Ab Initio Computational Study of Reaction Mechanism of Peptide Bond Formation on HF/6-31G(d,p) Level

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Abstract. Peptide plays an important role in modulation of various cell functions. Therefore, formation reaction of the peptide is important for chemical reactions. One way to probe the reaction of peptide synthesis is a computational method. The purpose of this research is to determine the reaction mechanism for peptide bond formation on Ac-PV-NH_2 and Ac-VP-NH_2 synthesis from amino acid proline and valine by ab initio computational approach. The calculations were carried out by theory and basis set HF/6-31G(d,p) for four mechanisms (path 1 to 4) that proposed in this research. The results show that the highest of the rate determining step between reactant and transition state (TS) for path 1, 2, 3, and 4 are 163.06 kJ.mol^{-1}, 1868 kJ.mol^{-1}, 5685 kJ.mol^{-1}, and 1837 kJ.mol^{-1}. The calculation shows that the most preferred reaction of Ac-PV-NH_2 and Ac-VP-NH_2 synthesis from amino acid proline and valine are on the path 1 (initiated with the termination of H^+ in proline amino acid) that produce Ac-PV-NH_2.

1. Introduction

The application of peptide as a drug to treat brain diseases is hampered by the difficulty in the delivery system of peptide past the Blood-Brain Barrier (BBB). [1,2] In general, there is only one way that can be passed by peptide molecules that is a paracellular pathway. However, this pathway is blocked by a tight junction which is the result of cadherin-cadherin interactions between cells. One way to open this pathway is to modulate cadherin protein by their peptide derivatives synthesis. Peptide syntheses that is used to modulate these interactions are ADT (Ac-QGADTPPVGV-NH2) and HAV (Ac-LFSHAVSSNG-NH2) which are derived from the bulge and groove region on EC1 domains. [3,4] The sequence of amino acids in the peptide domain EC1 or ADT contained amino acids proline (P) and valine (V) with proline-valine (Ac-PV-NH2) sequence are tend to be formed, while the sequence valine-proline (Ac-VP-NH2) is not formed. Based on this fact, there is a preferred reaction mechanism in peptide synthesis from proline and valine amino acid. So it is important to learn that mechanisms on the thermodynamics and kinetics aspect. The reaction of proline and valine peptide synthesis is a reaction between two active groups on the amino acids, the amine group, and the carboxyl group. [5-10] Therefore there are several possible products that can be formed, that are Ac-PV-NH2and Ac-VP-NH2. Each product will be through different mechanism reactions. In this research, there are four

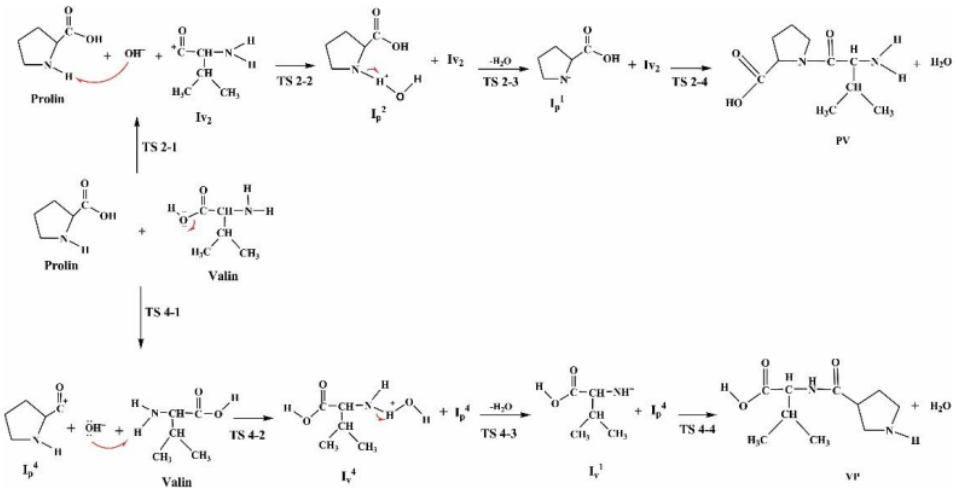
reaction mechanisms (path 1 to 4) which allow for the synthesis of peptides from proline and valine amino acid (Scheme 1).

One method that can be used to study the reaction mechanism of peptide synthesis is ab initio computational methods. [11-18] Computational method has a high level of accuracy. In the present study, we used the level of theory and basis set HF / 6-31G (d, p) to calculate the molecular energy of the reactants, products, intermediates and transition state (TS). Data of energies that obtained were used to determining the reaction mechanism are preferred.

2. Computational Method

This research is done using ab initio method on HF/SCF string theory and 6-31G(d,p) basis set. Calculating software that used are Gaussian03 (Linux operating system) Meanwhile, Gauss view05, Chemcraft, Avogadro, and Jmol are used as visualization software. File input construction are done using notepad++.

The calculation is done on each single and transition state molecules. The directive on determining transition state is QST3 and the command of "freq" is used to obtain the vibration frequencies from each pertinent molecules. [19-23]



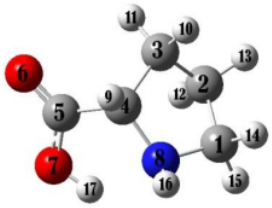
Scheme 1. Mechanism reaction of Ac-PV-NH_2 and Ac-VP-NH_2 peptide in various pathway

3. Result And Discussion

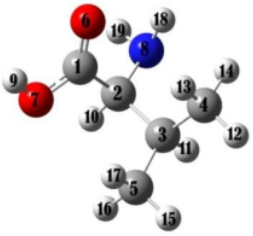
Path 1 and 3 is a reaction pathway that begins with the termination of hydrogen bonds in the amine group. The difference between them are situated on compounds that initiate the reaction, and then resulting product is different. Termination of hydrogen bonds on path 1 generate an intermediate I_p^1 with the enthalpy is 414 kcal.mol^{-1}, while the enthalpy formation of the molecular path 3 generates the intermediate I_v^3 at 416 kcal.mol^{-1}. The thermodynamic data shows that the intermediate I_p^1 is more easily formed than I_v^3. The stability of the molecule is evidenced by the distribution of the charge on each constituent atom of the compound.[5,6]

Termination of hydrogen bonding to the amine group can be shown by changes in some parameters of the molecular structure that involved in this reaction stage (figure 1). The most significant changes can be seen in the bond length in the reaction area (N-H). The N-H bond length on the proline molecule is 0.997 Å while in the transition state structure (TS 1-1) was obtained 4.101 Å. Similarity

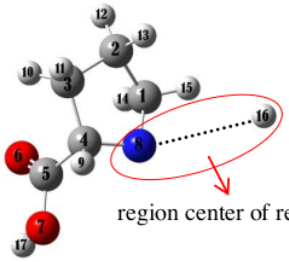
occurs on molecule valine which the N-H bond from 1 Å to 1.009 Å on its transition state. This condition strengthened by the imaginary vibrational frequencies on the center reaction area (υ=-40.88 cm^{-1}). The molecular structure of TS 3-1 also indicates the imaginary vibrational frequency in the central area of the reaction(υ=-191.41cm^{-1}).



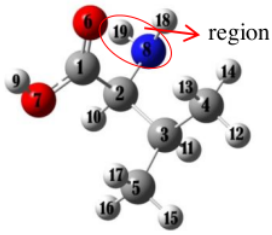
a) Proline
r(N8-H16) 0.997 Å α(C1-N8-H16) 113°
r(C5-O7) 1.317 Å α(C4-C5-O7) 115°
r(C5-O6) 1.185 Å



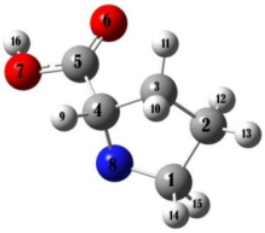
a) Valine
r(N8-H19) 1 Å r(C1-O7) 1.328 Å
r(N8-H18) 1 Å α(C2-N8-H19) 110°
r(C1-O6) 1.189 Å α(C2-C1-O7) 113°



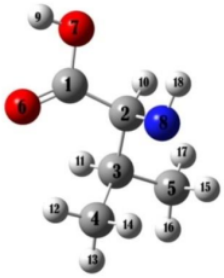
b) TS 1-1
r(N8-H16) 4.101 Å α(C1-N8-H16) 98°



c) TS 3-1
r(N8-H19) 1.009 Å α(C2-N8-H19) 122°



e) I_p^1
r(C1-N8) 1.426 Å α(C1-N8-C4) 106°
r(N8-C4) 1.441 Å α(N8-C4-C5) 104°



f) I_v^3
r(C2-N8) 1.428 Å α(C1-C2-N8) 109°
r(N8-H18) 1.011 Å τ(C1-C2-N8-H18) -75°

Figure 1. Calculated structures of pertinent stationary points along the first step

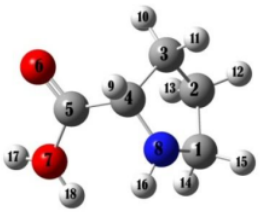
In the insertion reaction of H^+ on the path 1 produces intermediate I_v^1, while on the path 3 produces I_p^3. The calculations show the energy of I_v^1 is -1.05×10^6 kJ.mol^{-1} and the enthalpy is -174.9 kcal.mol^{-1}. It also refers to the energy of I_p^3 that is -1.05×10^6 kJ.mol^{-1} with the enthalpy is -150.7 kcal.mol^{-1}. The

value of negative enthalpy indicates an exothermic reaction, which is the energy to be used to break the ties.

Both of this intermediates contain H_2O group which is a good leaving group, so this reaction step tended to release the H_2O group. It is proved that the intermediates have high reactivity. This second reaction step also involves the large activation energy (Ea). The activation energy that has passed by valine to become I_v^1 is 398.83 kJ.mol^{-1} and the Ea of proline to become I_p^3 is 397.74 kJ.mol^{-1}. The transition state in the second reaction step (TS 1-2) was found an imaginary vibrational frequency on the center reaction area, υ = -1096.69 cm^{-1}. It also occurs on proline, the reaction between H^+ ions with carboxylate groups on valine shows the imaginary vibration frequencies, υ = -246.89cm^{-1}).

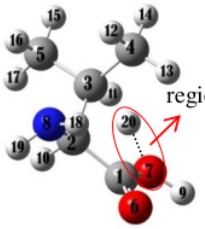
a) I_v^1

r(C1-O7) 1.489 Å α(O6-C1-O7) 112°
r(O7-H9) 0.960 Å α(H9-O7-H20) 115°



b) I_p^3

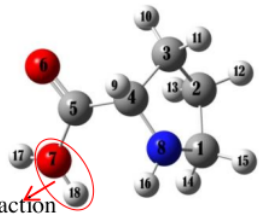
r(C5-O7) 1.489 Å r(O7-H18) 0.960 Å
α(O6-C5-O7) 113° α(H17-O7-H18) 115°



region center of the reaction

c) TS 1-2

r(O7-H20)1.376 Å α(H20-O7-H9) 139°
r(C1-O6) 1.165 Å α(O6-C1-O7) 123°



region center of the reaction

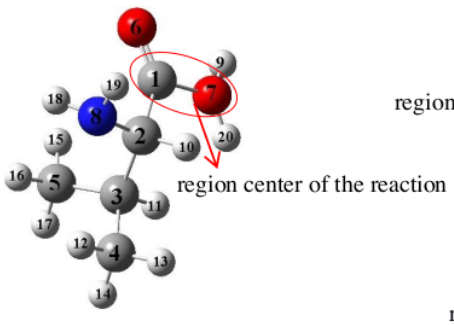
d) TS 3-2

r(O7-H18) 3.060 Å α(H17-O7-H18) 106°
r(C5-O6) 1.099 Å α(O6-C5-7) 98°

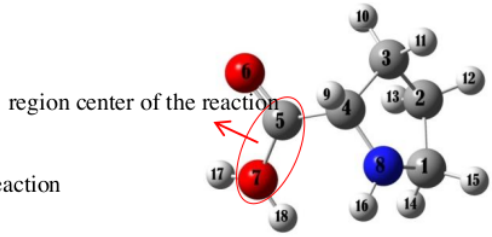
Figure 2. Calculated structures of pertinent stationary points along the second step

Furthermore, in the reaction step of releasing H_2O produces intermediates that are I_v^2 in the path 1, while on the path 3 produces I_p^4. The enthalpy of I_v^1 to become I_v^2 is 47,730 kcal.mol^{-1}, while the enthalpy of I_p^3 to become I_p^4 is 47,690 kcal.mol^{-1}. The high enthalpy value in intermediates is caused the molecular energy of this intermediates are high. It indicated that the intermediates are unstable which the molecular energy of I_v^2 and I_p^4 are -851,000 kJ.mol^{-1} and -848,000 kJ.mol^{-1}. The activation energy which is traversed by this reaction steps higher than the previous reaction step.

In the process of bond termination conduces change of some parameters of intermediates structure with each transition state (figure 3). The bond length of C-O in the transition state structure of I_p^3 to become I_p^4 (TS 3-3) is 2.07 Å, while the transition state structure of I_v^1 to become I_v^2 (TS1-3) not be found. The transition state structure of I_p^3 to become I_p^4 has an imaginary frequency that characterized by the value of wavenumber (υ=-85.941 cm^{-1}).

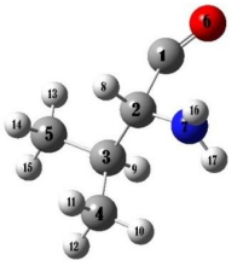


a) TS 1-3



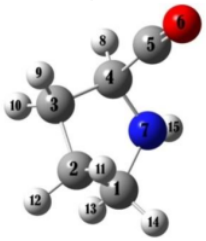
b) TS 3-3

r(C5-O7) 2.076 Å α(C4-O5-O7) 93°
r(C5-O6) 1.121 Å α(O6-C5-O7) 104°



c) I_v^2

r(C1-O6) 1.2 Å α(C2-C1-O6) 140°
r(C2-C1) 1.616 Å τ(C3-C2-C1-O6) -143°

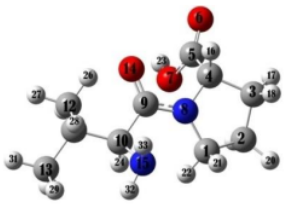


b) I_p^4

r(C5-O6) 1,2 Å α(C4-C5-O6) 174°
r(C4-C5) 1,611 Å τ(C3-C4-C5-O6) 68°

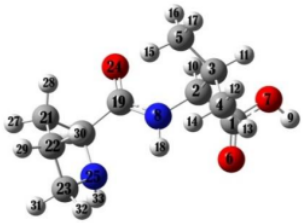
Figure 3. Calculated structures of pertinent stationary points along the third step

On the last step, peptides are formed by an establishment of C-N bond from intermediates I_v^2 with I_p^1 in the path 1 and I_p^4 with I_v^3 in the path 3. The product that produces from path 1 is Ac-PV-NH2, while on path 3 produce Ac-VP-NH2. The enthalpy of Ac-PV-NH2 formation on the path 1 is -257.58 kcal.mol^{-1}, while the enthalpy of Ac-VP-NH2 formation on path 3 is -253.50 kcal.mol-1. In the reaction of peptide formation is found an imaginary vibrational frequency that can be seen by the value of the wave number. The imaginary vibration frequency in the Ac-PV-NH2 formation is -211.997cm^{-1}, while in the Ac-VP-NH2 is -6.18 cm^{-1}.



a) Ac-PV-NH_2

r(C9-N8) 1,352 Å α(N8-C9-C10) 118°



b) Ac-VP-NH_2

r(C19-N8) 1.345 Å α(N8-C19-O24)124°

Figure 4. Calculated structure of stationary points

Overall, the reaction on path 1 needed an enthalpy 47,708 kcal.mol^{-1}. It is indicated endothermic reaction occurs. In the path 3 the entirety of enthalpy is 47,702 kcal.mol^{-1}. It also indicated that the reaction in path 3 is an endothermic reaction. However, the enthalpy that is traversed by the path 1 is lower than path 3. The lowest of activation energy in path 1 are on step 3. Similarly, it is obtained at step 3 in the path 3. According to the Arrhenius equation, $k = Ae^{-E_a/RT}$, getting smaller of activation energy will generate the greater of the rate constant, which v=k[A][B] so the rate become faster, according to esterification reaction [5,6].

Based on the computational calculation, the value of each step on the path 1 and 3 (Figure 5) shows that the path 1 is a reaction pathway that is more likely than the path 3 because on the third step in path 3 obtained elevated activation energy (Ea) that is 5,685 kJ.mol^{-1}. Therefore, by following the reaction in path 1, the products tend to be stable and easier to obtain Ac-PV-NH2.

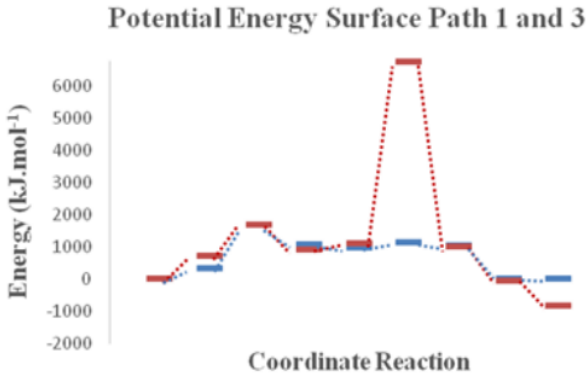


Figure 5. Calculated reaction path 1 and 3

In the path 2 and 4 is begins with the termination C-O bonds in the carboxylic group. Dissolution of C-O bond in path 2 produce intermediate I_p^2 with the enthalpy is 47,550 kcal.mol^{-1}, while in the path 4 produce intermediate I_p^4 with the enthalpy is 47,540 kcal.mol^{-1}. Based on the enthalpy that is obtained in this reaction, it requires large energy to break the C-O bond. The termination reaction can be verified through the vibrational transition state structure (figure 6) which have negative value. The transition state structure of step 1 in the path 2 (TS 2-1) was given the frequency -87.055 cm^{-1}, while in the path 4 (TS 4-1) was given frequency -40.677 cm^{-1}.

The next step is an insertion of OH^-, which in the path 2 occurs in proline molecule while in the path 4 it occurs on valine. Insertion of OH^- in path 2 produce intermediate I_p^2 with the enthalpy is -46,995 kcal.mol^{-1}, while in the path 4 produce intermediate I_v^4 with the enthalpy -47,003 kcal.mol^{-1}. The energy value is proved by the high reactivity of this intermediates due to the presence of H_2O as a good leaving group. Furthermore, the transition state structure could be proven through imaginary vibrational frequency. The imaginary frequency of transition state structure in path 2 is -2,183.96 cm^{-1}, whereas in the path 4 is-2,241.371cm^{-1}.

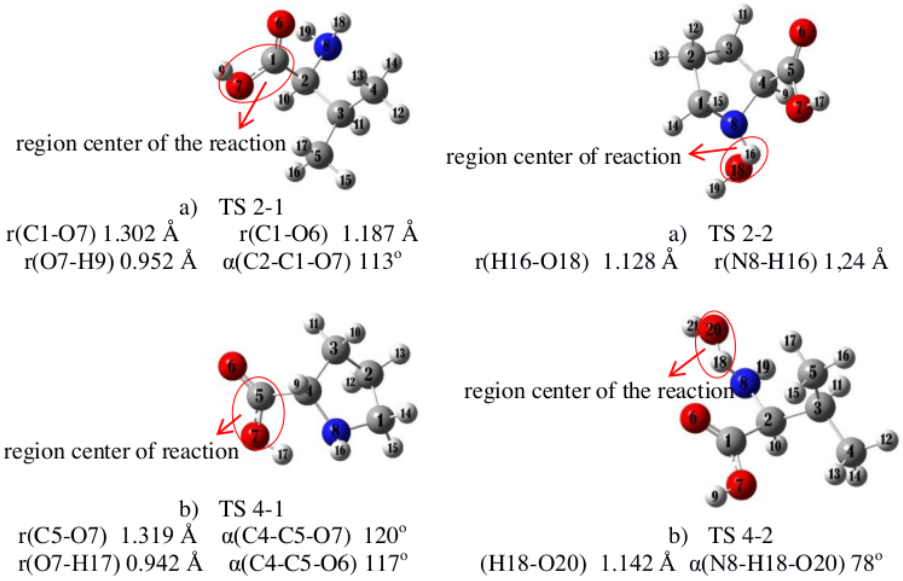


Figure 6. Calculated structures of transition in first and second step

On the next step, the termination of N-H bond in intermediates I_p^2 and I_v^4 occur and H_2O molecules are released. In the second step on path 2, the results obtained enthalpy 47,400 kcal.mol^{-1}, while on the path 4 give an enthalpy 548,000 kcal.mol^{-1}.

The transition state structure in this reaction step can be proved by the molecular vibration, which is the transition state of I_p^2 to become I_p^1 (TS 2-3) was obtained the imaginary frequency that is -1420,437 cm^{-1}, while the transition state of I_v^4 to become I_v^3 is not found because the reaction run rapidly.

The last step of this reaction pathway much the same with the reaction in path 1 and 3, which is a product formation. The product that produces from path 2 is Ac-PV-NH2 and on path 4 is Ac-VP-NH2. Based on computational calculations, the mechanism more likely is through the reaction path 4 with the Ac-VP-NH2 product. However, between path 1 and 4 the mechanism is preferred to the path 1 because the lower activation energy (Ea) that be passed in this reaction.

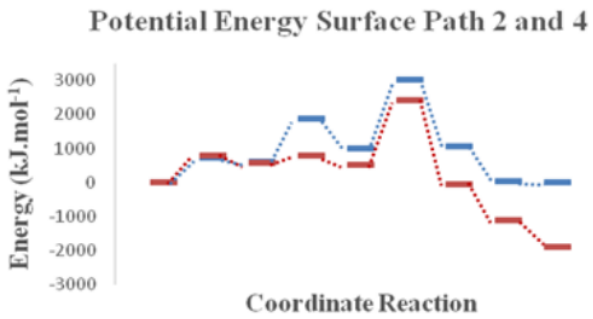


Figure 8. Calculated reaction path 2 and 4.

4. Conclusion

Peptide formation reaction from proline and valine amino acid can produce Ac-PV-NH2 and follow the reaction path 1. It is also can produceAc-VP-NH2with the reaction that occurred is on path 4. However, followed by the activation energy, the reaction on path 1 have a faster reaction rate so it is enabled to prefer label more to pass by the reaction of peptide bond forming. The rate determining step on path 1 is obtained in step 3 which H_2O molecules are released from valine with the activation energy is163,06 $kJ.mol^{-1}$.

5. References

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