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# The Effect of Configuration to Interaction Energy Between The Segments of Chitosan and Ascorbic Acid Molecule: Theoretical Study of Drug Release Control

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**Abstract.** Polymer systems plays an important role in drug delivery, which can control the time release of the drug, reduce the rate of degradation of the drug, and can reduce the toxic properties of the drug. Chitosan is a polymer of N-acetyl glucosamine that is biocompatible, biodegradable, and have active groups that can be used as a drug carrier matrix to control the release rate of the drug in the human body. The related research has been conducted experimentally by applying chitosan as a matrix to control the release rate of ascorbic acid by in vitro in an aqueous medium. So that, this study aimed to describe the interactions that occur between segments of chitosan and ascorbic acid theoretically using ab initio computational methods. Software used is Gaussian03, while the level of theory and basis set calculations determined is HF-SCF / 6-31G (d, p). The results for the nine configuration interaction calculations indicate hydrogen bonds between ascorbic acid molecules and chitosan segment. The interaction energy obtained is different for each configuration. It can be used as a basis for explaining the gradual release of ascorbic acid molecule from chitosan matrix. Ascorbic acid molecules that bound to the matrix of chitosan with lower energy will be easier to release on the medium that used.

**Keywords:** chitosan, drug release, ab initio, interaction energy

## Introduction

Polymer systems plays an important role in drug delivery, which can control the timing of the release of the drug, reducing the rate of degradation of the drug, and can reduce the toxic properties of the drug. Drug delivery systems occurs when drugs or other active substances incorporated into the polymer (synthetic or natural). The amount of active ingredient or drug issued will then be controlled. One of the goals of drug delivery systems is to obtain sustained-release preparations (Malmsten, 2002).

Dosage sustained release has several advantages over dosage forms of conventional, namely to reduce the fluctuations of drug levels in the blood so that their pharmacological effects are more stable, reducing the frequency of administration, can avoid the use of drugs at night, improving the comfort and satisfaction of the patient, is able to make lower daily costs for because fewer patients dosage units should be used, and overall allowing increasing confidence in therapy (Ansel et al, 1995, Simon 2001, and Shargel et al., 2005). As for the various ways of making and working mechanism of sustained-release preparations that were found in circulation among others, microencapsulation, osmotic pumps, complex formation, forming ion exchange resins, membranes controlled system, and the system matrix (Lee and Robinson, 1978).

In the previous studies, chitosan has been designed as a matrix to control the release of vitamin C in aqueous media. The results showed that the matrix of chitosan is able to adsorb vitamin C so that this formulation will have a gradual solubility in water. It is responsible for this process is the presence of different intermolecular interactions between molecules of vitamin C that one and the other with a matrix of chitosan. So in this study conducted computational studies of the interactions between the molecules of vitamin C with chitosan in a variety of configurations.

## Methodology

The study was based on computational methods for determining the interaction

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energy anata chitosan with vitain C. Software calculation used is Gaussian03 with the basis set RHF 6-31G (d, p). GaussView05 used for visualization. Computational procedure was conducted on the two stages, namely a single molecular geometry optimization and optimization of molecular geometry pairs.

### Optimization of the geometry of a single molecule

The objective of the single molecular geometry optimization is to obtain a stable structure of a molecule of vitamin C and chitosan. Stability parameters can be seen from the price of energy obtained from the calculation. This stage begins with this input file creation were turned away internal Z-matrix coordinates.

### Optimization of geometry of the molecules in pairs

Results of single molecular geometry optimization is then used as an input file for calculation of the interaction energy. In this study, the calculation of the interaction between molecules of vitamin C with chitosan segment nine configurations. In this study, all modeled molecules in the gas phase.

## Results and Discussion

### Optimization of the geometry of a single molecule

Results geometry optimization of chitosan segments showed that chitosan molecules be linear with total energy -32,846.105 kj/mol.

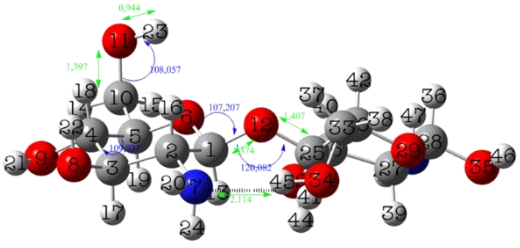

Figure 1. Optimized chitosan dimer structure. Description: ● = Atom C, ○ = Atom H, ● = O atoms, and ● = Atom N

Chitosan dimer optimization results also indicate the existence of intramolecular hydrogen bonding that occurs between nitrogen atoms ($N_7$) with hydrogen atoms ($H_{45}$). The hydrogen bond has a bond length of 2.114Å thus classified as hydrogen bonds (moderate). And dihedral angles that form a bondβ (1.4) of the atoms $C_1$-$C_{25}$ and $C_{24}$-$O_{11}$-$O_{12}$-$C_1$-$C_6$ amounted to 120.082 and -113.807, Intramolecular interaction causes the chitosan-shaped linear dimer structures are linked by glycoside. The results of the calculation with computational known that chitosan has many active groups that causes the chitosan can interact with other molecules that can be applied in drug delivery (Koef et al, 2010).

The results of geometry optimization of vitamin C show that vitamin C has a total energy -17,881.105kj/mol.

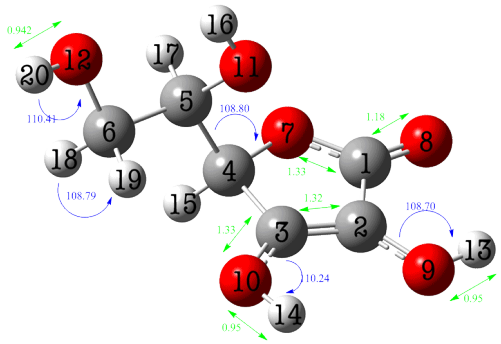

Figure 2. Optimized structure of vitamin C

Description: ● = Atom C, ○ = H atom, and ● = Atom O

Energy value obtained from the calculation is slightly different from the results of calculations performed by Singh et al. (2010) in the amount -17,984.105 kJmol-1. The difference in value is due to the energy levels of the base set is used differently, not only energy, but also affect the value of the difference parameters generated.

In the geometry optimization, vitamin C molecules undergo conformational changes sedimikian so that various parameters such as the distance and angle between the atoms is the most stable state. $C_1$-$O_8$ known distance by 1.18Å which is a double bond (carbonyl) whereas $O_{11}$-$H_{13}$ distance of 0.95 Å. Distance and angle information in full can be found in the appendix.

**Dimer geometry optimization kiosan···vitamin C**

Optimization of geometry interaction chitosan dimer association of vitamin C was conducted to determine the most stable structure of the interaction of chitosan dimer geometry···The structure of chitosan and vitamin C. Vitamin C has many active sites, therefore this research will be carried out several configurations to determine the position of the most stable interactions. Geometry optimization results show that optimization of the interaction of vitamin C chitosan dimer geometry configuration 1 has a total energy -39.155 kJmol-1.

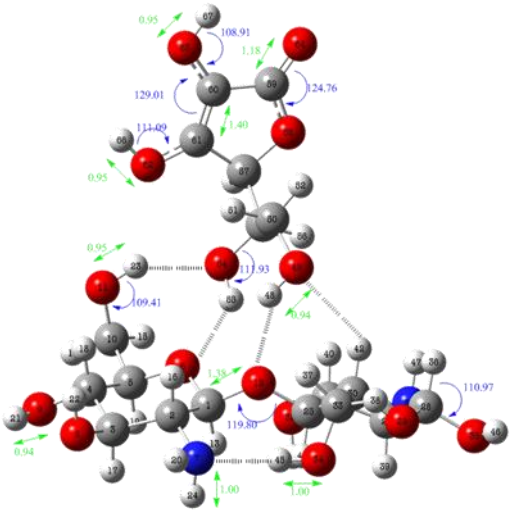

Figure 3. Optimized interaction between chitosan with vitamin C configuration 1

Description: = Atom C, = Atom H, = O atoms, and = Atom N

From the calculation of the interaction energy can be seen that there is interaction between chitosan and vitamin C. This interaction occurs through multiple hydrogen bonds are formed. $O_6$ atom of hydrogen bonds between the chitosan with vitamin C atom at the H55 has a bond length of 2.274Åa type weak hydrogen bonds (weak). Hydrogen bonding between atoms H23on chitosan by atom $O_{54}$ on vitamin C has a bond length of 2.123Åis a type of hydrogen bond (moderate). Hydrogen bonding between atoms H42on chitosan by atom $O_{49}$ on vitamin C has a bond length of 2.641Å is a type of hydrogen bond weak (weak). Acid-base ionic bonds may be formed if the interaction occurs between the amine group in chitosan hydroxyl group in vitamin C. This has been done in previous studies by the Goddess (2011) and the results of computational calculations showed that there was a significant interaction in the area. This study chose a different configuration by considering that the interaction can occur in any configuration. Although only through hydrogen bonding that occurs at some point but have shown that chitosan may interact with vitamin C and allow its use as a drug delivery matrix system (Koef et al, 2010).

The atoms in a molecule that interacts with other molecules will change orientation due to changes in the environment (the atoms of which are in the vicinity). O6 atoms are in a stable condition having chargeas big as -0.695 Change becomes more electronegative charge is equal to -0.712 and H55 adjacent atoms have additional chargefrom becoming +0.376 +0.374. Increasing negative character O atom and increasing the positive character of H atoms resulted in the hydrogen bonds between the atoms.

In the dimer geometry optimization chitosan interaction of vitamin C 2 configuration (Figure IV.11), performed interaction in the down position. Geometry optimization results show that optimization of the interaction of vitamin C chitosan dimer geometry configuration 1 has an energy of -71.617kJmol-1.

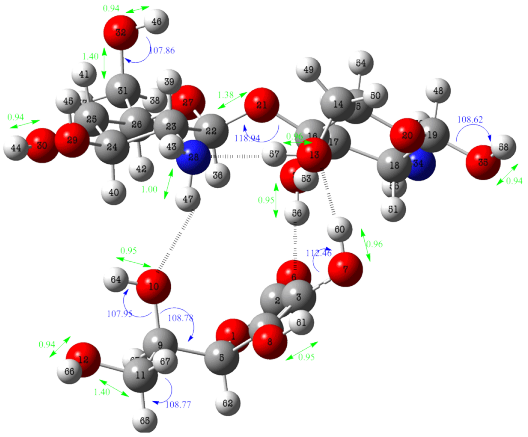

Figure 4. Optimized interaction between chitosan with vitamin C configuration 1

Description:, = Atom C, = Atom H, = O atom and = Atom N

From the calculation of the interaction energy can be seen that there is interaction

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between the cellulose with vitamin C. This interaction occurs through multiple hydrogen bonds are formed. Hydrogen bonds between the atoms O13 on chitosan with vitamin C atom at the H60 has a bond length of 1.886Åa type hydrogen bonding (moderate). Hydrogen bonding between atoms H47on chitosan by atom O10 on vitamin C has a bond length of 2.248Åis a type of hydrogen bond weak (weak). Hydrogen bonding between atoms H56The cellulose by atom O6 on vitamin C has a bond length of 2.152Å is a type of hydrogen bond (moderate).

The atoms in a molecule that interacts with other molecules will change orientation due to changes in the environment (the atoms of which are in the vicinity). $H_{47}$ atoms are in a stable condition having chargeby +0,361 changes become more electronegative charge is equal to +0.3716 $O_{10}$ atom adjacent and have additional charge of -0.65517 be -0.678210, Increasing negative character O atom and increasing the positive character of H atoms resulted in the hydrogen bonds between the atoms. The calculation is repeated until nine configuration and data obtained interaction energies for nine configurations.

| Configuration | The interaction energy (kj / mol) |
|---|---|
| 1 | -39.1550 |
| 2 | -71.6170 |
| 3 | -59.5988 |
| 4 | -32.8187 |
| 5 | -39.3825 |
| 6 | -69.5757 |
| 7 | -58.2861 |
| 8 | -70.1008 |
| 9 | -43.3207 |

## Conclusion

In conclusion the results for the nine configuration interaction calculations indicate hydrogen bonds between ascorbic acid molecules and chitosan segment. The interaction energy obtained is different for each configuration. It can be used as a basis for explaining the gradual release of ascorbic acid molecule from chitosan matrix. Ascorbic acid molecules that bound to the matrix of chitosan with lower energy will be easier to release on the medium that used.

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