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Random-coiled conformation of polypeptide chains

4. Theoretical conformational analysis of poly(L-valine)

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SUMMARY

Random-coiled conformation of poly(L-valine), which has β-branched side-chain, was theoretically analyzed by a conformational energy calculation based on intra-residue interactions. Calculated characteristic ratio 9.59 was obtained by using the transformation matrix statistically averaged over the entire side-chain conformational space of L-Val residue. This value is smaller than those of poly(L-phenylalanine)(11.24) and poly-(L-tyrosine)(12.33) but larger than that of poly(L-leucine)(7.62). The obtained results indicate that the overall stability of the backbone conformation is the essential factor affecting the characteristic ratios but the position of side-chain branching is not so important for the characteristic ratio.

INTRODUCTION

Theoretical analysis[1-3] of the random-coiled conformation of non-β-branched polypeptide chains such as poly(L-phenylalanine), poly(L-tyrosine), poly(L-glutamine), poly(L-glutamic acid) and poly(L-leucine) using ECEPP(Empirical Conformational Energy Program for Peptides)[4] has shown that the 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. That is, the characteristic ratios of poly(L-phenylalanine) and poly(L-tyrosine)(11.24 and 12.33, respectively)[1] are larger than that of poly-(L-leucine)(7.62)[3] although these polypeptides are composed of γ-branched side-chains. The difference of the characteristic ratios is caused by the difference of side-chain groups attaching to C^{γ}-atom. L-Phe and L-Tyr residues have aromatic groups, but L-Leu residue has two methyl groups. Then, rotational states around C^{β}-C^{γ} bond are different between the former and latter residues(six- and three-fold rotations, respectively). Theoretical results[1] indicate that E conformation of L-Phe and L-Tyr residues is favorable conformation which is stabilized by the side-chain/backbone interactions correlated with the aromatic side-chain group, and hence poly(L-phenylalanine) and poly(L-tyrosine) have large characteristic ratios. Moreover, theoretical results[3] also indicate that C, D and A conformations of L-Leu residue are relatively stabilized by the side-chain/backbone interactions correlated with the two methyl groups attached to C^{γ}-atom, and hence poly(L-leucine) has small characteristic ratio. L-Val residue has a branch at C^{β}-atom, therefore two methyl groups attached to C^{β}-atom situate in a close range of backbone atoms in comparison with two methyl groups attached to C^{γ}-atom of L-Leu

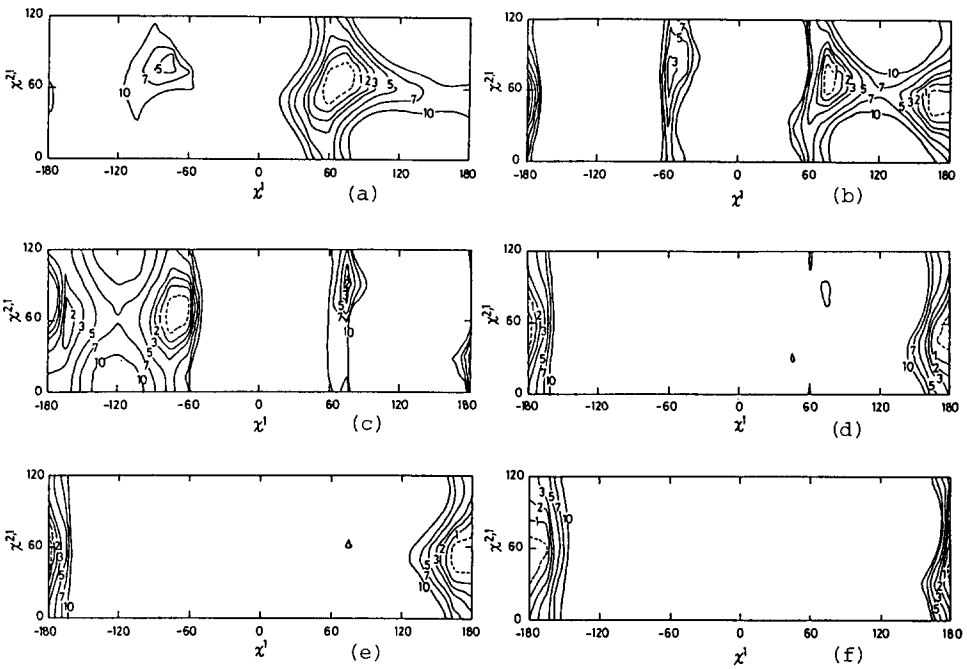

Figure 1. Energy contour (χ^1,$\chi^{2,1}$) maps of the L-Val residue for the specified backbone conformations and $\chi^{2,2}$=60° at 15° interval. The contour lines are labeled as energy in kcal mol^{-1} above the minimum energy point. The dashed lines indicate the 0.5 kcal mol^{-1} energy contour lines.

(a) E conformation (ϕ,ψ)=(-154°,142°) with E_{min}=-1.012 kcal mol^{-1}
(b) F conformation (ϕ,ψ)=(-69°,141°) with E_{min}=-0.033 kcal mol^{-1}
(c) D conformation (ϕ,ψ)=(-135°, 40°) with E_{min}= 1.428 kcal mol^{-1}
(d) C conformation (ϕ,ψ)=(-88°, 98°) with E_{min}=-1.692 kcal mol^{-1}
(e) A conformation (ϕ,ψ)=(-83°,-48°) with E_{min}=-0.790 kcal mol^{-1}
(f) A*conformation (ϕ,ψ)=(56°, 75°) with E_{min}= 1.667 kcal mol^{-1}

residue. It is supposed that the side-chain/backbone interactions of L-Val residue are more characteristic than those of L-Leu residue, and also that energetically favorable regions of L-Val residue are fairly different from those of L-Leu residue.

In this work, the side-chain and backbone conformations of poly(L-valine) were theoretically analized based on the intra-residue interactions. Moreover, the characteristic ratio of poly(L-valine) was calculated by averaging the chain conformation over the entire (ϕ,ψ,χ^1) space.

THEORETICAL

The nomenclature and conventions adopted are those recomended by an IUPAC-IUB nomenclature commision[5]. Assumptions and definitions used in this work are the same as those used in the previous works[1-3]. Conformational Energy $E_i(\phi_i,\psi_i,\chi^1_i)$ of residue i was calculated for a model single-residue peptide with two blocking end groups, acetyl- and N-

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

χ^1	ΔE(kcal mol^{-1})[a]	$\langle R^2\rangle_{o,\infty}/nl^2$
180	0.000	12.27
60	0.815	210.1
165	1.117	5.89
75	1.287	21.67
-60	1.668	35.78
-75	2.163	14.93
-165	2.355	18.44
45	2.784	152.4

[a] $\Delta E=E-E_{min}$; E_{min}=-1.642 kcal mol^{-1} for $(\phi,\psi,\chi^1)=(-90°,90°,180°)$, and E is the lowest energy in (ϕ,ψ) space for each specified χ^1.

methylamide(i.e., Ac-L-Val-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 equation (1) of ref 1 (or ref 3) with the conformational energy E_i based on the intra-residue interactions. The statistically averaged transformation matrix $\langle T_i\rangle$ and the characteristic ratio $\langle R^2\rangle_{o,\infty}/nl^2$ are obtained by equations (3) and (5) of ref 1 (or equations (2) and (3) of ref 3).

Conformational energy calculations were carried out for Ac-L-Val-NHMe using the energy function of ECEPP[4]. 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 angle χ^1 of L-Val residue was also changed at three kinds of intervals, i.e., 15°, 30° and 120°, and ($\chi^{2,1}$, $\chi^{2,2}$) of L-Val were fixed at 60°.

RESULTS AND DISCUSSION

The conformational energies of Ac-L-Val-NHMe were calculated at 15° intervals of two side-chain dihedral angles χ^1 and $\chi^{2,1}$ with $\chi^{2,2}$=60° and fixing the backbone conformation at one of the following single-residue minimum conformations specified by (ϕ,ψ)=(-154°,142°), (-69°,141°), (-135°,40°), (-88°,98°), (-83°,-48°) and (56°,75°) with the letter codes [6], E, F, D, C, A and A*, respectively. The calculated $(\chi^1,\chi^{2,1})$ energy contour maps are shown in Figure 1. F and D conformations have three local minima with $\Delta E<3$ kcal mol^{-1} around χ^1=180°, -60° and 60°. However, rotational states χ^1=180° and -60° of E conformation is unstable because of the repulsive interaction between H-atom of methyl group and O-atom of acetyl group. For C, A and A* conformations, χ^1=180° is the only energetically allowed conformation. χ^1=-60° and 60° of C and A conformations are unstable ones with $\Delta E\simeq 8\sim 17$ kcal mol^{-1}. Especially those of A* conformations are fairly unstable ones with $\Delta E<50$ kcal mol^{-1} because of the favorable repulsive interaction between O-atom of acetyl group and H-atom of methyl group at γ_1- and γ_2-positions for χ^1=60° and -60°, respectively. Energetically favorable regions exist around $\chi^{2,1}$=-180°, -60° and 60°, and they are independent of backbone conformations.

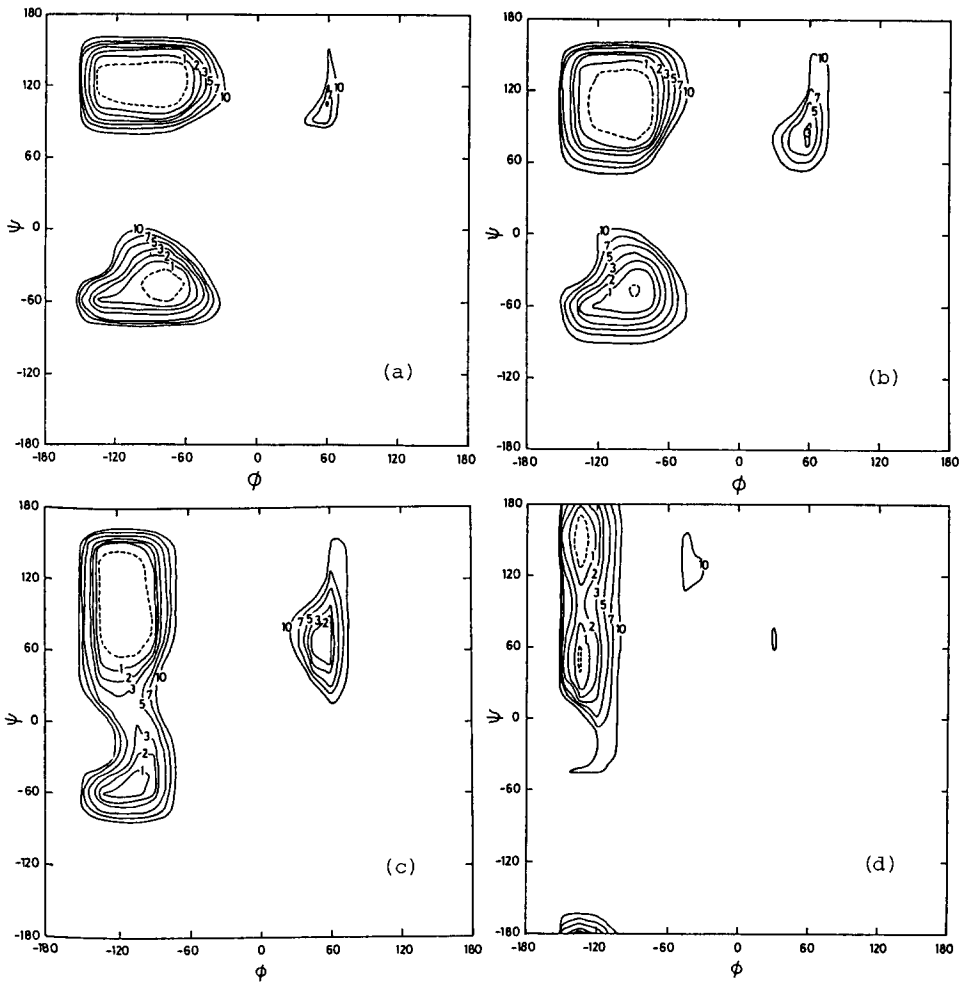

Figure 2. Energy contour (ϕ,ψ) maps of the L-Val residue for the specified side-chain conformations and $\chi^{2,1}=\chi^{2,1}=60°$ at 15° interval.

(a) χ^1= 165° with E_{min}=-0.525 kcal mol^{-1}
(b) χ^1= 180° with E_{min}=-1.642 kcal mol^{-1}
(c) χ^1=-165° with E_{min}= 0.713 kcal mol^{-1}
(d) χ^1= -75° with E_{min}= 0.521 kcal mol^{-1}
(e) χ^1= -60° with E_{min}= 0.026 kcal mol^{-1}
(f) χ^1= 45° with E_{min}= 1.142 kcal mol^{-1}
(g) χ^1= 60° with E_{min}=-0.827 kcal mol^{-1}
(h) χ^1= 75° with E_{min}=-0.355 kcal mol^{-1}

The (ϕ,ψ) energy contour maps of L-Val residue fixing χ^1 at one of the value of 15° intervals were calculated. For eight values of χ^1, the lowest energy in the (ϕ,ψ) space for each specified χ^1 of the 15° interval was found with $\Delta E<3$ kcal mol^{-1} ($\Delta E=E-E_{min}$, E is the lowest energy in the

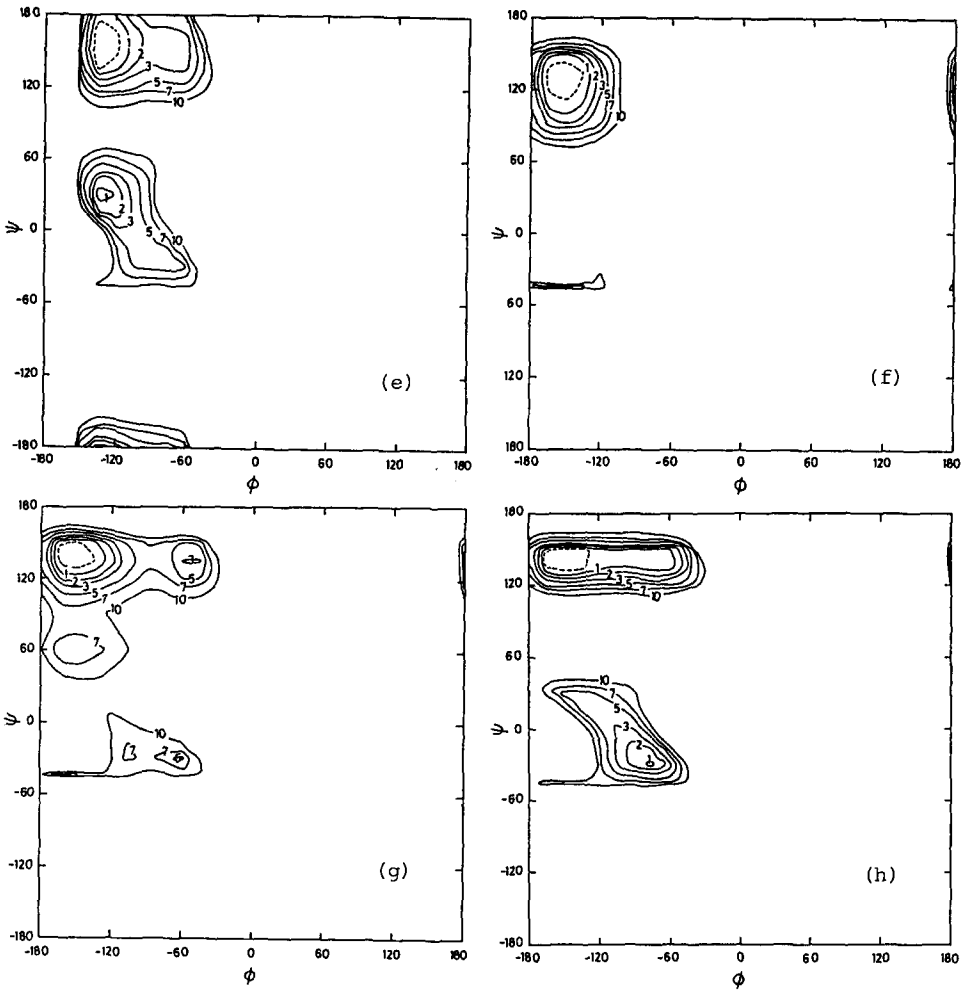

Figure 2 e-h.

(ϕ,ψ) space for each specified χ^1 of the 15° interval and E_{min} is the global minimum of the 15° grid in the (ϕ,ψ,χ^1) space.) All χ^1 and ΔE of them are listed in Table I and the energy-contour (ϕ,ψ) maps are shown in Figure 2. The (ϕ,ψ) maps fixing χ^1 around 180° indicate that both of the extended and α-helical conformations are favorable. On the contrary, the extended conformations are only favorable for the specified side-chain conformations around χ^1=-60° and 60°. That is, the energy difference of the local minima between the extended and α-helical regions are almost 5 kcal mol^{-1} for χ^1=-60° and 60°. Figure 2 explicitely shows that the energetically favorable regions of the L-Val residue are more restricted than those of the L-Ala residue[1], and that the shape of the contour lines with ΔE=1 kcal mol^{-1} are affected by the small change of $\chi^1(\pm 15°)$. The calculated characteristic ratios(12.27, 5.89 and 18.44) for the particular side-chain conformations(χ^1=180°, 165° and -165°) indicate that

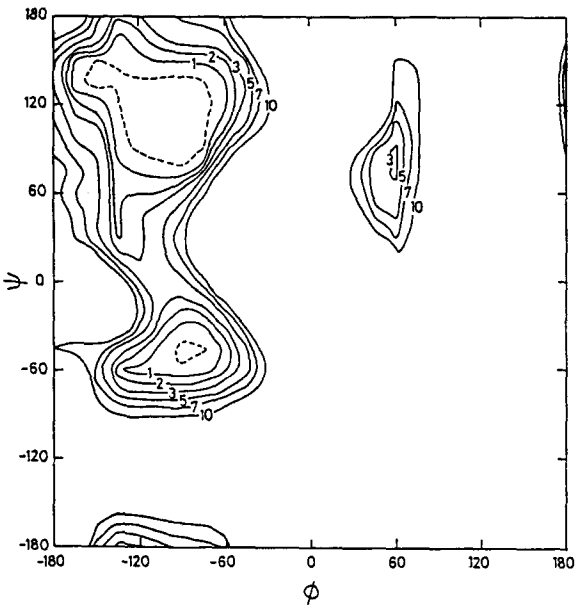

Figure 3. Energy contour (ϕ,ψ) map of L-Val residue averaged over χ^1 at 15° interval with $\chi^{2,1}=\chi^{2,2}=60°$.

characteristic ratios are very sensitive for the side-chain conformation. The low-energy regions of the extended conformations with $\chi^1=165°$ are restricted to more narrow region than those of L-Ala residue, however, the minimum energy of α-helical conformation with$\chi^1=165°$ is lower than that of L-Ala residue. Therefore, the calculated characteristic ratio of poly-(L-valine) with $\chi^1=165°$ is smaller than that of poly(L-alanine). As shown in Figure 2, the only extended conformation is stable for the case of $\chi^1=-60°$ and 60°, but both of the extended and α-helical conformations are stable for $\chi^1=180°$. Therefore, the calculated characteristic ratios of the former ones are larger than that of the latter one(Table I).

In Figure 3, the energy contour map of the backbone conformation of the L-Val residue averaged over the side-chain conformation χ^1 at 15° interval is shown. A comparison with the results for the alanine-type residues, which have not branches at β-carbon atom(i.e., L-Ala[1], L-Phe[1], L-Tyr[1], L-Gln[2], L-Glu[2] and L-Leu[3]), shows that energetically favorable regions of the L-Val residue with $\Delta E<1$ kcal mol^{-1} are more restricted to narrow regions than those of the alanine-type residues, but that A conformation of the L-Val residue are more stabilized than those of the L-Phe and L-Tyr residues. The (ϕ,ψ) energy contour maps of the L-Val residue averaged over χ^1 at 30° and 120° intervals are almost as same as that of 15° interval with one exception that the regions with $\Delta E<0.5$ kcal mol^{-1} of 30° and 120° intervals are smaller than those of 15° interval. The averaged transformation matrix of L-Val at 15° interval calculated by equation (3) of ref 1(or equation (2) of ref 3) is

$$\langle T \rangle_{L\text{-Val}} = \begin{bmatrix} 0.369 & -0.064 & 0.674 \\ -0.161 & -0.691 & -0.010 \\ 0.824 & -0.228 & -0.311 \end{bmatrix} \quad (1)$$

Table II. Theoretically Evaluated Characteristic Ratio

Polypeptides	Oka et al.	Miller et al.[a]
Val	9.59	10.7
Ala	8.15[b]	8.0
Gly	2.15[b]	2.0
Phe	11.24[b]	8.9
Tyr	12.33[b]	8.9
Gln	6.62[c]	8.9
Glu	7.51[c]	8.9
Leu	7.62[d]	8.9

[a] From reference 7, and the value for a chain with n=500 except for Gly(n=∞).

[b] From reference 1

[c] From reference 2

[d] From reference 3

and calculated characteristic ratios are 9.59, 10.79 and 10.82 for 15°, 30° and 120° intervals, respectively. These results indicate that characteristic ratios depend on the value of the intervals, and also the 15° interval is a more desirable one for calculating the partition function Z_i by equation (1) of ref 1 (or ref 3) than the 30° and 120° intervals as already shown in the previous works[1,3]. The calculated characteristic ratio of poly(L-valine) is larger than those of poly(L-alanine), poly(L-glutamine), poly(L-glutamic acid) and poly(L-leucine), but smaller than those of poly(L-phenylalanine) and poly(L-tyrosine).

Miller and Goebal[7] treated two methyl groups at the γ-position of the L-Val residue as the C^{γ}-atoms with 1.85 Å van der Waals radius. They calculated the characteristic ratio of poly(L-valine) with χ^1=180° and n=500(n is number of the virtual bond), and obtained 10.7. Their value is smaller than our value 12.27 with χ^1=180° and n=∞. As already mentioned above, the characteristic ratios show explicite dependence on the side-chain conformation χ^1. That is, the characteristic ratios are 5.89, 12.27 and 18.44 for χ^1=165°, 180° and -165°. Therefore, their treatment fixing χ^1=180° is not adequate to calculate the characteristic ratio of poly(L-valine). The partition function Z_i should be summed over the whole value of χ^1 as treated in this work.

Theoretical results summarized in Table II indicate that the intra-residue side-chain/backbone interactions are very important for the characteristic ratio of polypeptide chains but the bulkiness of side-chain groups and the position of side-chain branching are not so important for the characteristic ratio; that is the overall stability of the backbone conformation is the essential factor affecting the characteristic ratio.

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