

## Comparison of Structural Types of Proline Pentamer by Quantum Chemical Calculation (QCC)

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### Abstract

In this study, Proline pentamer model was used to investigate change in the dihedral angle, intramolecular hydrogen bonding and formation energies during structural optimization. L-Proline (LP, as an imino acid residue) pentamers having four conformation types [ $\beta$ :  $\phi/\psi=t-/t+$ ,  $\alpha$ :  $\phi/\psi=g-/g-$ ,  $PP_{II}$ :  $\phi/\psi=g-/t+$  and P-like:  $\phi/\psi=g-/g+$ ] were carried out by QCC [B3LYP/6-31G(d,p)]. The optimized structure and formation energy were examined for designated structure. In LP, P-like and  $PP_{II}$  types did not change by optimization, and  $\beta$  types were transformed into  $PP_{II}$  having no H-bond independently of the designated  $\psi$  values.  $PP_{II}$  was more stable than P-like by about 2.2 kcal/mol/mu. The hydrogen bond distances of d2(4-6) type H-bonds were 1.94 - 2.00 Å. In order to understand the processes of the transformations, the changes of  $\phi/\psi$ , distances of NH-OC ( $d_{NH/CO}$ ) and formation energies ( $\Delta E$ , kcal/mol/mu) were examined.

**Keywords:** Conformation, Oligopeptide, Proline Pentamer, Quantum Chemical Calculation (QCC), Structural Optimization

## 1. INTRODUCTION

Understanding conformation of oligopeptide is important because the conformation often reflects the chain propagation and folding process, and decides the fundamental properties such as stability and activity. Many experimental and theoretical studies concerning the conformations of oligopeptides have been reported [1, 2]. Eker *et al.* studied the Raman, FTIR, and CD spectra of alanine trimer in water and postulated that the trimer existed as a 50:50 mixture of polyproline II helix (hereinafter referred to as  $PP_{II}$ ) and extended  $\beta$ -strand-like conformation (hereinafter referred to as  $\beta$ ) [3, 4]. Shi *et al.* found from <sup>1</sup>H-NMR spectrum that alanine heptamer dominantly possessed polyproline II helix conformation [5]. The conformational populations of oligopeptide oligomers reported, as mentioned above, have been different with conditions such as sequence lengths, gaseous or aqueous state, experimental or computational methods, and so on.

We have investigated the structural type of gaseous and hydrated alanine oligomer models by incorporating the quantum chemical calculation (QCC). In our previous study [6], we found that alanine heptamer has three stable conformers of shrunken polyproline II (hereinafter referred to as P-like),  $\alpha$ -helical (hereinafter referred to as  $\alpha$ -helix), and extended  $\beta$ -strand-like (hereinafter referred to as  $\beta$ -extended) conformation, in the order of

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stability, by convergent calculation starting from alanine dimer models using quantum chemical calculation (QCC).

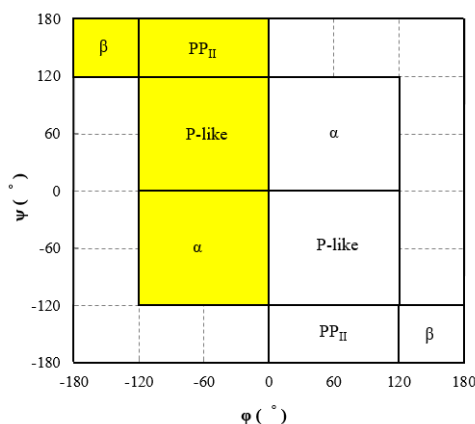
In this paper, in order to deepen the understanding of conformations of oligopeptide, the conformations of oligopeptide having imino acid residues were studied by QCC. Using L-proline (as an imino acid residue) pentamer model, the changes of dihedral angles ( $\varphi/\psi$  values), intra-molecular hydrogen bonds and formation energies in the structure optimization processes were examined.

## 2. QUANTUM CHEMICAL CALCULATIONS (QCC)

### 2.1 Calculation models

The L-proline pentamer (hereinafter LP) model ( $\text{CH}_3\text{CO}-[\text{N}-\{(\text{CH}_2)_3\}-\text{CHCO}]_5-\text{NHCH}_3$ ), molecular weight 558.76 used in this study. Acetyl ( $\text{CH}_3\text{CO}-$ ) and methyl amino ( $-\text{NHCH}_3$ ) groups were used as end groups of amino (N-end) and carboxyl (C-end) terminals

In designations of LP, four conformation types ( $\beta$ -extended:  $\varphi/\psi=t-/t+$ ,  $\alpha$ -helix:  $g-/g-$ ,  $\text{PP}_{\text{II}}$ :  $g-/t+$  and P-like:  $g-/g+$ ) were used as shown in Figure 1. The broken line in each figure shows the boundary between the designated and optimized conformation types. The  $\varphi_n/\psi_n$  is the combinations of dihedral angles ( $\tau_n$ ) repeated for the unit of  $\text{CN}-\text{C}^\alpha\text{C}/\text{NC}^\alpha-\text{CN}$  bonds. The conformations were specified based on the IUPAC rule [7] as follows:  $\tau_n$  of trans ( $t\pm$ ) and gauche ( $g\pm$ ) are  $\pm 120^\circ$  to  $\pm 180^\circ$  and  $\pm 0^\circ$  to  $\pm 120^\circ$ , respectively. The types of  $\varphi_n/\psi_n$  ( $n = 5$ ) were specified as follows: trans and gauche types are ( $t/t$ ) and ( $g/t$ ,  $t/g$ , or  $g/g$ ), respectively, using the average value of  $\varphi_n/\psi_n$  ( $n = 1-5$ ). As designated values of  $(\chi_n/\varphi_n/\psi_n)_{n=1-5}$  of  $\beta$ -extended, P-like, and  $\alpha$ -helix, the values obtained for pentamers by convergent calculation from our previous report result were used [6]. For the  $(\chi_n/\varphi_n/\psi_n)_{n=1-5}$  value of  $\text{PP}_{\text{II}}$ , the values of three kinds ( $\varphi_n/\psi_n = -60/140^\circ$ ,  $-60/160^\circ$  and  $-60/175^\circ$  reported by Graf, et al. [8],) were used. The designated  $\varphi_n/\psi_n$  values are shown in Table 1.



**Figure 1. Four conformation types ( $\varphi/\psi$ ). The  $\beta$  ( $\beta$ -extended:  $t-/t+$ ),  $\text{PP}_{\text{II}}$  ( $g-/t+$ ), P-like ( $g-/g+$ ) and  $\alpha$  ( $\alpha$ -helix:  $g-/g-$ ) with yellow marks were used in designations.**

### 2.2 Structural optimizations

Conformational analyses (structure optimizations) for each model were carried out by quantum chemical calculation method (QCC). The “Gaussian 03W” (Gaussian Inc.) software was used [9]. In the structural

optimizations for LP, B3LYP as a density functional theory (DFT) was used with the self-consistent field (SCF) method. 6-31G(d,p) (d,p: polarization) was used as a basis set. Energies (E: HF, 1 Hartree = 627.51kcal/mol) and structural parameters such as dihedral angle, molecular length and hydrogen bond length were obtained from the optimized structures.

**Table 1. Structure optimization results for L-proline pentamer (LP) <sup>a</sup>**

Designated type ( $\varphi/\psi$ , °)	Optimized type ( $\varphi/\psi$ , Av°)	Number of intra-molecular H-bond		Dipole moment	Molecular length L(Å) <sup>d</sup>	Formation energy	
		N <sub>NH/CO</sub>	(d <sub>NH/CO</sub> , Å) <sup>b</sup>	$\mu$ (Debye) <sup>c</sup>		E (HF)	$\Delta E_{\beta}$ <sup>e</sup> (kcal/mol/mu)
$\beta$ (-160/164) <sup>f</sup>	PP <sub>II</sub> (-76/124)	1	1.94	2.56	14.58	-1872.2962	0.00
$\alpha$ (-72/-14) <sup>g</sup>	-	-	-	-	-	-	-
P-like (-85/69)	P-like (-68/49)	1	2.00	2.42	11.33	-1872.2788	2.18
PP <sub>II</sub> (-60/140) <sup>h</sup>	PP <sub>II</sub> (-76/125)	1	1.95	2.56	14.55	-1872.2962	0.00

<sup>a</sup> Calculated by B3LYP/6-31G(d,p).

<sup>b</sup> The H-bonds were formed between CO of 4 position and NH of C-end [d2(4-6) type H-bond]. The d<sub>NH/CO</sub> is the length of intra-molecular hydrogen bond, and was defined by  $\leq 2.30$  Å.

<sup>c</sup>  $\mu = (\mu_x^2 + \mu_y^2 + \mu_z^2)^{1/2}$ .

<sup>d</sup> The L is non-bonding distance between N atom in N-end (NH) and C atom in C-end (CO).

<sup>e</sup> The  $\Delta E_{PP_{II}}$  values were calculated based on the energy of PP<sub>II</sub> structure.

<sup>f</sup> The results of “ $\beta$  (-160/140)” and “ $\beta$  (-160/175)” were eliminated because of the same as the result of “ $\beta$  (-160/164)”.

<sup>g</sup> The  $\alpha$  type was not obtained in its designation.

<sup>h</sup> The results of “PP<sub>II</sub> (-60/140)” and “PP<sub>II</sub> (-60/175)” were eliminated because of the same as the result of “PP<sub>II</sub> (-60/160)”.

The conformations were specified as mentioned in the calculation models section. Molecular length was defined by L (Å), where the L is non-bonding distance between N atom in N-end and C atom in C-end (CO). The formation of hydrogen bond (H-bond) distance was confirmed by the NH-CO distances with reference (2.74 Å in regular ice [10], 2.85 Å in liquid [10], and 2.98 Å in vapor [11, 12]. The NH-CO distances [d<sub>NH/CO</sub> (Å)] of H-bond were shorter than 2.30Å, and those having no H-bond were longer than 2.7Å, according to the calculated results. Add a diagram representing discussed angles and distances used in this structure optimization.

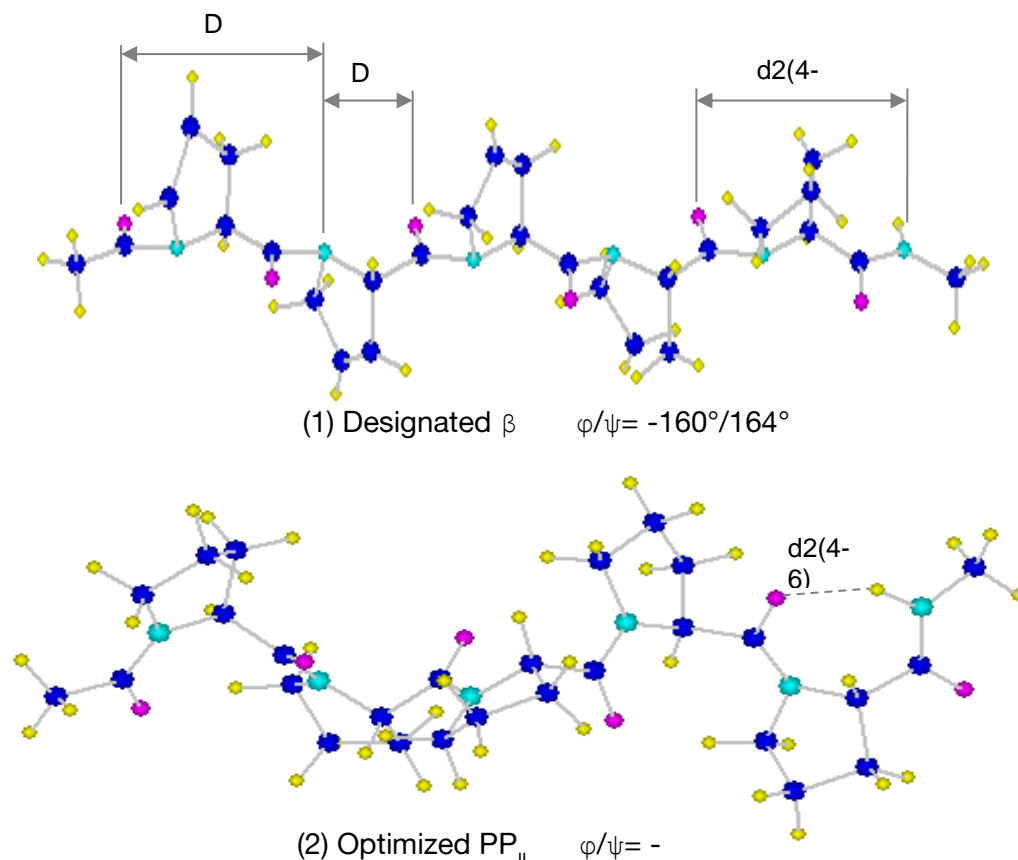
### 3. RESULT AND DISCUSSION

L-proline pentamer (LP, as an imino acid residue) models, each having four conformation types [ $\beta$ -extended:  $\varphi/\psi=t-/t+$ ,  $\alpha$ -helix:  $g-/g-$ , PP<sub>II</sub>:  $g-/t+$  and P-like:  $g-/g+$ , see Figure 1] were compared with various structure types by the QCC methodology, and the optimized structure and formation energy were examined for each designated structure.

#### 3.1 Optimized structure and energy

Table 1. lists the results optimized for L-proline pentamer (LP). The models designated with  $\beta$  were transformed into PP<sub>II</sub> structure independently of the designated  $\psi$  values of 140, 164 and 175°. All PP<sub>II</sub> conformers were equivalent. Figure 2 depicts the designated  $\beta$  (1) and optimized PP<sub>II</sub> (2) structures of LP. The model designated with  $\alpha$  was not obtained because of the “unusual closeness of atoms” caused by the

pyrrolidine ring. The model designated with P-like was optimized into P-like. The models designated with PP<sub>II</sub>



**Figure 2. Designated  $\beta$  (1) and optimized PP<sub>II</sub> (2) structures of L-proline pentamer (LP).**

The D1 and D2 in the figures show the distances (Å) between O and N [D(O-N)], D1 and D2 are the distances between those in the same units and the units with one separated units, respectively. - - -: hydrogen bond.

were optimized into the same PP<sub>II</sub> structure independently of the designated  $\psi$  values of 140, 160 and 175°, and the optimized PP<sub>II</sub> was the same as PP<sub>II</sub> obtained from  $\beta$ . LP has no NH group leading to no H-bond except for H-bond between NH group in C-end, which made d2(4-6) type H-bond. The hydrogen bond distances (1.94 - 2.00 Å) of d2(4-6) type H-bonds were almost same as those in P-like and  $\beta$ 2 conformers of L-alanine Pentamer [13]. Formation energy of PP<sub>II</sub> conformer was smaller than that of P-like conformer by about 2.2 kcal/mol/mu, as shown by  $\Delta E_{PP_{II}}$  in Table 1, indicating that PP<sub>II</sub> was the main conformation of LP.

### 3.2 Optimization process

The conformations of LP designated with  $\beta$  were transferred into PP<sub>II</sub>. Therefore, in order to understand the processes of such conformational transformations, the optimization processes were examined in detail. Figures 3, 4 and 5 depict the results of the processes of optimizations for the designated  $\psi$  values of 140, 160 and 175°, respectively. In each figure, (1) shows the changes of averaged dihedral angles [ $\varphi_n$  and  $\psi_n$ ,  $n=1-5$ , °] and formation energies ( $\Delta E$ , kcal/mol/mu, based on E value of the converged conformer). D1 [D1(O-N)] and D2 [D2(O-N)] in (2) of each figure are the un-bonded distances between O and N atom (O...N) in the same units

and the units with one separated units, respectively [see (1) of Figure 2]. As shown in each figure, the effects of designated  $\psi$  values on the changes of structural parameters were almost nil, and each conformer was converged to the same PP<sub>II</sub> structures. As shown (1) of each figure, the averaged  $\psi$  values increased at early states, and  $\beta$  was transformed into PP<sub>II</sub> at 15 to 17 cycles. As shown (2) of each figure, D2 values decreased with increases of  $\psi$  values. The d2(4-6) values in C-ends decreased at early states, and after 40 cycles, PP<sub>II</sub> conformers had the d2(4-6) type H-bond (1.94 - 1.95 Å).

As shown in (1) of each figure, the effects of designated  $\psi$  values on the formation energies ( $\Delta E$ ) of conformers in transformation points were almost nil. The energies ( $\Delta E_1$ ) of  $\beta$  structures designated with  $\psi$  of 160 and 175°, which were calculated based on E of  $\beta$  structure designated with  $\psi$  of 140°, were 0.54 and 0.58 kcal/mol/mu, respectively, as also shown in the foot-notes of each figure, and the stabilities of  $\beta$  structures designated for LP were almost independent of designated  $\psi$  values.

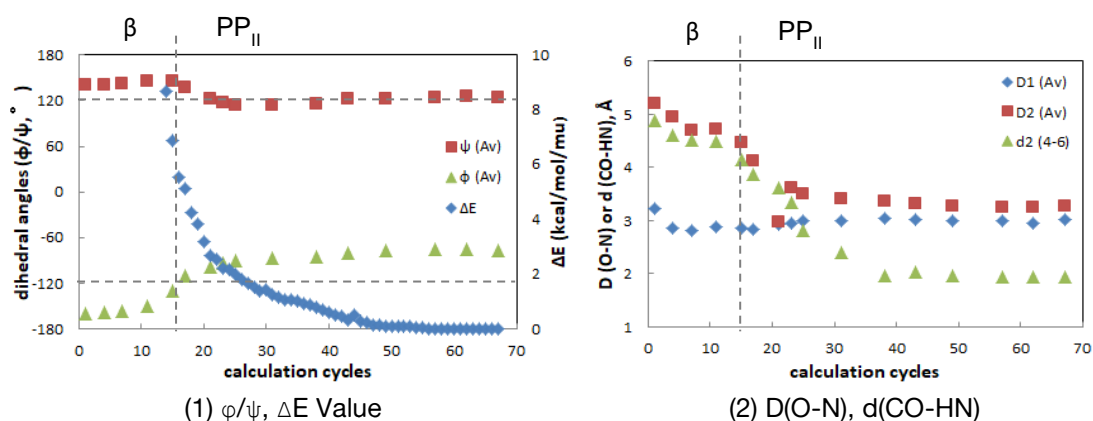


Figure 3. Structure optimization process of LP designated with  $\beta$  ( $\phi/\psi = -160^\circ/140^\circ$ ).

The designated structure was transformed into PP<sub>II</sub> ( $\phi/\psi = -76^\circ/124^\circ$ ). (1)  $\phi/\psi$  (Av) and  $\Delta E$  values. Initial energy at the 1st calculation cycle ( $E_1$ ) was -1870.9655 (HF). (2) distances (Av) between O and N [D(O-N)], D1 and D2 are the distances between those in the same units and the units one separated units, respectively.

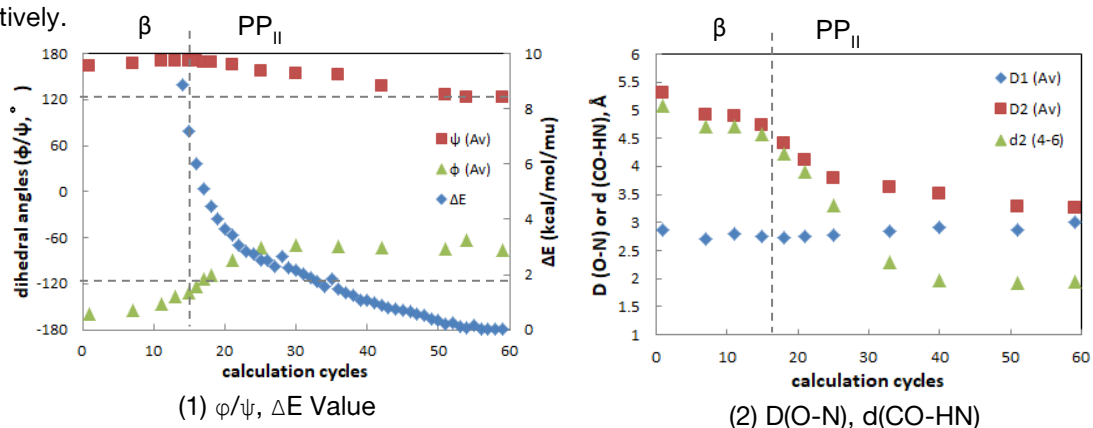
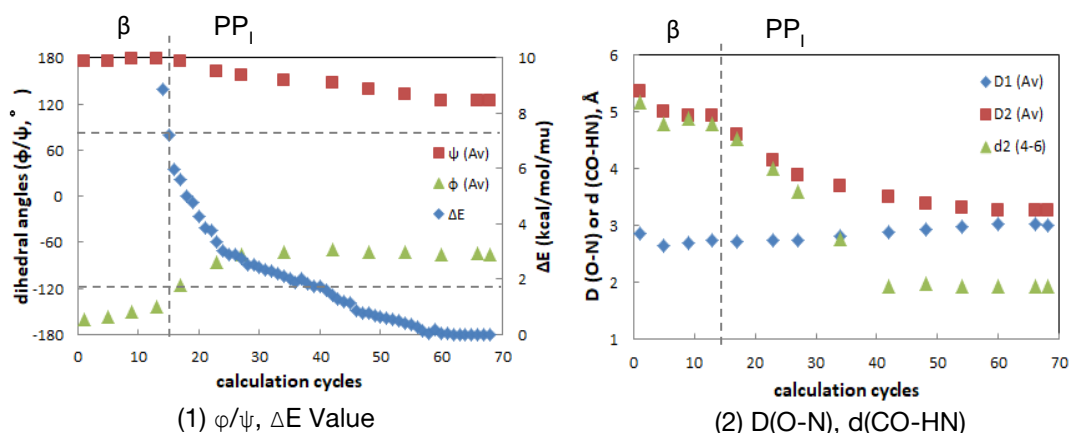


Figure 4. Structure optimization process of LP designated with  $\beta$  ( $\phi/\psi = -160^\circ/164^\circ$ ).

The designated structure was transformed into PP<sub>II</sub> type ( $\phi/\psi = -76^\circ/124^\circ$ ). (1)  $\phi/\psi$  (Av) and  $\Delta E$  values. Initial energy at the 1st calculation cycle ( $E_1$ ) was -1870.9612 (HF), and  $\Delta E_1 = 0.54$  kcal/mol/mu based in the case of  $\phi/\psi = -160^\circ/140^\circ$ . (2) distances (Av) between O and N [D(O-N)], D1 and D2 are the distances between those in the same units and the units with one separated units, respectively.



**Figure 5. Structure optimization process of LP designated with  $\beta$  ( $\phi/\psi = -160^\circ/175^\circ$ ).**

The designated structure was transformed into  $PP_{II}$  type ( $\phi/\psi = -76^\circ/124^\circ$ ). (1)  $\phi/\psi$  (Av) and  $\Delta E$  values. Initial energy at the 1st calculation cycle ( $E_1$ ) was -1870.9609 (HF), and  $\Delta E_1 = 0.58$  kcal/mol/mu based in the case of  $\phi/\psi = -160^\circ/140^\circ$ . (2) distances (Av) between O and N [D(O-N)], D1 and D2 are the distances between those in the same units and the units with one separated units, respectively.

#### 4. CONCLUSION

The comparison between the conformations of oligopeptides having imino acid residues was studied by QCC. In L-proline pentamers (LP) having no H-bond in the main chain, the conformer  $PP_{II}$  was the most stable. Furthermore, the  $\beta$  designated was transformed into  $PP_{II}$  independently of those. The optimization result of each conformer, designated average  $\psi$  values increased at early states, and  $\beta$  was transformed into  $PP_{II}$  at 15 to 17 cycles. D2 values decreased with increases of  $\psi$  values. The d2(4-6) values in C-ends decreased at early states, and after 40 cycles,  $PP_{II}$  conformers had the d2(4-6) type H-bond (1.94 - 1.95  $\text{\AA}$ ).

It was found that the effects of imino acid residues on the conformational transformations were attributed to the presence or absence of amino proton in the amino acid residue, and the conformational transformation of oligopeptide having amino acid residue was strongly affected by the intra-molecular hydrogen bonding between the main chain and the C-end having NH group, simultaneously by intra-molecular hydrogen bonding between the main chain.

#### ACKNOWLEDGEMENT

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