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To cite this article: P Siahaan *et al* 2018 *IOP Conf. Ser.: Mater. Sci. Eng.* **349** 012049

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Ab initio computational study of –N-C and –O-C bonding formation : functional group modification reaction based chitosan

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Abstract. Chitosan application in pharmaceuticals and cosmeceutics industries is limited by its solubility issue. Modification of -NH₂ and -OH functional groups of chitosan by adding carboxyl group has been shown to improve its solubility and application. Attempt to synthesize carboxymethyl chitosan (CMC) from monochloroacetic acid (MCAA) has been done prior this report. However no information is available whether -OH (-O-C bonding formation) or -NH₂ (-N-C bonding formation) is the preference for -CH₂COOH to attach. In the current study, the reaction mechanism between chitosan and MCAA reactants into carboxymethyl chitosan (CMC) was examined by computational approach. Dimer form of chitosan used as a molecular model in calculation. All the molecular structure involved in the reaction mechanism was optimized by ab initio computational on the theory and basis set HF/6-31G(d,p). The results showed that the -N-C bonding formation via S_N2 than the -O-C bonding formation via S_N2 which have activation energy 469.437 kJ/mol and 533.219 kJ/mol respectively. However, the -O-C bonding formation more spontaneous than the -N-C bonding formation because ΔG the formation of O-CMC-2 reaction is more negative than ΔG of formation N-CMC-2 reaction is -4.353 kJ/mol and -1.095 kJ/mol respectively. The synthesis of N,O-CMC first forms -O-CH₂COOH, then continues to form -NH-CH₂COOH. This information is valuable to further optimize the reaction condition for CMC synthesis.

1. Introduction

Chitosan is a copolymer of glucosamine and N-acetyl glucosamine monomer linked by 1,4-glycosidic bonds [1]. It is commonly obtained from deacetylation of chitin produced by crustacean. Chitosan has high biocompatibility, relatively non toxic and biodegradable, promoting wide use of this polymer in drug delivery, antibacterial, cosmetic, food film and water purifier [2,3]. This polymer has reactive groups -NH₂ and -OH that been associated with its insolubility at neutral and alkaline solutions [3]. Some strategies has been performed to increase the solubility of chitosan. One of them by reacting chitosan with monochloro acetic acid (MCAA) to produce carboxymethyl chitosan (CMC) [4]. The hydrophilic group (-CH₂COOH) in MCAA group increased chitosan solubility. Modification of chitosan into CMC occurs via nucleophilic substitution reactions with the formation of -N-C and -O-C bonds resulting in N-CMC (-NHCH₂COOH) and O-CMC (-O-CH₂COOH) [1]. The O-CMC synthesis occurs



at 30 °C with 40-50% NaOH concentration, while N-CMC synthesis occurs at 90 °C with 25% NaOH and at 60 °C yields N,O-CMC product [5]. Previous studies done in our lab shown that modification of chitosan to CMC improved its solubility and encapsulation efficiency [6]. However from those studies it is not known if the substitution present on -NH₂ and -OH groups. In real experimental setting it is costly to study intermediate. Thus, in this studies, the formation preference between -N-C with -O-C bond will be examined through ab-initio computational method.

The term ab-initio means "from first principle" which means the total wave function, molecular orbital, and energy are calculated respectively without empirical parameters [7]. The ab initio computational method has been efficiently predicted the formation mechanism of -N-C(=O)- on the cadherin peptide synthesis [8]. Computational methods are also able to determine the mechanism of glycine formation of CO₂, H₂ and H₂C=NH which lead to a conclusion that glycine formation was via joint reaction pathway where CO₂, H₂ and H₂C=NH react together [9].

This research used ab-initio computational method with theory and basis set RHF / 6-31G (d, p) to determine the stable structure and energy of each molecule (R: reactant, TS-m-n: transition state, I-m-n: intermediate and P-n : Product) involved in CMC formation reaction mechanism. The energy obtained becomes the basis for determining the most likely mechanisms to occur. The molecular model used is chitosan dimer. Analysis of the mechanism of the reaction was carried out on six mechanism models, two via S_N1 (monomolecular nucleophilic substitution) that produced P_O-1 (O-CMC-1) and P_N-1 (N-CMC-1), and four via S_N2 (bimolecular nucleophilic substitution) produced P_O-2 (O-CMC-2), P_N-2 (N-CMC-2), P_{N,O}-1 (N, O-CMC-1) and P_{N,O}-2 (N, O-CMC -2). The proposed reaction mechanism is as follows:

Mechanism 1 : ClCH₂COOH → ⁺CH₂COOH + Cl⁻ + chitosan-OH → chitosan-OHCH₂COOH → chitosan-O-CH₂COOH + HCl

Mechanism 2 : ClCH₂COOH → ⁺CH₂COOH + Cl⁻ + chitosan -NH₂ → chitosan-NH₂CH₂COOH → chitosan -NH-CH₂COOH + HCl

Mechanism 3: chitosan-OH + ClCH₂COOH → chitosan-OH-CH₂COOH + Cl⁻ → chitosan-O-CH₂COOH + HCl

Mechanism 4 : chitosan-NH₂ + ClCH₂COOH → chitosan-NH₂-CH₂COOH + Cl⁻ → chitosan-NH-CH₂COOH + HCl

2. Computational Methods

All molecular calculations are performed with linux-based Gaussian 03 applications and all molecules are visualized with chemcraft software with input files created using a notepad++. In this research all calculations using the theory and basis set RHF / 6-31G (d, p). The stable structure at the stationary point in PES (Potential Energy Surface) as well as the minimum energy is determined by the "opt (CalcFC)" command, while the TS structure is determined by "opt (calcfc, ts, noeigentest)" command. Frequency of harmonic vibration is calculated by the "freq" command to determine the correction of zero-point vibration energy (ZPVE) for all molecules. Frequency is also used to determine the TS structure by ensuring that there is only one imaginary frequency, whereas the molecule at the stationary point has no imaginary frequency. In addition, the frequency calculation is also to know the free energy of Gibbs of each molecule involved in the reaction mechanism [10,11].

3. Results and Discussion

Before studying the mechanism, computational study of reactants was done to determine bond characteristic. Reactant in this synthesis was chitosan dimer and MCAA. Chitosan dimer has two types of -NH₂ bound to C4 and C9 and two types of -OH bound to C17 and C22 (**Figure 1.a**). We found that substitution of carboxymethyl groups occurred at -NH₂ bound to C4 and -OH bound to C17. Substitution reactions did not occur in -C9-NH₂ and -C22-OH, although N and O atoms have a more negative charge than -C4-NH₂ and -C17-OH but the steric blockages in C9-NH₂ and C22-OH are larger. Large steric hindrances make substitution reactions difficult because the chitosan molecule undergoes a flip that makes the transition state structure difficult to form.

A stable structure of MCAA, a hydrophil group donor for CMC formation, was depicted at **Figure 1.b**. The minimum energy structures of chitosan dimer and MCAA are -328.35×10^4 kJ/mol and -180.28×10^4 kJ/mol respectively. From the frequency calculation, the enthalpy energy (H) and free energy Gibbs (ΔG) for chitosan dimer molecule are -328.34×10^4 kJ/mol and -328.36×10^4 kJ/mol. The enthalpy energy and ΔG for MCAA molecules are -180.277×10^4 kJ/mol and -180.287×10^4 kJ/mol. The energy of chitosan enthalpy is negative which signifies exotherm [12].

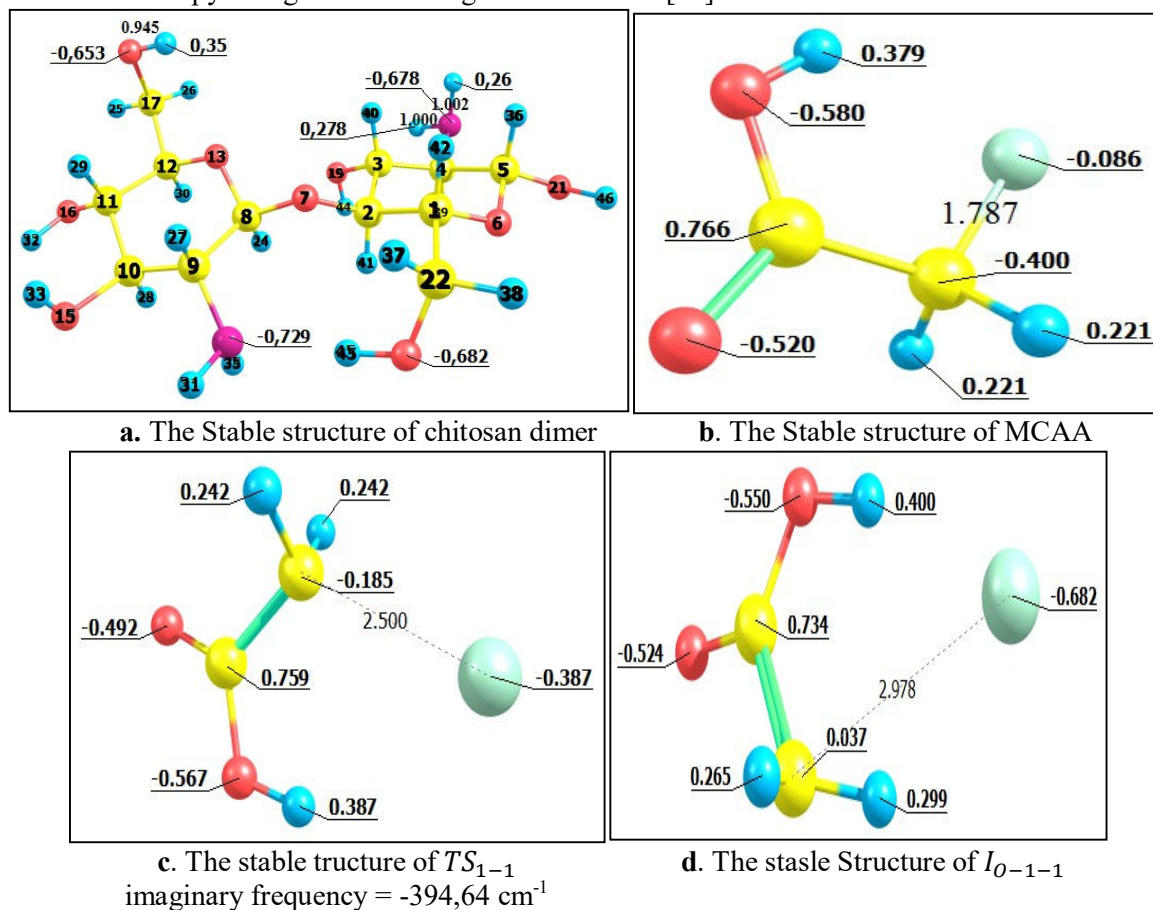


Figure 1. The stable structure of reactant, TS_{1-1} and I_{O-1-1}



3.1. The mechanism of synthesis reaction of O-CMC

The mechanism of synthesis reaction of O-CMC is a CMC synthesis substituted through the -OH group. This synthesis passes through two paths of reaction mechanism is S_N1 path and S_N2 path. The mechanism of synthesis reaction of O-CMC-1 is the reaction of S_N1 pathway. The mechanism of this reaction begins with a weakened C-Cl bond which is indicated by the longer bonding distance of the TS_{O-1-1} molecule the bond length of C-Cl is 2.5 Å (**Figure 1.c**), compared to in MCAA (1.787 Å). This result is supported by an imaginary vibrational frequency on the center reaction area ($\nu = -394.64 \text{ cm}^{-1}$). Weak bonds cause the C-Cl bond to break into carboxymethyl ions ($+CH_2COOH$) and Cl ions, which are the first intermediates (I_{O-1-1}).

The second stage is the attack of carbocation by the nucleophile group of chitosan (-OH) through the transition state (TS_{O-2-1}) with the bond length between -O-C is 1.8 Å. The transition state structure is confirmed by the presence of an imaginary vibrational frequency of the freq calculation ($\nu = -288.53 \text{ cm}^{-1}$). After the E_a from the second state is passed the molecule will formed I_{O-2-1} with the formation of the -OH- CH_2COOH bonds with the bond length -O-C to 1.437 Å, and the length of the oxygen bonds

with hydrogen weakened from 0.947 Å to 0.98 Å (**Figure 2.a**). This is because the molecules I_{0-2-1} is charged +1 where the oxygen atom binds 3 atoms [13].

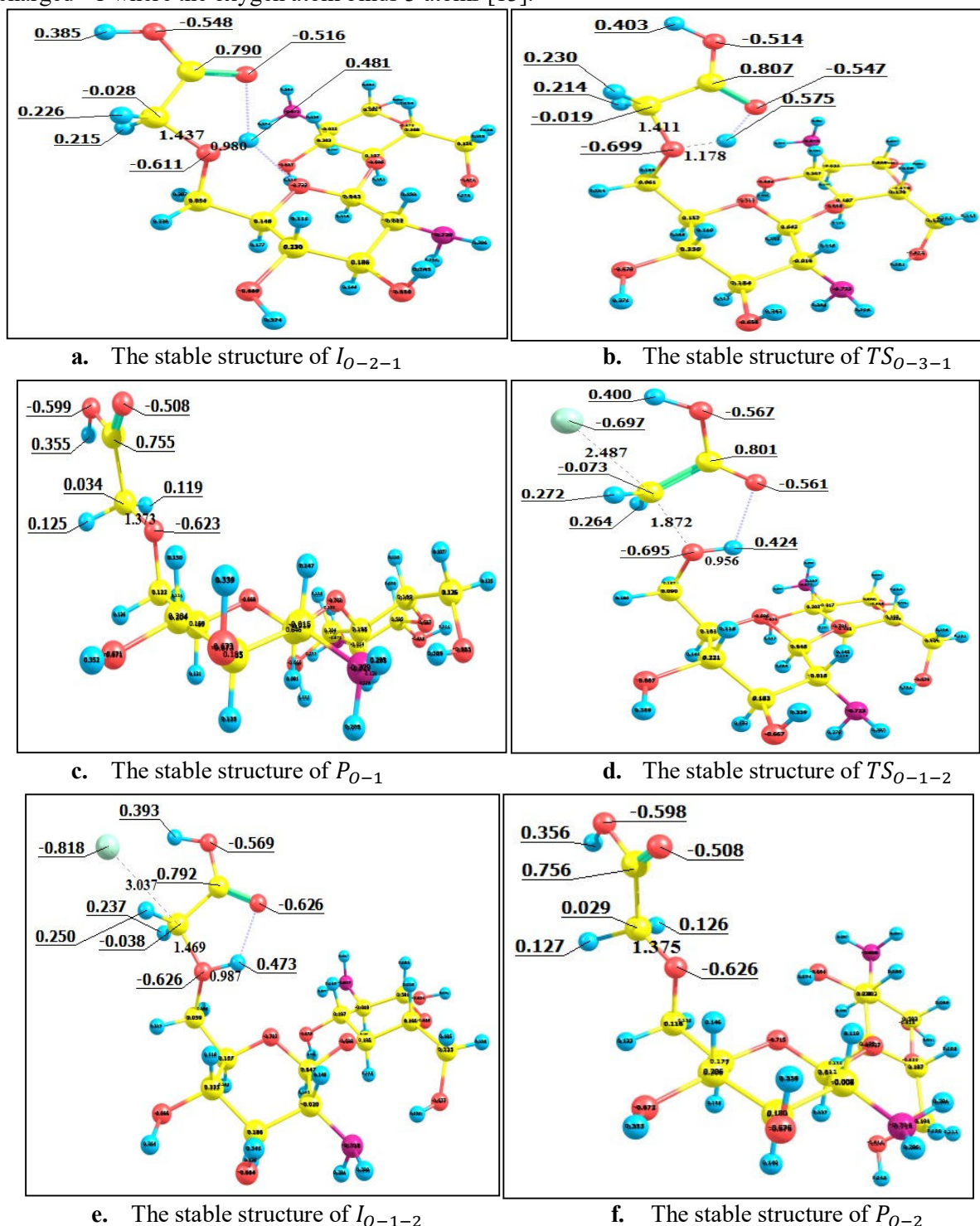


Figure 2. The stable structure of the O-CMC synthesis via S_N1 and S_N2 pathway

The I_{0-2-1} molecules is highly reactive and unstable, so they must release an atom is hydrogen atom, this is the third reaction step. The third reaction stage begins with the formation of TS_{0-3-1} which H atoms begin to move away from O with bond lengths to 1.178 Å (**Figure 2.b**). The transition state is confirmed by an imaginary vibrational frequency of -1550.36 cm^{-1} . The length of the H bond with O

will be longer and finally H is released forming O-CMC-1 and H^+ ions. H^+ ions react with Cl^- ion to form HCl, as a by-product. The length of the O-C bond becomes 1.373 Å (**Figure 2.c**). The minimum energy of all molecules involved in the reaction mechanism of the O-CMC bond formation of S_N1 path is presented in the energy potential (**Figure 3**) [14].

The mechanism of synthesis reaction of O-CMC-2 is the reaction of S_N2 pathway. The mechanism of this reaction begins with the Cl^- ion starting away and the nucleophile groups of chitosan (-OH) begin to approach simultaneously, forming TS_{O-1-2} . As a result of this process there is a change in the length of bond and charge shown in **Figure 2.d**. The most significant changes are in the reaction areas (-OH-C-Cl). The Cl^- charge on the MCAA molecule is -0.086, while in the TS_{O-1-2} molecule to -0.765, which makes the Cl^- ion more easily released. It is supported by an imaginary vibrational frequency on the center reaction area $\nu = -506,29 \text{ cm}^{-1}$. TS_{O-1-2} through the formation of intermediates I_{O-2} which is the +1-charged molecules at the reaction center that are formed -OH- CH_2COOH ions (**Figure 2.e**). In this stage the bonds between -O-H is getting weaker with each bond length to 0.987 Å.

The intermediate substance is not a stable molecule so release its hydrogen forming TS_{O-2-2} . The second stage transition state (TS_{O-2-2}) was confirmed by an imaginary vibrational frequency is -1408.61 cm^{-1} . The weak hydrogen bonds with bond length O-H to 1.161 Å make the hydrogen easily loose to form O-CMC-2 (**Figure 2.f**) with a by-product of HCl. The minimum energy of all molecules involved in the reaction mechanism of the O-CMC bond formation of S_N2 path is presented in the energy potential (**Figure 3**) [14].

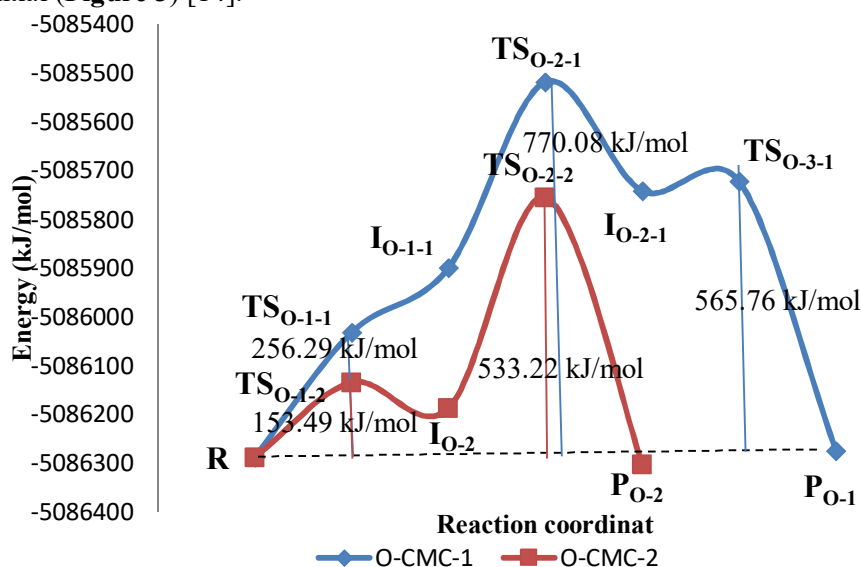


Figure 3. Potential energy surface of the reaction mechanism of the O-CMC synthesis

Figure 3 shows the reaction rate determinant for O-CMC-1 and O-CMC-2 is the second stage, because it has the greatest activation energy. According to the Arrhenius equation ($k = Ae^{-E_a/RT}$), the greater the value of the activation energy (E_a) the value of the rate constant (k) will be smaller and the reaction rate will be slow at that stage. The value of the rate constant (k) obtained is presented in **Table 1**. From **Table 1**, it can be seen that the mechanism of the reaction of O-CMC formation most preferred is through the path S_N2 . This is because The E_{a2} of S_N2 pathway is lower than S_N1 pathway, It is also because the value of the k of S_N2 pathway is greater than the S_N1 pathway, so the reaction is faster. Abou-zied et al., (2013) stated that carboxymethyl groups are formed by the reaction of S_N2 [1]. The S_N2 reaction path is preferable because the positive C atoms of the MCAA are primary C-type in the reaction path S_N2 has the fastest reaction rate [15, 16]. From the data of gibbs free energy (ΔG) known that the O-CMC-1 reaction is not spontaneous and the O-CMC-2 reaction is spontaneous [14]. The O-CMC-1 formation reaction is an endothermic reaction, whereas the O-CMC-2 formation reaction is an exothermic reaction.

3.2. The mechanism of synthesis reaction of N-CMC

The mechanism of synthesis reaction of N-CMC is a CMC synthesis substituted through the -NH_2 group. This synthesis passes through two paths of reaction mechanism is $\text{S}_{\text{N}}1$ path and $\text{S}_{\text{N}}2$ path. The mechanism of synthesis reaction of N-CMC-1 is the reaction of $\text{S}_{\text{N}}1$ pathway. The first stage of this mechanism is the same as the first stage of O-CMC-1 synthesis via the $\text{S}_{\text{N}}1$ pathway.

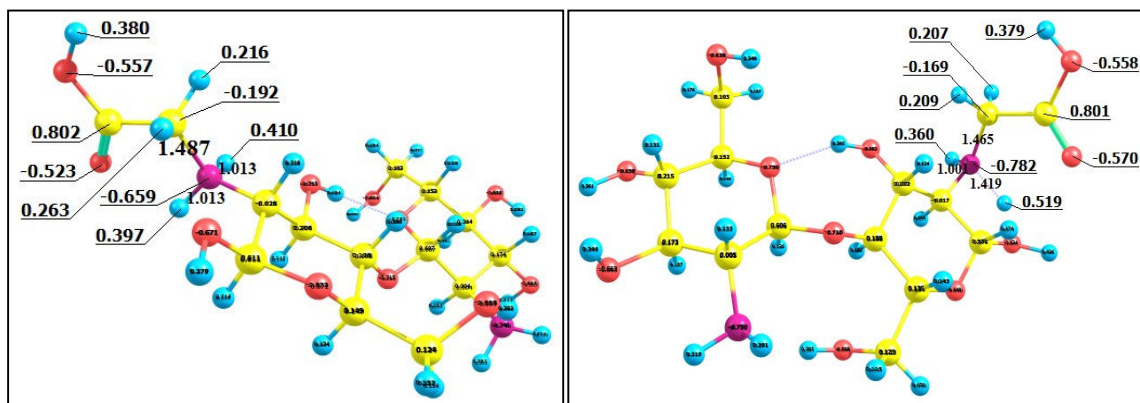
The second stage is the attack of carbocation by the nucleophile group of chitosan (-NH_2) through the transition state ($TS_{\text{N}-2-1}$) with the bond length between -N-C is 2.162 Å. The transition state structure is confirmed by the presence of an imaginary vibrational frequency of the freq calculation ($\nu = -338.657 \text{ cm}^{-1}$). After the E_a from the second state is passed the molecule will formed $I_{\text{N}-2-1}$ with the formation of the $\text{-NH}_2\text{-CH}_2\text{COOH}$ bonds with the bond length -N-C to 1.487 Å, and the length of the -N-H bond weakened from 0.947 Å to 0.98 Å (**Figure 4.a**). This is because the molecules $I_{\text{N}-2-1}$ is charged +1 where the nitrogen atom binds 4 atoms.

The $I_{\text{N}-2-1}$ molecules is highly reactive and unstable, so they must release an atom is hydrogen atom, this is the third reaction step. The third reaction stage begins with the formation of $TS_{\text{N}-3-1}$ which H atoms begin to move away from N with bond lengths to 1.42 Å (**Figure 4.b**). The transition state is confirmed by an imaginary vibrational frequency of -1295.77 cm^{-1} . The length of the H bond with N will be longer and finally H is released forming N-CMC-1 and H^+ ions. H^+ ions reacts with Cl^- ion to form HCl, as a by product. The length of the N-C bond becomes 1.434 Å (**Figure 4.c**). The minimum energy of all molecules involved in the reaction mechanism of the N-CMC bond formation of $\text{S}_{\text{N}}1$ path is presented in the energy energy potential (**Figure 5**).

The mechanism of synthesis reaction of N-CMC-2 is the reaction of $\text{S}_{\text{N}}2$ pathway. The mechanism of this reaction begins with the Cl^- ion starting away and the nucleophile groups of chitosan (-NH_2) begin to approaching simultaneously, forming $TS_{\text{N}-1-2}$. As a result of this process there is a change in the length of bond and charge shown in **Figure 4.d**. The most significant changes are in the reaction areas ($\text{-NH}_2\text{-C-Cl}$). The Cl^- charge on the MCAA molecule is -0.086 , while in the $TS_{\text{N}-1-2}$ molecule to -0.768 , which makes the Cl^- ion more easily released. It is supported by an imaginary vibrational frequency on the center reaction area $\nu = -563.23 \text{ cm}^{-1}$. $TS_{\text{N}-1-2}$ through the formation of intermediates $I_{\text{N}-2}$ which is the +1-charged molecules at the reaction center that are formed $\text{-NH}_2\text{-CH}_2\text{COOH}$ ions (**Figure 4.e**). In this stage the bonds between -N-H is getting weaker with each bond length to 1.012 Å.

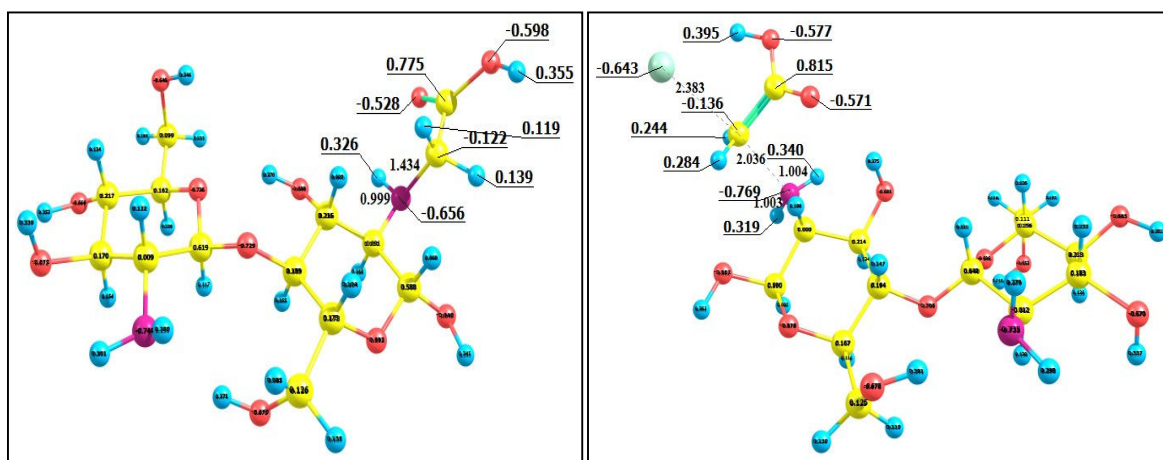
The intermediate substance is not a stable molecule so release its hydrogen forming $TS_{\text{N}-2-2}$. The second stage transition state ($TS_{\text{N}-2-2}$) was confirmed by an imaginary vibrational frequency is -1558.81 cm^{-1} . The weak hydrogen bonds with bond length N-H to 1.378 Å make the hydrogen easily loose to form N-CMC-2 (**Figure 4.f**) with a by-product of HCl. The minimum energy of all molecules involved in the reaction mechanism of the O-CMC bond formation of $\text{S}_{\text{N}}2$ path is presented in the energy energy potential (**Figure 5**).

Figure 5 shows the reaction rate determinant for N-CMC-1 and N-CMC-2 is the second stage, because it has the greatest activation energy. According to the Arrhenius equation ($k = Ae^{-E_a/RT}$), the greater the value of the activation energy (E_a) the value of the rate constant (k) will be smaller and the reaction rate will be slow at that stage. The value of the rate constant (k) obtained is presented in **Table 1**. From **Table 1**, it can be seen that the mechanism of the reaction of N-CMC formation most preferred is through the path $\text{S}_{\text{N}}2$. This is because The E_{a2} of $\text{S}_{\text{N}}2$ pathway is lower than $\text{S}_{\text{N}}1$ pathway, It is also because the value of the k of $\text{S}_{\text{N}}2$ pathway is greater than the $\text{S}_{\text{N}}1$ pathway, so the reaction is faster. The $\text{S}_{\text{N}}2$ reaction path is preferable because the positive C atoms of the MCAA are primary C-type in the reaction path $\text{S}_{\text{N}}2$ has the fastest reaction rate [15, 16]. From the enthalpy energy (ΔH) and gibs free energy, both the N-CMC-1 and N-CMC-2 forming reactions are exothermic and spontaneous.



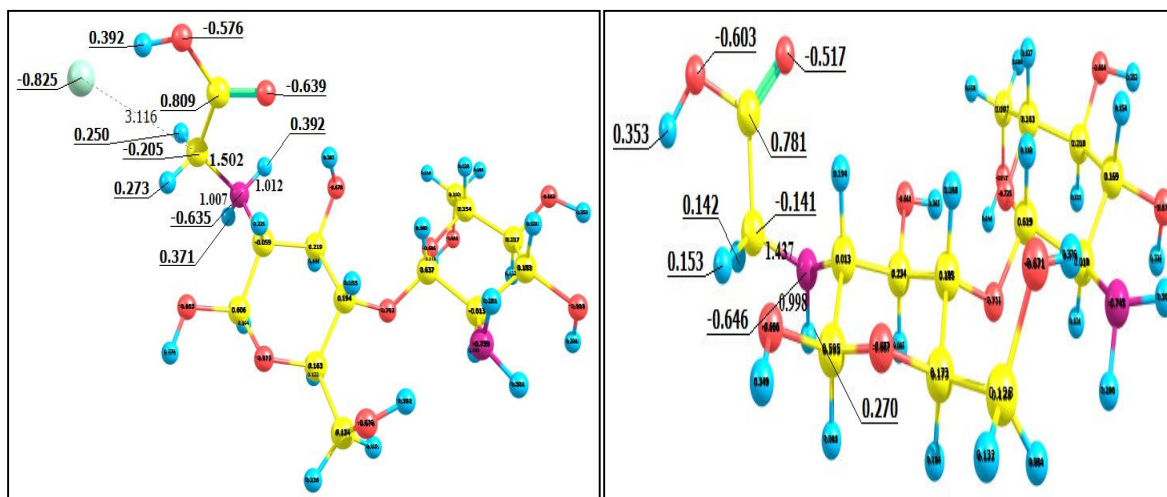
a. The stable structure of I_{N-2-1}

b. The stable structure of TS_{N-3-1}



c. The stable structure of P_{N-1}

d. The stable structure of TS_{N-1-2}



e. The stable structure of I_{N-1-2}

f. The stable structure of P_{N-2}

Figure 4. The stable structure of the N-CMC synthesis via S_N1 and S_N2 pathway

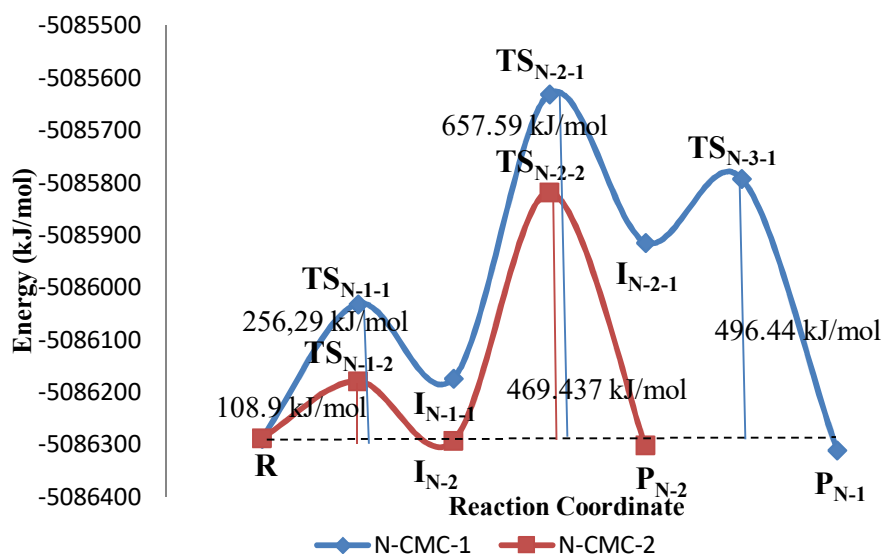


Figure 5. Potential energy surface of the reaction mechanism of the O-CMC synthesis

Table 1. Parameters determining the most likely reaction mechanism.

Parameter	O-CMC		N-CMC				N,O-CMC	
	SN1 CMC-1)	(O- SN2 CMC-2)	(O- SN1 CMC-1)	(N- SN2 CMC-2)	(N- SN1 CMC-1)	(N, SN2 CMC-2)	(N,O- SN1 CMC-1)	(N,O- SN2 CMC-2)
E _a (kJ/mol)	770.08	533.22	657.59	469.437	533.22	469.437	533.22	469.437
k	1.203x10 ⁻¹³⁵	3.79x10 ⁻⁹⁴	6.15x10 ⁻¹¹⁶	5.67x10 ⁻⁸³	3.79x10 ⁻⁹⁴	5.67x10 ⁻⁸³	3.79x10 ⁻⁹⁴	5.67x10 ⁻⁸³
ΔH (kJ/mol)	17.35	-9.341	-19.707	-11.628	-33.47	-17.48	-33.47	-17.48
ΔG (kJ/mol)	24.629	-4.353	-8.097	-1.948	-4.95	15.47	-4.95	15.47

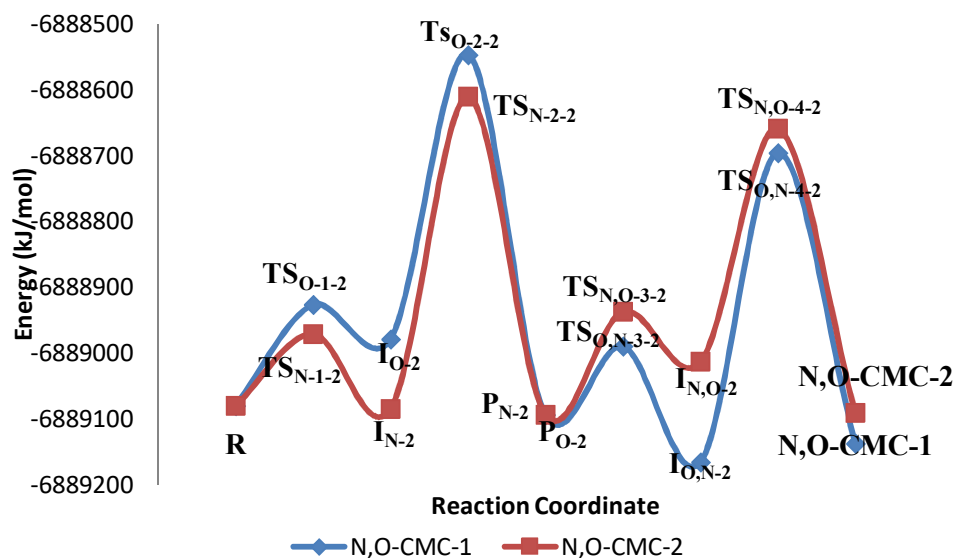


Figure 6. Potential energy surface of the reaction mechanism of the N,O-CMC synthesis

The CMC synthesis not only produces O-CMC and N-CMC but also can produce N,O-CMC, substituted carboxymethyl ions in both groups -OH and -NH₂. The mechanism of the N,O-CMC synthesis reaction is formed by continuing the reaction mechanism through the S_N2 reaction pathway. N,O-CMC-1 is a synthesis of N,O-CMC which begins with substitution of -OH group then substituted

in the $-NH_2$ group, while N,O-CMC-2 begins substitution in the $-NH_2$ group then substituted in the $-OH$ group. The results obtained are presented in **Figure 6**. In the N,O-CMC-1 synthesis, the third and fourth phase E_a is smaller than the second stage, so the reaction rate determinant stage is the second stage such as O-CMC-2. As well as the N,O-CMC-2, E_{a3} and E_{a4} are smaller than E_{a1} and E_{a2} . It's means substitution via the $-NH_2$ group is easier after the chitosan is substituted in the $-OH$ group, because the atomic charge N of $-NH_2$ is initially -0.678 become more negative that is to be -0.685 . As well as the N,O-CMC-2 synthesis with the stage of reaction rate at the second stage. It's means substitution of $-OH$ groups is easier to occur after substitution of the $-NH_2$ group.

ΔH and ΔG the synthesis reaction of N,O-CMC-1 is -33.47 kJ/mol and -17.48 kJ/mol, whereas ΔH and ΔG the synthesis reaction of N,O-CMC-2 is -4.95 kJ/mol and 15.47 kJ/mol. From the ΔG data it suggest that the N,O-CMC-2 synthesis is positive so that the reaction is not spontaneous and difficult to occur so that the reaction mechanism of N,O-CMC occurs through substitution $-OH$ first, then new $-NH_2$ substituted. Oleh karena itu, untuk mensintesis N, O-CMC secara eksperimental dengan membuat kondisi reaksi untuk O-CMC terbentuk terlebih dahulu, kemudian lanjutkan untuk mengendalikan kondisi reaksi yang akan diganti pada kelompok $-NH_2$.

4. Conclusion

A mechanism for the carboxymethyl chitosan synthesis by dimer chitosan and monochloro acetic acid by HF calculation was presented. The results showed that the reaction of CMC synthesis via S_N2 reaction pathway, based on the kintecs data, the N-CMC-2 synthesis is most easily formed with E_a determinant of reaction rate is 469.44 kJ/mol, while from the thermodynamic data, ΔG of the O-CMC-2 synthesis is -4.353 kJ/mol more spontaneous than the N-CMC-2 synthesis. Both N-CMC-2 and O-CMC-2 are exothermic reactions. The synthesis of N,O-CMC occurs through the formation of $-O-CH_2COOH$ the first and then proceeds to form $-NH-CH_2COOH$, which is indicated by low and negative ΔH and ΔG values of -33.47 kJ/mol and -17.48 kJ/mol.

Acknowledgements

Thanks to Prof. Teruna J. Siahaan, Ph.D. (Pharmacy Department, University of Kansas, US), for the valuable direction and discussion of encapsulation and drug delivery systems. Thanks to the Directorate General of Higher Education. Last but not least Faculty of Science and Mathematics, which has funded this research through the Research Funding Scheme 2016.

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