMARY

Random-coiled conformation of poly(L-leucine), which has γ-branched side-chain, was theoretically analyzed by a conformational energy calculation based on intra-residue interactions. Calculated characteristic ratio 7.62 was obtained by using the transformation matrix statistically averaged over the entire side-chain conformational space of L-Leu residue. This value is smaller than those of poly(L-phenylalanine)(11.24) and poly-(L-tyrosine)(12.33) which have γ-branched side-chain.

INTRODUCTION

Theoretical analysis[1,2] of the random-coiled conformation of non-β-branched polypeptide chains such as poly(L-phenylalanine), poly(L-tyrosine), poly(L-glutamine) and poly(L-glutamic acid) using ECEPP(Empirical Conformational Energy Program for Peptides)[3] has shown that side-chain/backbone interactions are very important to stabilize the backbone conformations and also that the characteristic ratio depends on the nature of side-chain group. That is, calculated characteristic ratios of poly(L-phenylalanine)(11.24) and poly(L-tyrosine)(12.33) are larger than that of poly(L-alanine)(8.15)[1]. The increase of the characteristic ratios of poly(L-phenylalanine) and poly(L-tyrosine) are caused by the favorable side-chain/backbone interactions which relatively stabilize the extended conformations in comparison with other conformations of L-Phe and L-Tyr residues. Calculated characteristic ratios of poly(L-glutamine)(6.62) and poly(L-glutamic acid)(7.51) are smaller than those of poly(L-alanine) [2]. The decrease of the characteristic ratio of poly(L-glutamine) and poly(L-glutamic acid) are caused by the residue-characters that both α-helical and extended conformations are stable ones for the L-Gln and L-Glu residues. L-Leu residue has branch at C^{γ}-atom as L-Phe and L-Tyr residues, but the groups attached to C^{γ}-atom of the former residue are different from those of the latter ones. L-Leu residue has two methyl groups at the δ-position and rotation around C^{β}-C^{γ} bond is the three-fold rotation, however, L-Phe and L-Tyr residues have two methyne groups at the δ-position and rotation around C^{β}-C^{γ} bond is the six-folded rotation. Then, it is supposed that the side-chain and backbone stabilities of L-Leu residue are different from those of L-Phe and L-Tyr residues.

In this work, side-chain and backbone conformations of poly(L-leucine) were theoretically analized based on the intra-residue interactions. Moreover, the characteristic ratio of poly(L-leucine) was calculated by averaging the chain conformation over the entire $(\phi,\psi,\chi^1,\chi^2)$ space.

THEORETICAL

The nomenclature and conventions adopted are those recomended by an IUPAC-IUB nomenclature commission[4]. Assumptions and definitions used in this work are the same as those used in the previous works[1,2]. Conformational energy $E_i(\phi_i,\psi_i,\chi_i)$ of residue i was calculated for a model single-residue peptide with two blocking end groups, acetyl- and N-methylamide(i.e., Ac-L-Leu-NHMe). All interactions in this model peptide are refered to as the intra-residue interactions. The partition function Z_i of the i-th residue is calculated by

$$Z_i = \int\cdots\int \exp\{-\beta E_i(\phi_i,\psi_i,\chi_i)\}d\phi_i d\psi_i d\chi_i \qquad (1)$$

with the conformational energy E_i based on the intra-residue interactions, where $\beta=1/RT$ and RT is the gas constant times the temperature. The statistically averaged transformation matrix $\langle T_i\rangle$ is

$$\langle T_i\rangle = Z_i^{-1} \int\cdots\int T(\phi_i,\psi_i)\exp\{-\beta E_i(\phi_i,\psi_i,\chi_i)\}d\phi_i d\psi_i d\chi_i \qquad (2)$$

where, the matrix $T(\phi_i,\psi_i)$ transforming the coordinate system of polymer chain is defined by equation (2) of ref 1. The characteristic ratio is given by

$$\langle R^2\rangle_{0,\infty}/nl^2 = [(E_3+\langle T_i\rangle)(E_3-\langle T_i\rangle)^{-1}]_{11} \qquad (3)$$

where, E_3 is the 3×3 unit matrix, the subscript 11 denotes the 1,1-element of matrix.

Conformational energy calculations were carried out for Ac-L-Leu-NHMe using the energy function of ECEPP. The backbone dihedral angles (ϕ,ψ) were changed at 15° intervals, and all other backbone dihedral angles were fixed at 180°. The side-chain dihedral angles (χ^1,χ^2) of L-Leu residue were also changed at three kinds of intervals, i.e., 15°, 30° and 120°, and $(\chi^{3,1},\chi^{3,2})$ of L-Leu were fixed at 60°.

RESULTS AND DISCUSSION

Conformational energies of Ac-L-Leu-NHMe were calculated at 15° intervals of two side-chain dihedral angles, χ^1 and χ^2 with $\chi^{3,1}=\chi^{3,2}=60°$ and fixing the backbone conformations[5] specified by $(\phi,\psi)=(-150°,124°)$, $(-72°,147°)$, $(-149°,98°)$, $(-83°,87°)$, $(-155°,-60°)$, $(-73°,-49°)$, $(56°,57°)$, and $(-155°,155°)$ with the letter codes, E,F,D,C,G,A,A* and E, respectively. The calculated (χ^1,χ^2) energy contour maps are shown in Figure 1. Stable conformations are found around $\chi^1=180°$ and $-60°$, but the region around $\chi^1=60°$ is not energetically favorable one except for the case of E conformation with $(\phi,\psi)=(-155°,-155°)$. Similar stabilities were also found for L-Phe residue[1]. These facts indicate that the difference of groups attached to γ-carbon between L-Leu and L-Phe residues has minor effects on the rotational state around C^{α}-C^{β} bond. Energetically favorable regions exist in $60°\leq\chi^2\leq180°$, but the conformations around $\chi^2=-90°$ are unstable conformations even if they are stable conformations for L-Phe residue. Distributions of energetically favorable regions of the (χ^1,χ^2) maps of L-Leu residue are different from those of the (χ^1,χ^2) map of L-Phe residue (Figure 3 of ref 1). It is mainly caused by the difference of rotational states around C^{β}-C^{γ} bond between L-Leu and L-Phe residues. Relative stabilities of local minima in (χ^1,χ^2) map are affected by the backbone conformation. For example, relative stabilities of the local minima around

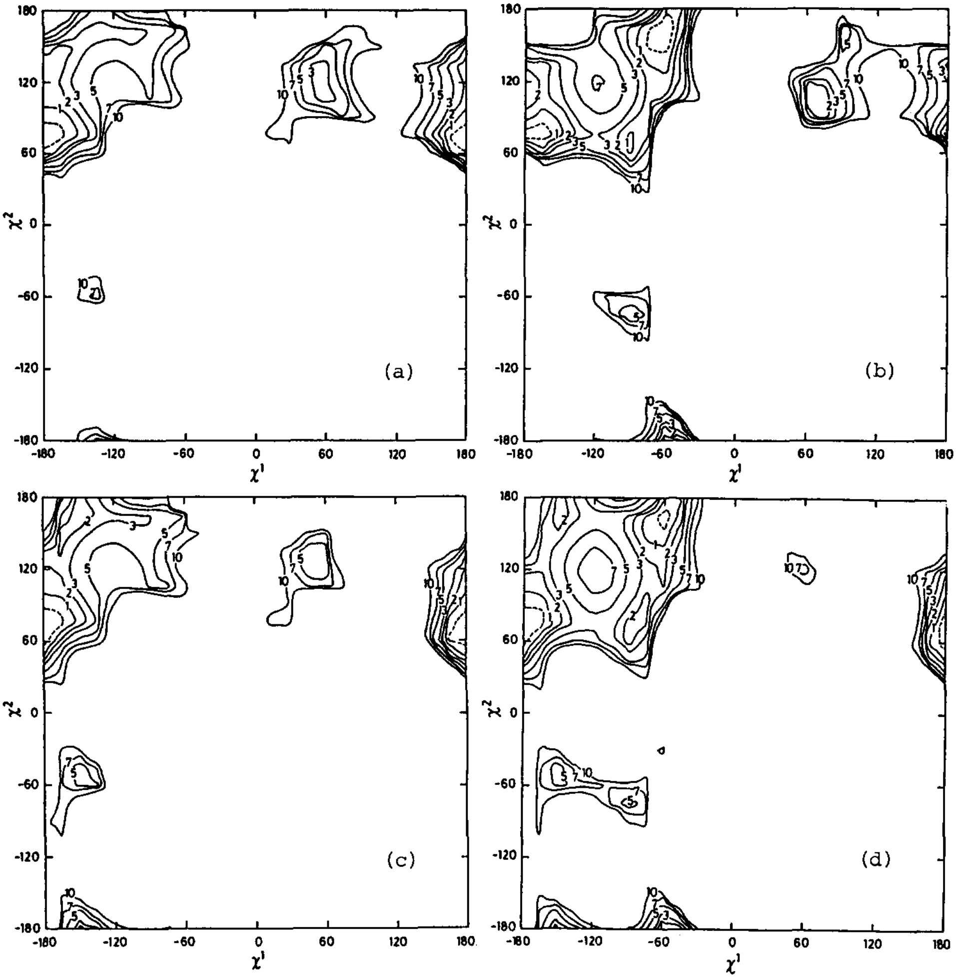

Figure 1. Energy contour (χ^1, χ^2) maps of the L-Leu residue for the specified backbone conformations and $\chi^{3,1}=\chi^{3,2}=60°$ at 15° interval.

(a) E conformation $(\phi,\psi)=(-150°,124°)$ with $E_{min}=-2.954$ kcal mol^{-1}
(b) F conformation $(\phi,\psi)=(-72°,147°)$ with $E_{min}=-2.036$ kcal mol^{-1}
(c) D conformation $(\phi,\psi)=(-149°,98°)$ with $E_{min}=-2.934$ kcal mol^{-1}
(d) C conformation $(\phi,\psi)=(-83°,87°)$ with $E_{min}=-3.606$ kcal mol^{-1}
(e) G conformation $(\phi,\psi)=(-155°,-60°)$ with $E_{min}=-2.505$ kcal mol^{-1}
(f) A confotmation $(\phi,\psi)=(-73°,-49°)$ with $E_{min}=-2.821$ kcal mol^{-1}
(g) A*conformation $(\phi,\psi)=(56°,57°)$ with $E_{min}=-1.803$ kcal mol^{-1}
(h) E conformotion $(\phi,\psi)=(-155°,155°)$ with $E_{min}=-1.368$ kcal mol^{-1}

$(\chi^1,\chi^2)=(60°,120°)$ are evidently changed with an increase of ψ as shown by comparison of Figure 1(a), 1(c), 1(e) and 1(h), or Figure 1(b), 1(d) and 1(f). 11 stable side-chain conformations of the L-Leu residue were found on the 30° grid in the (χ^1,χ^2) space with $\Delta E<3$ kcal mol^{-1} ($\Delta E=E-E_{min}$,

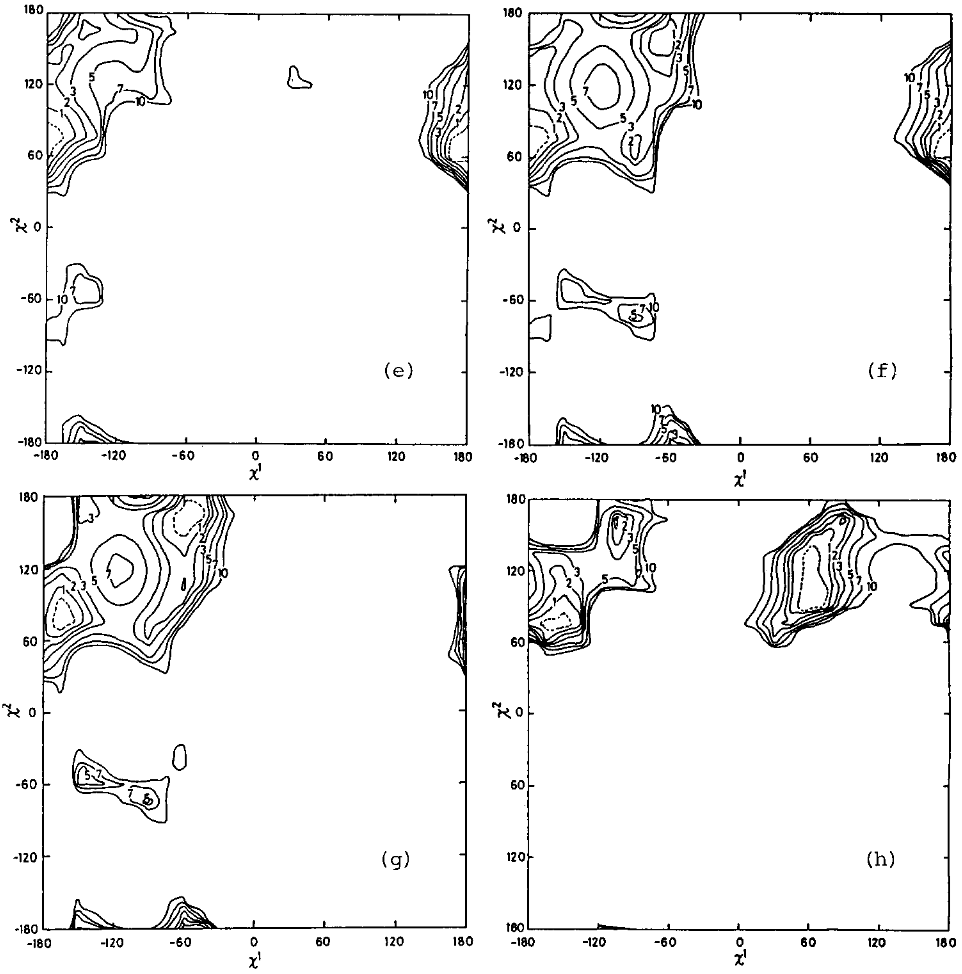

Figure 1 e-h.

E_{min}=-3.221 kcal mol^{-1} for $(\phi,\psi,\chi^1,\chi^2)=(-90°,90°,-180°,60°)$), and their (χ^1,χ^2) and ΔE were listed in Table I.

Conformational energies of the L-Leu residue at 15° intervals in the (ϕ,ψ) space were calculated for 11 specified (χ^1,χ^2) listed in Table I. As shown in Figure 2, calculated results with χ^1=180° indicate that D, C, and A backbone conformations are favorable, and that the shape of energy contours in (ϕ,ψ) maps are almost independent of χ^2 in the range of $60° \leq \chi^2 \leq 120°$. By the 30° increase of χ^1 from 180°, relative stabilities of A conformation is decreased. For the case of χ^1=-60°, only C and F conformations can be existed with ΔE<0.5 kcal mol^{-1}. The (ϕ,ψ) energy contour map with χ^1=60° indicates that the only E conformation is stable one with ΔE<1 kcal mol^{-1} as well as the calculated results for the L-Phe residue[1]. As shown in Table I, calculated characteristic ratio significantly depends on the side-chain conformations, and these results also support the previous conclusion[1] that the statistical averaged values calculated by fixing side-chain conformation at a particular one may not be usable as

Table I. Characteristic Ratio of Poly(L-leucine) for the Specified Side-Chain Conformations

χ^1	χ^2	ΔE(kcal mol^{-1})^a	$\langle R^2\rangle_{0,\infty}/nl^2$
180	60	0.000	6.94
-60	150	0.789	10.44
180	90	0.875	7.79
-60	180	1.402	11.30
-150	180	2.103	15.86
60	90	2.120	122.8
60	120	2.458	18.10
-60	120	2.461	10.19
180	120	2.611	5.98
-90	150	2.887	8.04
-150	150	2.916	9.86

[a] $\Delta E = E - E_{min}$; $E_{min} = -3.221$ kcal mol^{-1} for (ϕ, ψ, χ^1, χ^2)= (-90°,90°,180°,60°), and E is the lowest energy in (ϕ, ψ) space for each specified (χ^1, χ^2).

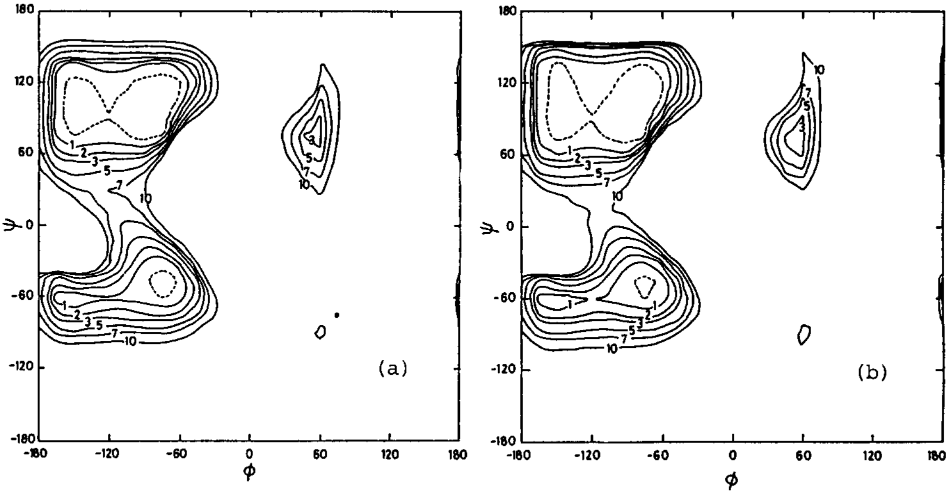

Figure 2. Energy contour (ϕ,ψ) maps of the L-Leu residue for the specified side-chain conformations and $\chi^{3,1}=\chi^{3,2}=60°$ at 15° interval.

(a) (χ^1,χ^2)=(180°, 60°) with $E_{min}=-3.221$ kcal mol^{-1}
(b) (χ^1,χ^2)=(180°, 90°) with $E_{min}=-2.346$ kcal mol^{-1}
(c) (χ^1,χ^2)=(-150°,180°) with $E_{min}=-1.118$ kcal mol^{-1}
(d) (χ^1,χ^2)=(-60°,150°) with $E_{min}=-2.432$ kcal mol^{-1}
(e) (χ^1,χ^2)=(-60°,180°) with $E_{min}=-1.819$ kcal mol^{-1}
(f) (χ^1,χ^2)=(60°, 90°) with $E_{min}=-1.101$ kcal mol^{-1}

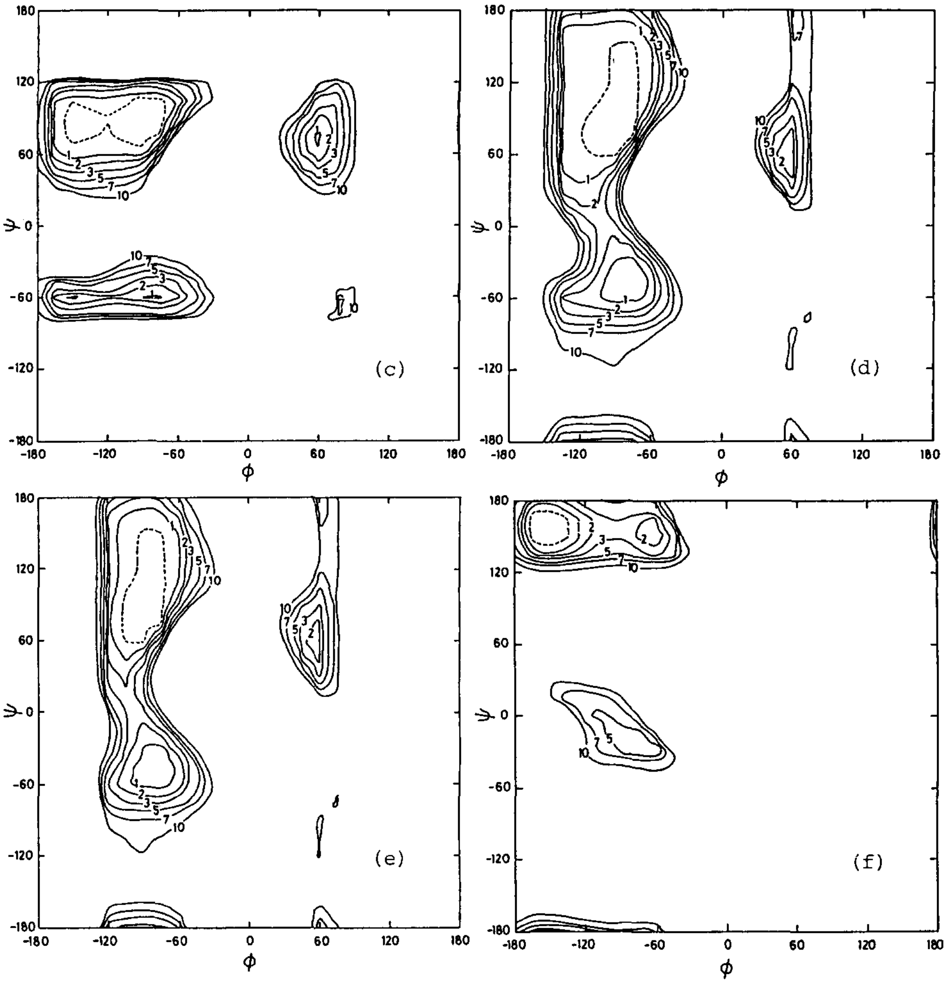

Figure 2 c-f.

approximated values.

In Figure 3, (φ,ψ) map of the L-Leu residue avaraged over the side-chain conformation (χ^1,χ^2) at the 15° interval is also shown. E and F conformations are less and A conformation is more stable than those of the L-Ala residue. The (φ,ψ) maps of the L-Leu residue averaged over χ^1 at the 30° and 120° intervals are almost same as that of the 15° interval with one exception that E conformation are destabilized for the case of the 120° interval. The statistically averaged transformation matrix calculated by Eq 2 and the energy contour map of the L-Leu residue at the 15° interval is

$$<T>_{\text{L-Leu}} = \begin{bmatrix} 0.314 & -0.196 & 0.639 \\ -0.140 & -0.594 & -0.145 \\ 0.791 & -0.172 & -0.229 \end{bmatrix} \qquad (4)$$

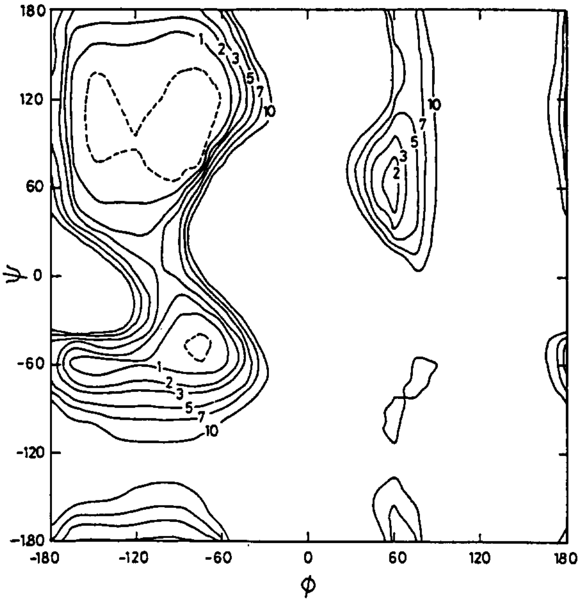

Figure 3. Energy contour (φ,ψ) map of L-Leu residue averaged over (χ^1,χ^2) at 15° interval with $\chi^{3,1}=\chi^{3,2}=60°$.

and the calculated characteristic ratios are 7.62, 7.45 and 7.09 for the 15°, 30° and 120° intervals, respectively. That is, the characteristic ratio of poly(L-leucine) presents the dependency on the value of intervals. The calculated value 7.62 is very close to that of poly(L-glutamic acid) (7.51), and smaller than those of poly(L-phenylalanine) (11.24) and poly(L-tyrosine) (12.33) which have branches at the C^{γ}-atom as poly(L-leucine).

Miller and Goebel[6] calculated the conformational energy of polypeptides composed of the residue with $-C^{\beta}H_2-C^{\gamma}CH_2R$ side chains taking van der Waals radii 1.70 and 1.85 Å for C^{β}-atom and $-C^{\gamma}H_2R$ group, respectively. Using the partition function summed over $\chi^1=180°$, -60° and 60°, they obtained the characteristic ratio 8.9 for n=500. However, their proposed characteristic ratio is not adequate by the following reasons. In the previous paper[1,2], we already made it clear (1) that poly(L-phenylalanine), poly(L-tyrosine),poly(L-glutamine) and poly(L-glutamic acid), which are poly(L-alanine)-type polypeptides with $-C^{\beta}H_2R$ side chain, have the different characteristic ratios following the different nature in the side-chain/backbone interactions, and also (2) that the three state approximations summed Z_i over only three values of χ^1 (i.e., 180°, -60° and 60°) are not adequate to calculate Z_i and the 15° interval of χ^1 and χ^2 should be used to calculate Z_i. These conclusions are also supported by the calculated results for poly(L-leucine) in this work. Both L-Phe and L-Leu residues have branches at γ-carbon, but their (φ,ψ) maps (Figure 5c of ref 1 and Figure 3) show the explicitely different distributions of stable regions, then they have different characteristic ratios 11.24 and 7.62, respectively. These results indicate that characteristic ratios of polypeptide chains are not decided by the position of side-chain branching, but essentially decided by the side-chain/backbone interactions followed by the nature of side-chain group.

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