Electronic properties study of reaction mechanism of C-N bonding formation in Ac-DT-NH₂ and Ac-TD-NH₂ peptide by ab initio computational on HF/6-31g** level

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Abstract. The peptide has many functions, which one of the function is delivering the drug to overcome some diseases in the brain. However, drug delivery to the brain is hindered by the paracellular pathway of Blood Brain Barrier (BBB). This pathway has a tight junction or a tight intersection which is the result of naturally intercellular cadherin-cell interactions. One approach to increase delivering of drug to the brain is by increasing the porosity of the paracellular pathway of tight junction which was already done by modulating the intercellular cadherin-cell interactions using the synthesized ADTC-1 (Ac-ADTPVC-NH₂) peptide which derived from natural cadherin. One the sequence of two amino acids in ADTC-1 peptide is Ac-DT-NH₂ between aspartate (D) and threonine (T) amino acids which is similar within natural cadherin and is not Ac-TD-NH₂. So that, the purpose of this research is to prove and determine the most preferred reaction mechanism between Ac-DT-NH₂ and Ac-TD-NH₂ peptide which occurred in natural cadherin. In this study, the computational approach on the level of theory and basis set HF/SCF 6-31g** was used to calculate the electronic properties of all molecules involved in Ac-DT-NH₂ and Ac-TD-NH₂ peptide synthesis to prove and determine the most preferred reaction mechanism. The results show that the I reaction mechanism which produced Ac-DT-NH₂ peptide formed with the activation energy Ea was 1329.23 kJmol⁻¹. While the IV reaction mechanism which produced Ac-TD-NH₂ peptide had Ea 2470.19 kJmol⁻¹. The study concluded that the I reaction mechanism produced Ac-DT-NH₂ which is similar within natural cadherin synthesis was proved more easily and preferred than the IV reaction mechanism. Both the I and IV reaction mechanisms were exothermic with ΔH reaction enthalpy -6.075 kJmol⁻¹ and -6.092 kJmol⁻¹ respectively.

Keyword: Ab initio, Aspartate, Threonine, Reaction mechanism, Synthesis peptide.

1. Introduction

Modelling of the reaction mechanism is very important in chemistry and biochemistry [1] which can be done with three methods of force field method, a combination of the force field, and quantitative mechanics and ab initio method. The most preferred method for modeling chemical reactions is the ab initio method. The ab initio method can be used to investigate the reaction mechanisms such as the SN₂ reaction. The study of the one the simple SN₂ reaction mechanism between Cl⁻ anion and methyl chloride in the gas phase, DMF solvent and water solvent show the different pattern of the potential curve of the
average force or change in free energy as a function of similar reaction coordinates. The difference is the activation energy of Cl...CH₃...Cl in the gas phase is smaller and there is a minimum energy for the ion-dipole complex of Cl...CH₃Cl. Activation energy in the solution phase is greater because there is solvation energy [2-4]. The study of S₅² reactions between Cl anion with methyl chloride in the gas phase can be applied and plays an important role in the synthesis of peptides [5, 6]. The synthesized peptides have many functions such as a drug and for modulating Blood Brain Barrier (BBB) cell functions. The development of peptides as a drug of diseases in brain is hampered due to the difficulty of delivering drugs to the target site [7]. The problem of delivering needs synthetic peptide as a modulating intercellular cadherin-cell interactions. The strategy of in vitro peptide synthesis was done by blocking of one the reactive groups in amino acids [8]. Previous study has synthesized ADTC-1 (Ac-ADTPV vinyl group) peptide which is a derivative of ADT6 or natural cadherin peptide. The ADT6 peptide was synthesized from the bulge area sequence of the EC1 domain [9]. Experimentally in vitro was able to increase the porosity of the paracellular pathway of tight junction by modulating intercellular cadherin-cell interactions using the synthesized ADTC-1 (Ac-ADTPV vinyl group) peptide which derived from natural cadherin. One the sequence of two amino acids between aspartate (D) and threonine (T) in ADTC-1 peptide is Ac-DT-NH₂ which is similar within natural cadherin and is not Ac-TD-NH₂. So that, the purpose of this research is to prove and determine the most preferred reaction mechanism between Ac-DT-NH₂ and Ac-TD-NH₂ peptide. In the previous study had been proved that the reaction mechanism of another sequence of two amino acids between proline (P) and valine (V) in ADTC-1 (Ac-ADTPV vinyl group) peptide is Ac-PV-NH₂ which is similar within natural cadherin synthesis and is not Ac-VP-NH₂.

Hipoetically the reaction mechanism of peptide synthesis from amino acids aspartate (D) and threonine (T) can produce two possible products namely the Ac-DT-NH₂ or Ac-TD-NH₂ peptides. In this study was selected four the reaction mechanism of peptide synthesis produces different products through the reaction pathways of I, II, III, and IV. Each of that reaction mechanism will form a transition state (TS) which is the most important step in reaction mechanisms and is difficult be obtained experimentally. However, this TS species which has the definite electronic properties can be used as a reference to determine the most likely reaction mechanism. The computational ab initio method is able to determine TS and to study the reaction mechanism [10-15]. The computational studies confirmed the electronic properties of all species reactants, products, intermediates, and TS involved in the reaction of peptide synthesis from the amino acids D and T as a component of the potential energy surfaces (PES) [16-18]. The different of electronic energy and other properties of all molecule species on PES calculated on the theory level and basis set HF/SCF 6-31g** used to prove and determine the preferred reaction mechanism. The basis set used is adjusted to the character of the molecule and the atoms that make up, where the higher the basis set, the greater the level of accuracy so that it can be used to calculate the energy of large molecules or complexes [19, 20].

2. Computational Methods
In this study all molecules were optimized by using ab initio method on theory level HF/SCF and basis set 6-31g**. All molecular calculations were performed with linux based NWCHEM software, Chemcraft software used for molecular visualization. The input file was created by using notepad++ software.

The calculations of all stable structure species at a stationary point of PES, as well as the minimum energy, were determined by the “task scf opt” command, while the TS structure species were determined by “task scf saddle” command. The frequencies of harmonic vibration were calculated by the “task scf freq” command to determine the correction of zero-point vibration energy (ZPVE) of all molecule species. Frequency was also used to determine the TS structure by ensuring that there was only one imaginary frequency, whereas the molecule at the stationary point has no imaginary frequency [21-25].

In this study, the proposed reaction mechanism of peptide synthesis from amino acids aspartate (D) and threonine (T) that produce two possible products namely the Ac-DT-NH₂ or Ac-TD-NH₂ peptides was selected four the reaction mechanism through the reaction pathways of I, II, III, and IV, scheme 1.
and scheme 2. Those proposed reaction mechanisms begin with the breaking of N-H bond of \(-\text{NH}_2\) functional group and C-OH bond of \(-\text{C}(=\text{O})\text{-OH}\) functional group all without involving catalyst that unusual in organic reaction.

**Scheme 1.** The I and III reaction mechanisms of synthesis Ac-DT-NH$_2$ and Ac-TD-NH$_2$ peptide.
Scheme 2. The II and IV reaction mechanism of synthesis Ac-DT-NH₂ and Ac-TD-NH₂ peptide.

3. Results and Discussion

3.1. Path I and III Reaction Mechanisms

The I reaction mechanisms begin with the dissociation of N-H bond in the –NH₂ group of the aspartate reactants, whereas the III reaction mechanism with the breaking of N-H in the –NH₂ group of the threonine. The product of the I and III reaction mechanism are Ac-DT-NH₂ and Ac-TD-NH₂ peptides, respectively, scheme 1.

The dissociation of N-H bond as a region center of reaction in the I reaction mechanism formed the first intermediate of aspartate, I₁D. The I₁D species formed through the first transition state, TS I-1, namely species which undergo the weakening of the N-H bond in the –NH₂ group of the aspartate. The weakening of the N-H bond is indicated by the increasing of the length of the N(5)-H(16) bond, which is initially 1.007 Å, Fig. 1a, to 1.517 Å, Fig. 1c, and the change of the H(16) atom partial charge of N-H becomes greater than +0.3 to +0.49. It can be seen that the N atom that binds the H atom at TS I-1 is negatively charged, that is -0.8, but in I₁D the charge of N atom is smaller which is -0.89, and so that I₁D
is formed. The structures of TS I-1 and I_D^1 are shown in Fig. 1. The optimized energy of TS I-1 is -133.69x10^4 kJmol^-1 which is strengthened by the presence of an imaginary vibration frequency is -1863.21 cm^-1, Fig. 1c, while the energy of I_D^1 is -133.58x10^4 kJmol^-1. From this result the I_D^1 species has an energy higher as much as 1100 kJmol^-1 than the TS I-1, indicating that the I_D^1 the molecule is unstable than TS I-1. This is because the N atom is more electronegative than the H atom so the N-H bond weakened.

![Figure 1. The optimized structure all species in the first step of I and III reaction mechanism. Color key: purple=carbon, orange=nitrogen, red=oxygen, blue=hydrogen](image)

The III reaction mechanism begins with the formation of a intermediate threonine, I_T^3. Before forming I_T^3 must go through the first transition state (TS III-1) by weakening the N-H bond on the threonine molecule. The weakening of the bond is indicated by increasing the length of the N-H bond which is initially 1.003 Å, Fig. 1b, to 1.731 Å, Fig. 1d, and the H atom charge becomes greater than 0.29 to 0.39. It can be seen that the N atom that binds H atoms on TS III-1 is negatively charged, that is -0.92, but in the I_T^3 atom N charge is smaller which is -0.96, and so that I_T^3 is formed. The optimized energy of TS III-1 is -114.36x10^4 kJmol^-1 which is strengthened by the presence of an imaginary vibration frequency of -245.87 cm^-1, Fig. 1d, while the energy of I_T^3 is -114.24x10^4 kJ.mol^-1. From these results the I_T^3
molecule has an energy higher as much as 1200 kJmol\(^{-1}\) than the TS I-1 molecule, indicating that the I\(T_1\) molecule is in unstable form than TS I-1.

The second step is the association between H\(^+\) ion and -O-H of carboxylic group of threonine and aspartate produced TS I-2 and then form I\(T_1\) in I reaction mechanism and TS III-2 and then form I\(D_3\) in mechanism III. The O(8)-H(18) bond distance of TS I-2 in I reaction mechanism is 1.547 Å, Fig. 2a, while in III reaction mechanism the O(3)-H(17) bond distance of TS III-2 is 1.466 Å, Fig. 2b. The optimized energy of TS I-2 is -247.97x10\(^4\) kJmol\(^{-1}\) with an imaginary vibration frequency of -1906.85 cm\(^{-1}\), while the optimized energy of TS III-2 is -247.95x10\(^4\) kJmol\(^{-1}\) with an imaginary vibration frequency of -847.49 cm\(^{-1}\). The O(3)-H(17) bond distance of TS III-2 is closer then O(8)-H(18) bond distance of TS I-2 and then form I\(D_3\) with O(8)-H(18) bond distance is 0.972 Å, Fig. 2c, while the I\(T_1\) with O(3)-H(17) bond distance is 0.948 Å, Fig. 2d. The optimized energy of I\(T_1\) and I\(D_3\) are -247.93x10\(^4\) kJmol\(^{-1}\) and -247.99x10\(^4\) kJmol\(^{-1}\). The energy difference of two species is 600 kJmol\(^{-1}\).
The third step is the process of releasing H₂O molecule from the carboxylic group of I₃ produced I₄ in I reaction mechanism, and from the carboxylic group of I₅ produced I₆ in III reaction mechanism. At third step, the transition state is more difficult to find. The release of H₂O groups specifically is the breakdown of C(5)-O(8)H₂ bond of carboxylic group of the I₃ in the I reaction mechanism, Fig. 3a, and I₅ in III reaction mechanism, Fig. 3b. The dissociation of the C(5)-O(8)H₂ shows that a more electronegative O(8) atom will draw electrons of C(5) atom so that the C(5) of carboxylic group of the intermediate I₃ and I₅ become more electropositive. In I reaction mechanism, the C(5)-O(8)H₂ bond length change from 1.364 Å to 2.456 Å and the partial charge of O(8) becomes more electronegative, -0.72. In III reaction mechanism, the C(2)-O(3)H₂ bond length change from 1.561 Å to 2.529 Å and the O(3) atom becomes more electronegative, which is -0.65. The TS I-3 and TS III-3 is known by the appearance of an imaginary vibration frequency in the area of the reaction center which are -370.42 cm⁻¹ and -370.28 cm⁻¹, respectively.

In the last or forth step of I and III reaction mechanism produce products Ac-DT-NH₂ peptide Ac-TD-NH₂ peptide, respectively. The formation of these two products at the fourth reaction stage involves two unstable intermediates. In the I reaction mechanism, the intermediate I₃ reacts with I₅, which have optimized energy are -94.47x10⁴ kJmol⁻¹ and -133.55x10⁴ kJmol⁻¹ and obtained the product Ac-DT-NH₂ peptide which has the optimized energy is -228.15x10⁴ kJmol⁻¹. In III reaction mechanism the intermediate I₅ reacts with I₆ which have optimized energy are -114.21x10⁴ kJmol⁻¹ and -113.82x10⁴ kJmol⁻¹ produce Ac-DT-NH₂ peptide with energy is -228.15x10⁴ kJmol⁻¹. In the I reaction mechanism the peptide formation reaction occurs between C'(5) carbocation of carboxylic group in I₃, Fig. 3c, and N'(5) nucleophile of amine group in I₅, Fig. 1e, to form C(16)-N(5) peptide bond in Ac-DT-NH₂, Fig. 4a. The C(16)-N(5) bond length in the Ac-DT-NH₂ peptide is 1.3649 Å with the partial charge of C(16) is +0.77 and N(5) is -0.73. In the III reaction mechanism the reaction occurs between C'(7) carbocation of carboxylic group in I₅, Fig. 3d, and N'(7) nucleophile of amine group in I₆, Fig. 1f, to form C(17)-N(7) peptide bond in Ac-DT-NH₂, Fig. 4b. The C(17)-N(7) bond length in the Ac-DT-NH₂ peptide is 1.3647 Å with the partial charge of C(17) and N(7) are 0.77 and -0.73.
respectively. The TS I-4 of Ac-DT-NH₂ peptide formation has an imaginary vibration frequency -36.97 cm⁻¹, whereas TS III-4 of Ac-TD-NH₂ peptide is -224.2 cm⁻¹. It is difficult to precisely determine the transition state of TS I-4 and TS III-4 in peptide formation because the intermediates involved are very reactive.

Figure 4. The optimized structure of the synthesis product Ac-DT-NH₂ and Ac-TD-NH₂ peptide. Color key: purple=carbon, orange=nitrogen, red=oxygen, blue=hydrogen

The PES of all species involved in I and III reaction mechanism used to determine the activation energy (Ea) which have some Ea, and to determine the reaction rate, Fig. 5. The highest activation energy (Ea) in I and III reaction mechanism is the second step, and used as the rate determining reaction. According to the Arrhenius equation, \( k = Ae^{-Ea/RT} \), the greater of Ea the smaller the rate constant, where \( v = k [A] [B] \), and so that the rate is slow at that stage of the reaction [26]. The I reaction mechanism which have Ea 1324.31 kJmol⁻¹ is preferred than III which have Ea higher namely 1625.03 kJmol⁻¹. Therefore, the product Ac-DT-NH₂ peptide is preferred.

Figure 5. Potential energy surface (PES) of the reaction mechanism of path I and III calculated by ab initio HF/6-31g**
3.2. Path II and IV Reaction Mechanisms

The II and IV reaction mechanism pathways are initiated by dissociation of the C-OH bond in carboxylic group of threonine produced Ac-DT-NH$_2$ peptide similar as in I reaction mechanism, and in carboxylic group of aspartate produced Ac-TD-NH$_2$ peptide similar as in III mechanism, respectively, scheme 1.

The first step is the dissociation of the C-OH bond which as a region center of reaction in the II reaction mechanism to produce an intermediate I$_{II-2}$ with the energy is -94.47x10$^4$ kJmol$^{-1}$, whereas in the IV reaction mechanism IV it produces an intermediate I$_{IV-2}$ with the energy is -113.82x10$^4$ kJmol$^{-1}$. The I$_{II-2}$ and I$_{IV-2}$ are obtained from transition state TS II-1 and TS IV-1, respectively, where the -OH group begins to move away by the C atom. The optimized energy of TS II-1 is -248.07x10$^4$ kJmol$^{-1}$ with an imaginary vibration frequency is -369.97 cm$^{-1}$, Fig. 6a, whereas the TS IV-1 is 248.11x10$^4$ kJmol$^{-1}$ with an imaginary vibration frequency of -98.96 cm$^{-1}$, Fig. 6b. From this result the I$_{II-2}$ species has an energy higher as much as 1100 kJmol$^{-1}$ than the TS II-1, indicating that the I$_{II-2}$ the molecule is unstable than TS I-1.

The second step is the association between OH$^-$ ions and H atom of –NH$_2$ group, which in II reaction mechanism occurs in aspartate molecules by forming the TS II-2, whereas in IV reaction mechanism...
occurs in threonine by forming TS IV-2. In II mechanism, the –HN(5)H(16)...O(17)H distance change to 1.548 Å, whereas the –HN(7)H(11)...O(18)H in the IV mechanism to 1.573 Å. The optimized energy of the TS II-2 molecule is -247.837x10^4 kJmol⁻¹ with an imaginary vibration frequency of -1346.77 cm⁻¹, Fig. 6c, while the TS IV-2 molecule is -247.862x10^4 kJmol⁻¹ with an imaginary vibration frequency of -2215.57 cm⁻¹, Fig. 6d. Then, the TS II-2 and TS IV-2 change to be an 1D intermediate in II mechanism and 1F in IV mechanism. In the 1D intermediate of II mechanism the –HN(5)H(16)-O(17)H covalent bond are formed with the bond length is 0.948 Å, while the 1F intermediate of IV mechanism formed the –HN(7)H(11)-O(18)H covalent bond with a bond length is 0.957 Å. The optimized energy of 1D and 1F are -153.368x10^4 kJmol⁻¹ and -133.937x10^4 kJmol⁻¹, respectively, and both 1D and 1F has a considerable reactivity.

![Figure 7](image_url)

**Figure 7.** The optimized structure of species in the third step of II and IV reaction mechanism. Color key: purple=carbon, orange=nitrogen, red=oxygen, blue=hydrogen

The next step is the process of releasing H₂O group from 1D in II mechanism and from 1F in IV mechanism. In this third step, the N-H covalent bond of -HN-H(16)O(17)H in the 1D and 1F intermediate begins to dissociate to form the transition state structure TS II-3 and TS IV-3. In II mechanism, the N(5)-H(16) bond length change from 1.011 Å to 1.503 Å and the H₂O group is released. Whereas in IV mechanism, the N(7)-H(11) bond length change from 1.025 Å to 1.525 Å. The optimized energy of transition state of TS II-3 is -247.971x10^4 kJmol⁻¹ with an imaginary vibration frequency of -119.65 cm⁻¹, whereas the optimized energy of TS IV-3 is -247.788x10^4 kJmol⁻¹ with imaginary vibration frequency amounting to -980.71 cm⁻¹.

The last step is the stage of peptide product formation which follows the similar path of the I and III reaction mechanism which produced Ac-DT-NH₂ peptide in II mechanism and Ac-TD-NH₂ peptide in IV mechanism. The II reaction mechanisms have some Ea, and the highest Ea is in the second step, while the highest Ea in IV mechanism takes place in the third step. Therefore, the second step in II reaction mechanism and the third step reaction in IV mechanism are the rate determining reaction. The highest Ea of the II reaction mechanism obtained in the second step is 2718.35 kJmol⁻¹, whereas in the IV reaction mechanism Ea is 2470.19 kJmol⁻¹, and the Ac-TD-NH₂ peptide is preferred. The potential energy all the species involved in the II and IV reaction mechanism of formation Ac-DT-NH₂ peptide and Ac-TD-NH₂ peptide is shown in the graph of potential energy surfaces (PES), Fig. 8.
4. Conclusion

The electronic properties of all species involved in reaction mechanisms show that the preferred reaction mechanism is the I reaction mechanism which produces the Ac-DT-NH₂ peptide and the IV reaction mechanism that produces the Ac-TD-NH₂ peptide. The I reaction mechanism is faster than IV reaction mechanism with Ea in the second stage 1329.23 kJmol⁻¹ and 2470.19 kJmol⁻¹, respectively. Both the I and IV mechanisms are exothermic reactions with ΔH reaction enthalpy -6.075 kJmol⁻¹ and -6.092 kJmol⁻¹, respectively.

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