# RESULTS AND DISCUSSIONS

This section proposes the geometrical parameters, the mechanism of drug release studied by polymer bond breaking of glucosamine(ethylene glycol) oligomers, the micelle formation for drug delivery and the effect of length of ethylene glycol in glucosamine(ethylene glycol) on drug release. The geometrical parameters of doxorubicin and glucosamine(ethylene glycol) molecules were studied by the relationship between molecular energy and optimization step numbers. The polymer bond breaking of glucosamine(ethylene glycol) oligomers capsule relates to drug release mechanisms. From geometrical parameters study, the charge structure of doxorubicin and the glucosamine(ethylene glycol) molecules can be formulated into micelle structure by H-bond linkage. The length of ethylene glycol chain plays a major role on doxorubicin and glucosamine(ethylene glycol) molecules to form micelle structure.

## Geometrical Parameters

The geometrical parameters are considered to propose the optimum structures of doxorubicin and glucosamine(ethylene glycol). These parameters are the bond length and the charge structure in the molecules which are calculated by semi-empirical AM1, PM3 and *ab initio* HF/6-31G methods.

### Doxorubicin

The optimum structures of doxorubicin obtained by semi-empirical AM1, PM3 and *ab initio* HF/6-31G methods have the same molecular structure. This doxorubicin structure is shown in Figure 15.

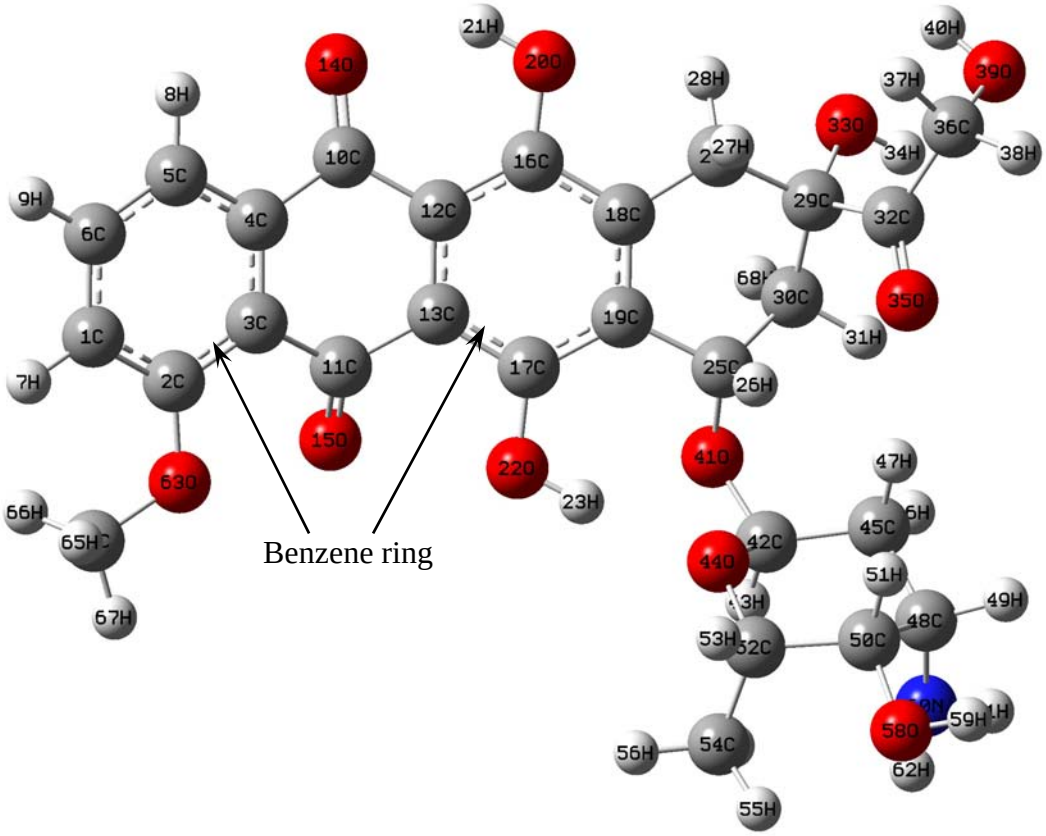



**Figure 15** Molecular structure of doxorubicin from simulation

The doxorubicin structure has benzene rings which the electron in conjugate double bond can delocalize to next bond in the ring. This electron delocalization makes the doxorubicin structure more stable.

**Molecular energy of doxorubicin in optimization**

The molecular optimization can be calculated from total molecular energy. The total energy will decrease until optimum structure can be obtained with the lowest molecular energy. The total energy decreases along with the molecular optimization steps as shown in Figure 16.

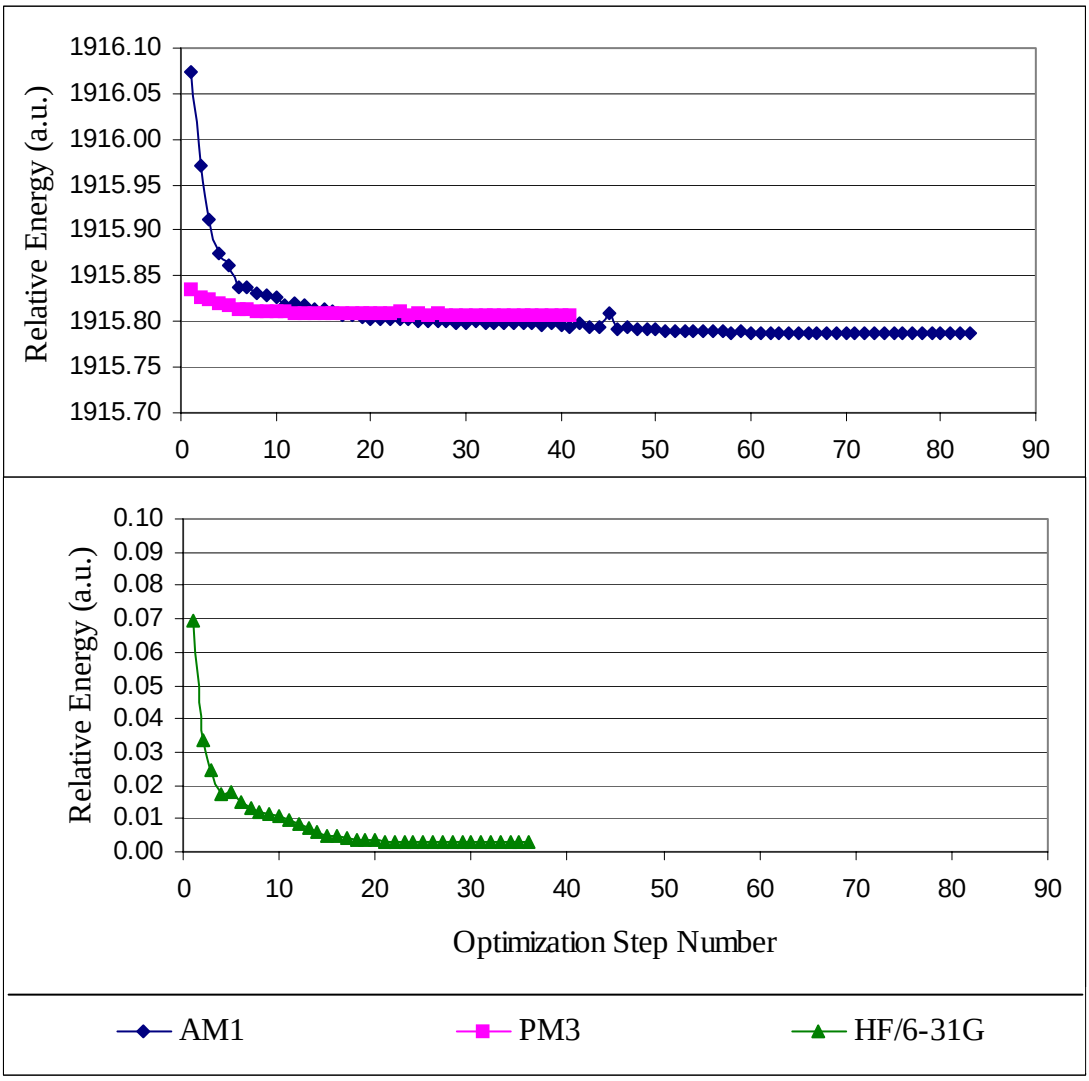



**Figure 16** Total energy of doxorubicin by AM1, PM3 and HF/6-31G optimization methods

The total energy of doxorubicin is optimized by AM1, PM3 and HF/6-31G methods. In AM1 method, the step optimization of doxorubicin structure is 83 steps which stable structure of optimization is in the range of 55-83 steps. The relative energy between input and output from optimization is -0.297 a.u. (1 a.u. = 627.51 kcal/mol). The stable structure is in the range of 31-41 steps when PM3 method is used. The relative energy from optimization is -0.286 a.u.. By HF/6-31G method, it is found that the stable structure of optimization is in the range of 25-36 steps. The relative energy from optimization is -0.07 a.u.. The optimization step by Hatree-Fock method is lower than the other twos because this method calculates from doxorubicin optimized by AM1, because the HF/6-

31G method can optimize structure better than AM1 and PM3 methods. Then, the step optimization is lower than other methods but the molecule is most stable. Refer to appendix A1, the molecular energies optimized by B3LYP/6-31G//AM1, B3LYP/6-31G//PM3, and B3LYP/6-31G//HF/6-31G methods can calculate the relative energy in optimum product structure. The B3LYP/6-31G//HF/6-31G can optimize better than B3LYP/6-31G//AM1 and B3LYP/6-31G//PM3. The relative energy is calculated from B3LYP/6-31G//HF/6-31G method because this method has lowest of optimum molecular energy. From this simulation, the molecular energy from B3LYP/6-31G//HF/6-31G method is lower than B3LYP/6-31G//HF/PM3 and B3LYP/6-31G//HF/AM1 which relative energy form difference of B3LYP/6-31G//HF/6-31G in calculation are 18.72 and 21.23 kcal/mol, respectively. According to the lower molecular energy the molecular structure high stable, the HF/6-31G can optimize molecular structure better than AM1 and PM3 methods, respectively.

**Bond length optimization**

The bond length of the doxorubicin molecule from the simulation of semi-empirical AM1 and PM3 and *ab initio* HF/6-31G methods is shown in Table 3. The bond length is Armstrong unit (Å).

**Table 3** Equilibrium geometrical parameters of doxorubicin molecule from Figure 15 in the ground state.

| **Parameter** | **Semi-empirical** | | ***Ab initio*** |
|---|---|---|---|
| | **AM1** | **PM3** | **HF/6-31G** |
| C64 - H66 | 1.117 | 1.096 | 1.082 |
| C64 - O63 | 1.424 | 1.406 | 1.429 |
| C2 - O63 | 1.376 | 1.375 | 1.359 |
| C16 - O20 | 1.374 | 1.363 | 1.363 |
| C3 - C11 | 1.480 | 1.495 | 1.492 |
| C19 - C25 | 1.504 | 1.511 | 1.518 |
| C29 - C32 | 1.533 | 1.558 | 1.532 |
| C48 - N60 | 1.450 | 1.488 | 1.451 |
| O20 - H21 | 0.971 | 0.962 | 0.959 |
| N60 - H61 | 0.999 | 0.998 | 0.996 |
| C11 = O15 | 1.233 | 1.213 | 1.215 |
| C1 = = C2 | 1.405 | 1.404 | 1.389 |

The bond lengths of optimum doxorubicin structure calculated from these three methods are in the same range. The bond length of structure depends on electron density and dipole moment between atoms. If electron density and dipole moment increase, the bond length will decrease. From simulation, the length of delocalization bond is shorter than single bond but longer than double bond because the electron delocalization makes the bond length shorter.

**Dihedral angle optimization**

An example of dihedral angle of doxorubicin structures optimized by the AM1, PM3 and HF/6-31G methods are shown in Table 4.

**Table 4** Dihedral angle of doxorubicin structure optimized by AM1, PM3 and HF/6-31G methods

| Dihedral angle | AM1 | PM3 | HF/6-31G |
|---|---|---|---|
| H65-C64-O63-C2 | -65.1 | -66.2 | -66.2 |
| C2-C3-C11-O15 | 28.6 | 41.8 | 31.7 |
| C13-C17-O22-H23 | -167.0 | 178.6 | 145.4 |
| C50-C48-N50-H61 | -143.1 | -162.3 | -175.9 |
| O35-C32-C36-O39 | 131.4 | 106.6 | 126.5 |
| H9-C6-C5-H8 | -0.4 | 0.3 | 0.1 |
| C5-C4-C10-O14 | -20.0 | -21.7 | -9.8 |
| O28-C16-C18-C24 | 0.5 | 0.1 | 0.7 |
| C10-C4-C3-C11 | -3.5 | -6.6 | -7.8 |

One can see that the dihedral angles of doxorubicin structure optimized by these three methods are very close together. These angles are shown efficiency in simulation of three methods which can calculate nearly molecular structure. Although, the C13-C17-O22-H23 dihedral angle is negative in AM1 calculation but is positive in PM3 and HF/6-31G calculations. But, this angle is not more difference because the positive and negative show the plan of bond angle. The negative angle is chain of O22-H23 is under the plan in AM1 method but the positive angle is upper the molecular plan in the PM3 and HF/6-31G methods. The H9-C6-C5-H8 angle is the same case.

**Charge structure in doxorubicin**

Charge structure in molecule has an effect on molecular stability and molecular formation to other molecules. The charge structure of doxorubicin is studied from molecular optimization by AM1, PM3 and HF/6-31G methods shown in Figures 17, 18 and 19, respectively.

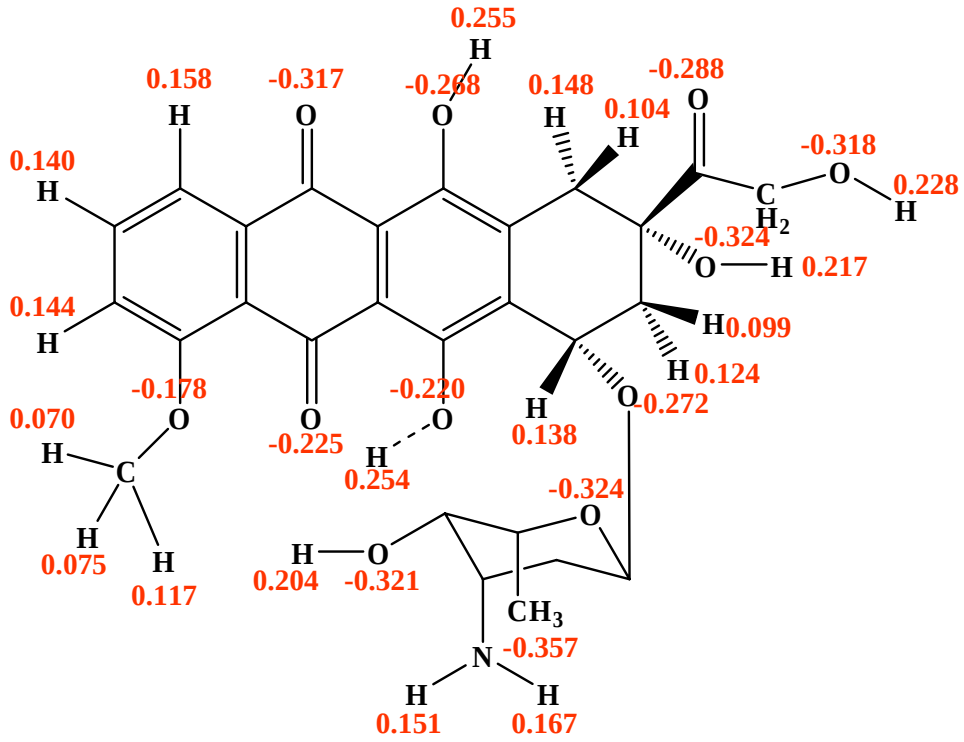



**Figure 17** Charge in doxorubicin molecule by AM1

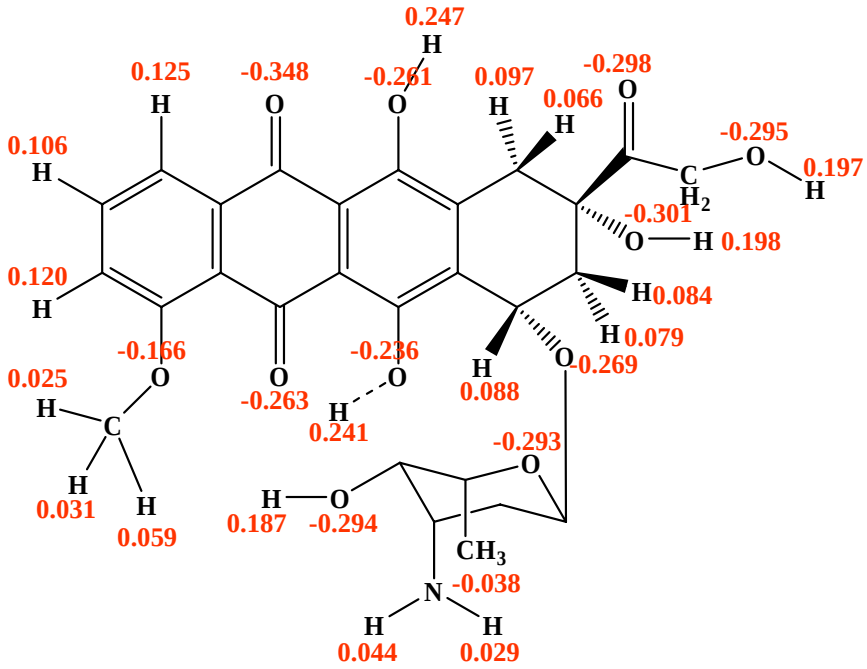



**Figure 18** Charge in doxorubicin molecule by PM3

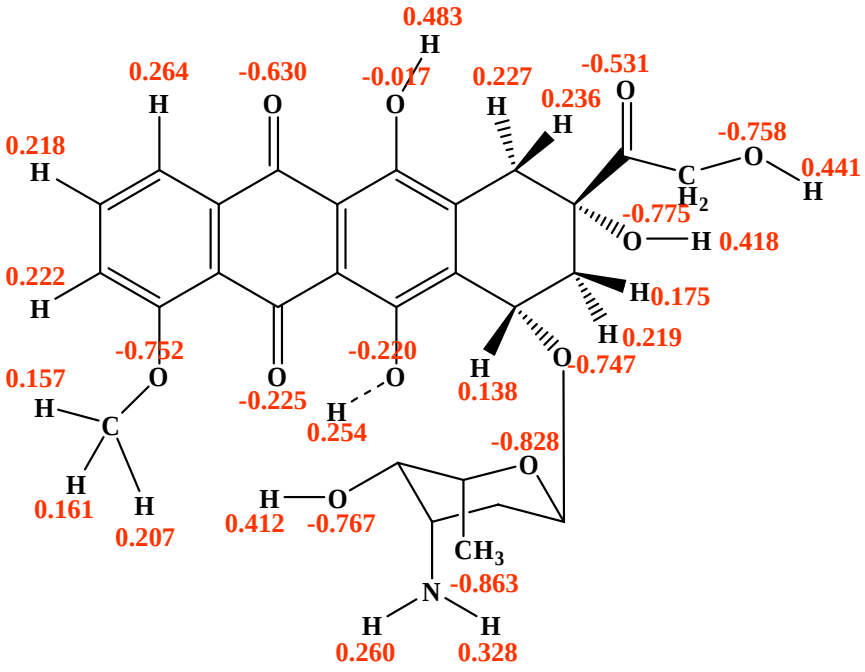



**Figure 19** Charge in doxorubicin molecule by HF/6-31G

The charge structure of optimum doxorubicin molecule calculated from semi-empirical method is lower than *ab initio* method because the semi-empirical method

neglects diatomic overlap. This diatomic overlap has an effect on charge structure and bond length in calculation. But, the charge structures and bond lengths from semi-empirical and *ab initio* methods have the same trend. The charge relates to electron density. The oxygen and nitrogen atom has a high electron density because these atoms have high electronegativity atom which can attract electron from lower electronegativity atoms in the molecule. Then, these atoms are negative charge. The hydrogen atom is positive charge because of this atom has low electronegativity. The hydrogen atom has low electron density, positive charge. The carbon atom can be positive and negative depending on dipole moment and electron density between atoms in molecule. From this simulation, the total charge of doxorubicin molecule is equal to zero. This electron density is enough to bind with the low electron density of other molecules such as micelle formation by consideration the negative charge of oxygen and nitrogen.

Notice from the optimization of doxorubicin molecule, the HF method can calculate to the optimum structure more than AM1 and PM3 methods. But the HF method uses computational time so more than semi-empirical. However, the optimum structure is the same trend from calculation by three methods.

**Glucosamine(ethylene glycol)**

The molecule of glucosamine(ethylene glycol) consists of glucosamine and ethylene glycol. The optimum structure of glucosamine(ethylene glycol) was simulated by three methods as mentioned earlier. The molecular structure optimization of glucosamine(ethylene glycol) from three methods gives the same optimum structure. This optimum structure is shown in Figure 20.

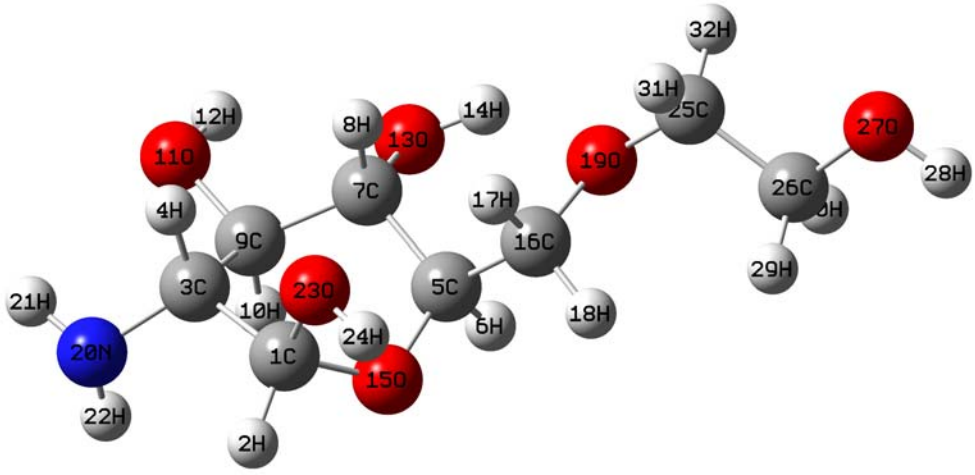



**Figure 20** Molecular structure of glucosamine(ethylene glycol) from simulations

**Molecular energy of glucosamine(ethylene glycol) in optimization**

Form simulation, the molecular energy of glucosamine(ethylene glycol) from molecular optimization shows that the total energy of optimum structure is lower than input structure. This simulation can be calculated from relative energy of molecular optimization between input and optimum molecule. The molecular energy is shown in Figure 21.

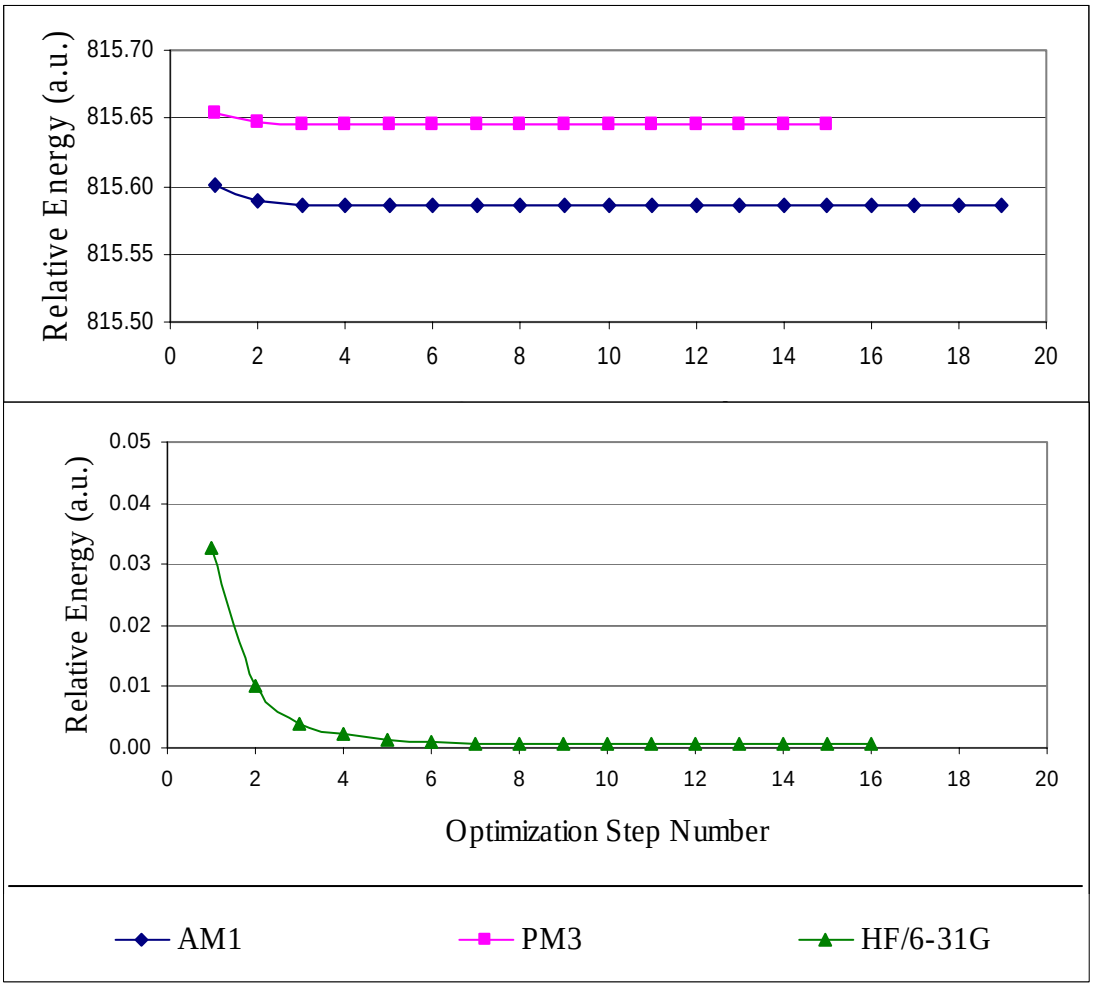



**Figure 21** Total energy of glucosamine(ethylene glycol) by AM1, PM3 and HF/6-31G optimization methods

The total energy of glucosamine(ethylene glycol) is optimized by AM1, PM3, HF/6-31G method. In AM1 method, the step optimization of glucosamine(ethylene glycol) structure is 19 steps which the stable structure of optimization is in the range of 6-19 steps. The relative energy between input and output from optimization is -0.015 a.u.. In PM3 method, the step optimization of glucosamine(ethylene glycol) structure is 15 steps which stable structure of optimization is in the range of 6-15 steps. The relative energy from optimization is -0.008 a.u.. In HF/6-31G method, the step optimization of glucosamine(ethylene glycol) structure is 16 steps which the stable structure is found in the range of 8-16 steps. The relative energy from optimization is -0.07 a.u.. The relative energy of difference from B3LYP/6-31G//HF/6-31G of B3LYP/6-31G//AM1 and B3LYP/6-31G//PM3 are 7.60 and 13.60 kcal/mol, respectively. From this simulation, the

method HF/6-31G can calculate better than AM1, and the AM1 method is better than PM3 methods.

**Bond length optimization**

The bond length of the glucosamine(ethylene glycol) molecule calculated by molecular simulation from semi-empirical AM1 and PM3 and *ab initio* HF/6-31G methods is shown in Table 5.

**Table 5** Equilibrium geometrical parameters of glucosamine(ethylene glycol) molecule from Figure 20 in the ground state

| **Parameter** | **Semi-empirical** | | ***Ab initio*** |
|---|---|---|---|
| | **AM1** | **PM3** | **HF/6-31G** |
| C3 - H4 | 1.134 | 1.121 | 1.079 |
| C1 - C3 | 1.552 | 1.555 | 1.534 |
| C3 - C9 | 1.548 | 1.549 | 1.529 |
| C1 - O23 | 1.409 | 1.401 | 1.420 |
| C1 - O15 | 1.415 | 1.410 | 1.426 |
| C3 - N20 | 1.445 | 1.482 | 1.452 |
| N20 - H22 | 1.002 | 0.999 | 0.998 |
| O11 - H12 | 0.967 | 0.948 | 0.953 |

The bond length of glucosamine(ethylene glycol) has only single bond which is C-C > C-N > C-O > C-H > N-H > O-H. According to the electronegativity in atom that is O > N > C > H, the electron in each atom has interaction between atom. The higher electronegativity atom can attract the electron from lower electronegativity atom and makes the bond length between atoms shorter. This effect makes electron density in the atom low. And the low electron density atom can bind with the high electron density molecule.

**Dihedral angle optimization**

From optimization of glucosamine(ethylene glycol), the dihedral angle calculated by three methods is shown in Table 6.

**Table 6** Dihedral angle of glucosamine(ethylene glycol) structure optimized by AM1, PM3 and HF/6-31G methods

| Dihedral angle | AM1 | PM3 | HF/6-31G |
|---|---|---|---|
| H21-N20-C3-1C | 169.9 | 164.2 | 157.9 |
| O11-C9-C7-O13 | -56.9 | -63.7 | -55.3 |
| C7-C5-C16-O19 | -62.5 | -73.1 | -56.8 |
| O19-C25-C26-O27 | 175.8 | 175.4 | -179.4 |
| C1-O15-C5-C16 | 93.9 | 89.0 | 104.4 |
| H22-H20-C3-H4 | 173.4 | 166.7 | 174.7 |
| H2-C1-O15-C5 | 175.6 | 166.7 | 174.2 |
| H6-C5-C16-O19 | 58.6 | 49.8 | 63.5 |
| H8-C7-C5-C16 | -30.1 | -20.1 | -39.8 |

The dihedral angle in the optimum structure of glucosamine(ethylene glycol) calculated by three methods shows nearly measurement of angle which three methods give the same structure. The dihedral angle of O19-C25-C26-O27 is the same reason in doxorubicin structure.

**Charge structure in glucosamine(ethylene glycol)**

Charge of molecule has an effect on stability and formation with other molecules. The charge structure of glucosamine(ethylene glycol) is studied from optimum molecule by three simulation methods shown in Figures 22, 23 and 24.

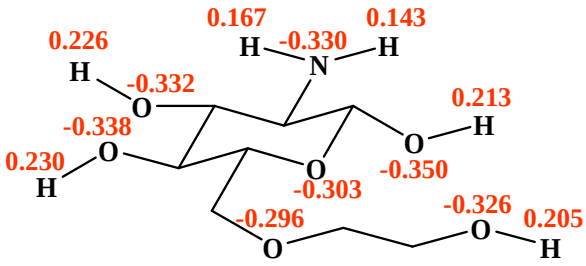



**Figure 22** Charge in glucosamine(ethylene glycol) molecule from optimization by AM1

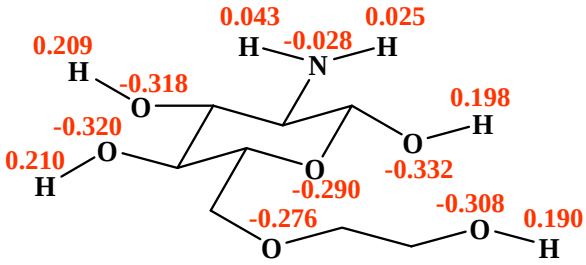



**Figure 23** Charge in glucosamine(ethylene glycol) molecule from optimization by PM3

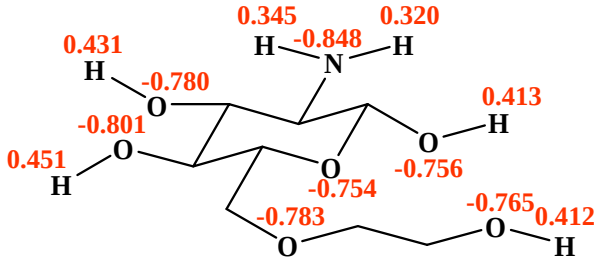



**Figure 24** Charge in glucosamine(ethylene glycol) molecule from optimization by HF/6-31G

The glucosamine(ethylene glycol) molecule contains two parts; glucosamine part and ethylene glycol. This charge of optimum glucosamine(ethylene glycol) structure calculated from semi-empirical is lower than *ab initio* method. The charge structure depends on electron density. The total charge of glucosamine(ethylene glycol) molecule is equal to zero. From these simulations, the electron density of hydrogen atom which bonds with oxygen atom is lower than bonds with nitrogen atom. The oxygen atom can attract the electron more than nitrogen. This hydrogen with low electron density can be bound with the molecule having high electron density such as oxygen atoms in doxorubicin molecule.

From the geometrical optimization, the molecule of doxorubicin and glucosamine(ethylene glycol) calculated by semi-empirical AM1 and PM3 methods and *ab initio* in HF method. Three methods calculate the same optimum structure. Then, the AM1, PM3 and HF methods can use to study the interaction of di glucosamine with $H_3O^+$, $H_2O$ and $OH^-$ in acid, normal and base condition, respectively. But, the HF method use more the computational time. So, the interaction of di glucosamine is study by semi-empirical AM1 and PM3 methods in drug release section.

## Drug release from capsule

Releasing of drug from capsule glucosamine(ethylene glycol) is associated with polymer bond breaking of glucosamine(ethylene glycol) oligomers reaction. The estimation of reaction can calculate from relative energy between total molecular energy of product and total molecular energy of reactant. This simulation showed that the condition in solution can break polymer bond of glucosamine(ethylene glycol) oligomers capsule in acid, normal, and base conditions. This simulation study consists of two steps. The first step is optimization molecular structure by semi-empirical AM1 and PM3 method. The second step calculates the molecular energy by *ab initio* HF/B3LYP/6-31G.

### In acid condition

This section studies the effect of polymer bond breaking in acid solution. The assumptions are 1) using di glucosamine(ethylene glycol) represents glucosamine(ethylene glycol) oligomers and 2) using $H_3O^+$ (Hydronium ion) represents acid condition. The glucosamine(ethylene glycol) oligomers are replaced by di glucosamine(ethylene glycol) because this study focuses on polymer bond breaking between monomers. The $H_3O^+$ can be considered as the acid condition because of hydronium ion interaction.

#### Reaction mechanism

The mechanism in this acid condition consists of reactant condition, transition state, and the product. The reaction mechanism is illustrated in Figure 25.

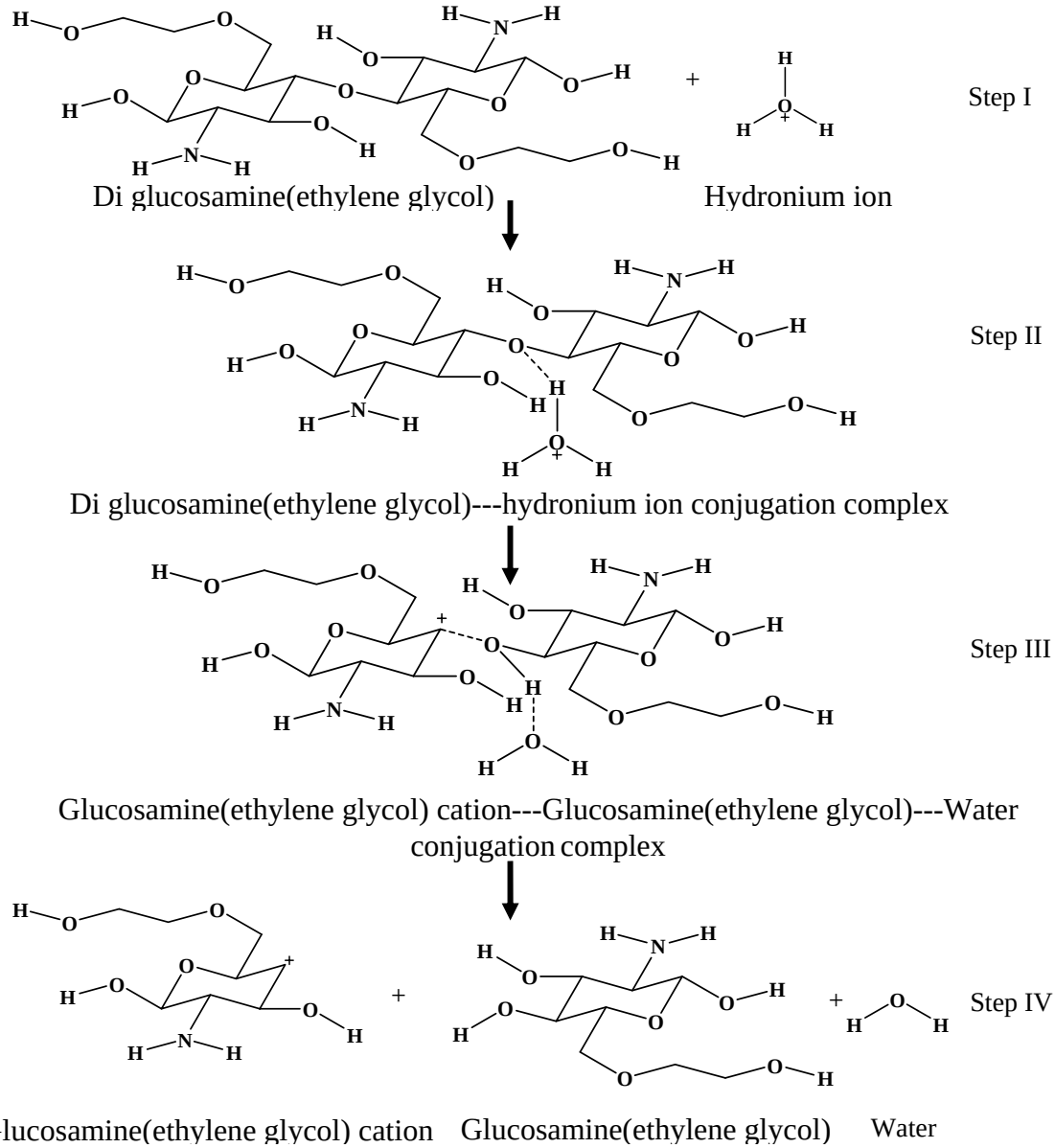



**Figure 25** Reaction mechanism of di glucosamine(ethylene glycol) in acid condition

This reaction has four continuous steps. In the first step, the hydronium ion attracts di glucosamine(ethylene glycol) at the polymer bond. The hydrogen atom in hydronium ion interacts with the oxygen atom in polymer bond of di glucosamine(ethylene glycol) called “Transition state” in the second step. This reaction occurs from high electron density of oxygen at polymer bond and low electron density of hydronium ion. The molecules of di glucosamine(ethylene glycol) and hydronium ion form complex structure. In the third step, this reaction generates the glucosamine(ethylene glycol), glucosamine(ethylene glycol) cation, and water molecules in complex formation. In the last step, the product molecules from reaction do not interact and separate from each other.

There are three different molecules in this final step; glucosamine(ethylene glycol) cation, glucosamine(ethylene glycol), and water. The relative energy of di glucosamine(ethylene glycol) in acid solution is concluded in Table 7.

**Table 7** Relative energy of di glucosamine(ethylene glycol) in acid solution

| **Substances in reaction** | **Relative energy (kcal/mol)** | |
|---|---|---|
| | **B3LYP/6-31G//AM1** | **B3LYP/6-31G//PM3** |
| Di glucosamine(ethylene glycol) + $H_3O^+$ | 0.00 | 0.00 |
| Di glucosamine(ethylene glycol)--- $H_3O^+$ | 176.58 | 145.51 |
| Glucosamine(ethylene glycol)--- Glucosamine(ethylene glycol) cation---Water | -49.46 | -92.61 |
| Glucosamine(ethylene glycol) + Glucosamine(ethylene glycol) cation + Water | 18.58 | -7.29 |

The relative energy of di glucosamine(ethylene glycol) with acid reaction can be defined in Figure 26.

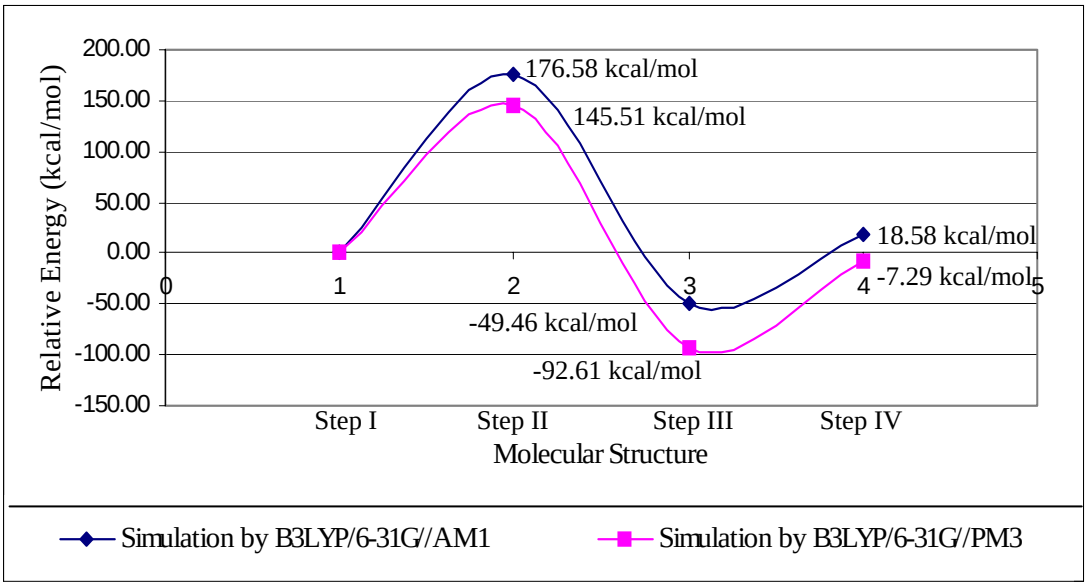



**Figure 26** Relative energy curve of reaction mechanism of di glucosamine(ethylene glycol) in acid condition containing four steps in molecular structure:

1. Di glucosamine(ethylene glycol) is attracted by hydronium ion.
2. Di glucosamine(ethylene glycol) and hydronium ion form complex.
3. Product complex contains glucosamine(ethylene glycol), glucosamine (ethylene glycol) cation, and water.
4. The products do not interaction.

Table 7 shows the possibility of reaction considered from relative energy in each reaction step. This reaction mechanism is simulated by B3LYP/6-31G//AM1 and B3LYP/6-31G//PM3 methods. The possibility of reaction is explained by the relative energy. If the relative energy is negative, the product has possibility to occur. When, the molecular energy increases which the molecular structure is more stable. This relative energy in each step is calculated by difference of molecular energy in step I. In step I, the molecules are reactants. The relative energy in the transition step is more than the first step because the hydronium ion needs energy to react with glucosamine(ethylene glycol). This energy is called “activated energy”. These relative energies are 176.58 and 145.51 kcal/mol from B3LYP/6-31G//AM1 and B3LYP/6-31G//PM3 methods, respectively. The relative energy of product must be considered by two structures. The first structure is the product complex of glucosamine(ethylene glycol), glucosamine(ethylene glycol) cation, and water. The relative energies are -49.46 and -92.61 kcal/mol from B3LYP/6-31G//AM1

and B3LYP/6-31G//PM3 methods, respectively. These negative sign relative energies imply that the complex molecule tries to adjust itself into more stable structure. In step IV, the product molecules have no interaction. This relative energy is 18.58 and -7.29 kcal/mol from B3LYP/6-31G//AM1 and B3LYP/6-31G//PM3 methods, respectively. The interaction between other molecules makes structure more stable. From simulation, the product has possibility to form in product complex (in step III) because the non interaction of product structure (in step IV) has high molecular energy. The stability of this structure is lower than product in complex structure (in step III).

This reaction can occur from difference of low electron density in hydrogen atom of hydronium ion molecule and high electron density in oxygen atom at polymer bond. An electron from oxygen atom attracts hydrogen atom of hydronium ion to generate the glucosamine(ethylene glycol) molecule. According to the results, there is a possibility of polymer bond breaking in acid condition because the relative energy of product is lower than the reactant calculated by B3LYP/-31G//PM3 method. The product complex has the relative energy lower than the non interaction of product because the interaction makes more stable molecular structure. This interaction is H-bond by using Van der Waal's force. This force helps complex structure to form stable molecule.

**In normal condition**

This section will study the effect of polymer bond breaking in normal solution. Assumptions of this simulation consist of using di glucosamine(ethylene glycol) as glucosamine(ethylene glycol) oligomers and $H_2O$ as normal condition.

**Reaction mechanism**

The mechanism of reaction involves the reactants condition, the transition state, and the product as shown in Figure 27.

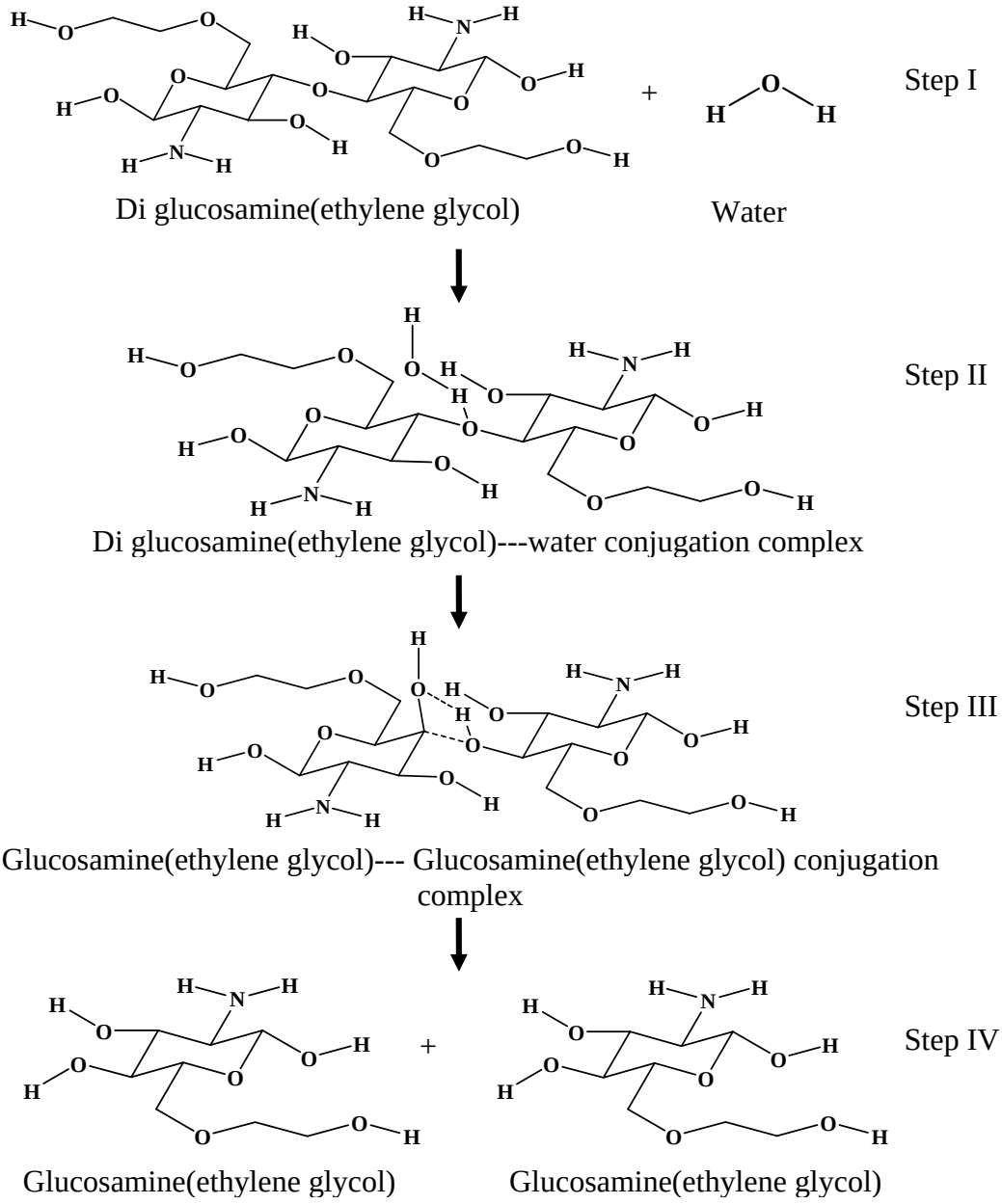



**Figure 27** Reaction mechanism of di glucosamine(ethylene glycol) in normal condition

This reaction contains four steps. Beginning with the water molecule ($H_2O$) attracts di glucosamine(ethylene glycol) at the polymer bond. In the second step, the hydrogen atom in water molecule interacts with the oxygen atom in polymer bond of di glucosamine(ethylene glycol), called this step “Transition state”. This step is the lower electron density of hydrogen in water molecule is interacted from high electron density of oxygen atom in polymer bond and the oxygen of water interacts with carbon atom in glucosamine molecule. The molecules of di glucosamine(ethylene glycol) and $H_2O$ form complex structure. In the third step, the complex structure rearranges molecular structure

to most stability structure. This reaction generates the two molecule of glucosamine(ethylene glycol) in complex formation. In the last step, the glucosamine(ethylene glycol) molecules do not interact. But, the molecular structure is most stable in step III. The relative energy of di glucosamine(ethylene glycol) in water solution is shown in Table 8.

**Table 8** Relative energy of di glucosamine(ethylene glycol) in water solution

| **Substances in reaction** | **Relative energy (kcal/mol)** | |
|---|---|---|
| | **B3LYP/6-31G//AM1** | **B3LYP/6-31G//PM3** |
| Di glucosamine(ethylene glycol) + $H_2O$ | 0.00 | 0.00 |
| Di glucosamine(ethylene glycol)---$H_2O$ | 166.60 | 135.78 |
| Glucosamine(ethylene glycol)---Glucosamine(ethylene glycol) | -9.62 | -17.16 |
| Glucosamine(ethylene glycol) + Glucosamine(ethylene glycol) | -0.25 | -19.93 |

The relative energy of di glucosamine(ethylene glycol) with water reaction can define in Figure 28.

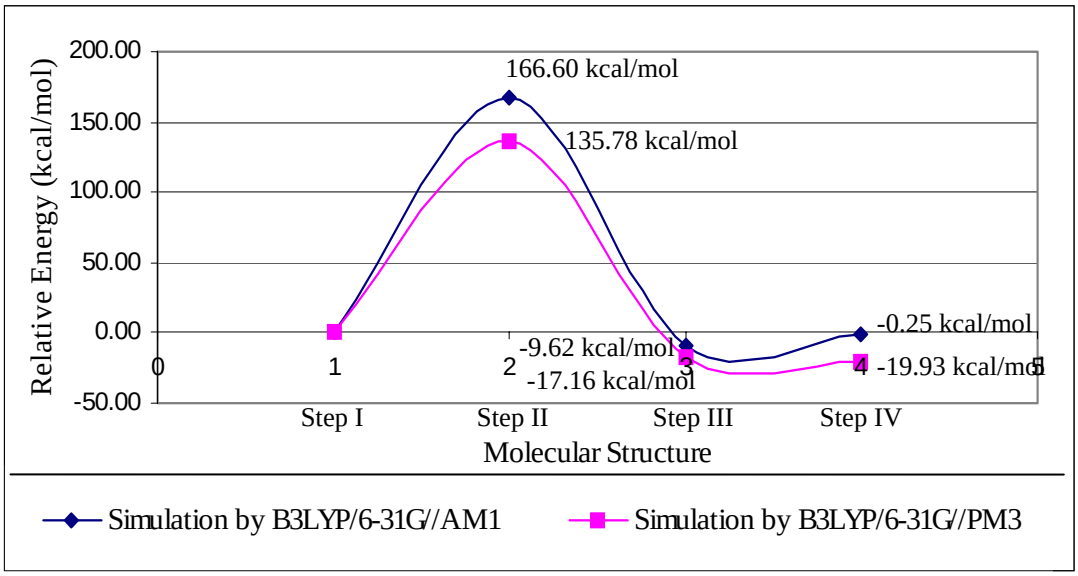



**Figure 28** Relative energy curve of reaction mechanism of di glucosamine (ethylene glycol) in normal condition containing four steps in molecular structure:

1. Diglucosamine(ethylene glycol) was attracted by water.
2. Diglucosamine(ethylene glycol) forms complex with water.
3. Product complex contains glucosamine(ethylene glycol), glucosamine (ethylene glycol) cation, and water.
4. Total energy of product such as glucosamine(ethylene glycol), glucosamine(ethylene glycol) cation, and water.

Table 7 shows the relative energy in the reaction step. In the transition step, the relative activated energies are 166.60 and 135.78 kcal/mol from B3LYP/6-31G//AM1 and B3LYP/6-31G//PM3 methods, respectively. The relative energy of product is considered from two structures. The first structure is the complex product containing two molecules of glucosamine(ethylene glycol). The relative energies are -9.62 and -17.16 kcal/mol. The second structure is the glucosamine(ethylene glycol) molecules with non-interaction between molecules. The relative energies are -0.25 and -19.93 kcal/mol from these two methods, respectively.

From this study in normal condition, the glucosamine(ethylene glycol) can occur from polymer bond breaking of di glucosamine(ethylene glycol) by interaction of $H_2O$ molecule because the relative energy of product (in step III) is lower than reactants (in step I). This effect from electron in oxygen atom at polymer bond attracts the hydrogen atom of

water and electron in oxygen atom of water interacts carbon atom of glucosamine molecule. This complex is easy to break polymer bond to occur the glucosamine(ethylene glycol) two molecules.

**In base condition**

This section studies polymer bond breaking in the base solution. The simulation uses di glucosamine(ethylene glycol) as glucosamine(ethylene glycol) oligomers and $OH^-$ to form the base condition. Using of $OH^-$ (hydroxide ion) insteads of base condition because the hydroxide ion in solution is a molecular activator.

Two types of reaction can occur in the base solution. In the first type, the hydroxide ion interacts with polymer bond. The hydroxide ion interacts with ethylene glycol in the second type. Consider the first reaction, hydroxide ion attracts oxygen in polymer bond but this molecule has very high electron density which has steric with the hydroxide ion to interaction. Hydroxide ion in the second type reaction attracts di glucosamine(ethylene glycol) at ethylene glycol by trapping hydrogen from ethylene glycol.

**Hydroxide ion attract polymer bond**

The reaction of di glucosamine(ethylene glycol) in base condition occurs by the interaction of the hydroxide ion with polymer bond. The mechanism is shown in Figure 29.

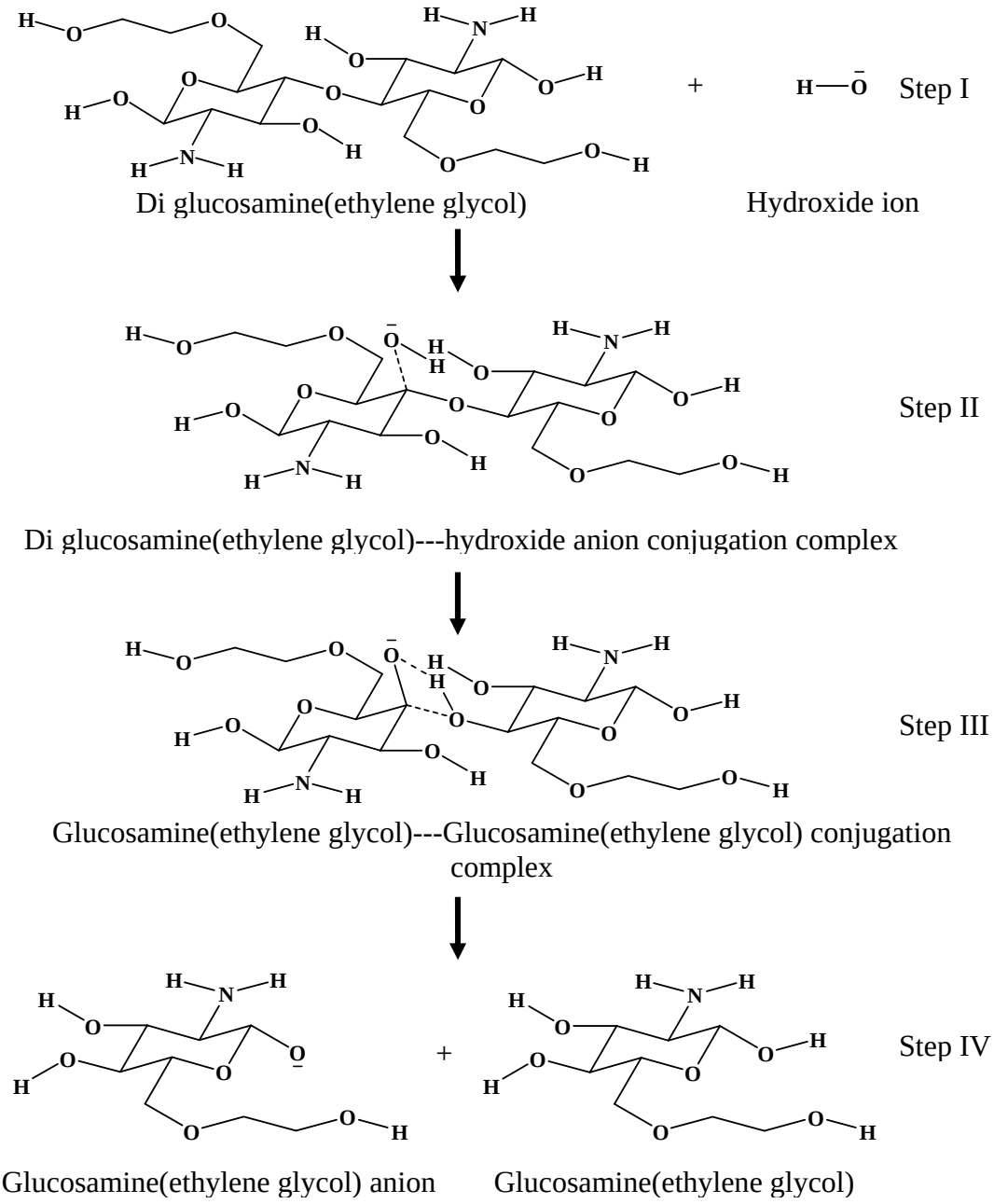



**Figure 29** Reaction mechanism of di glucosamine(ethylene glycol) in base condition; breaking at polymer bond of glucosamine(ethylene glycol) monomer

There are four step reactions. First step begins with the attraction of the $OH^-$ molecule di glucosamine(ethylene glycol) at the polymer bond. In the second step, the hydrogen atom of hydroxide ion interacts with the oxygen atom in the polymer bond. The oxygen of hydroxide interacts with carbon atom of glucosamine molecule. This step is "Transition state". The molecules of di glucosamine(ethylene glycol) and $OH^-$ form

complex structure as shown in the this figure. In the third step, this reaction generates glucosamine(ethylene glycol) and glucosamine(ethylene glycol) anion molecules in a complex formation. In the last step, glucosamine(ethylene glycol) and glucosamine(ethylene glycol) anion do not have an interaction. The relative energy of di glucosamine(ethylene glycol) in base solution is shown in Table 9.

**Table 9** Relative energy of di glucosamine(ethylene glycol) in base solution

| **Substance in reaction** | **Relative energy (kcal/mol)** | |
|---|---|---|
| | **B3LYP/6-31G//AM1** | **B3LYP/6-31G//PM3** |
| Di glucosamine(ethylene glycol) + $OH^-$ | 0.00 | 0.00 |
| Di glucosamine(ethylene glycol)---$OH^-$ | 257.57 | 287.60 |
| Glucosamine(ethylene glycol)--- Glucosamine(ethylene glycol) anion | -77.45 | -108.43 |
| Glucosamine(ethylene glycol) + Glucosamine(ethylene glycol) anion | -53.29 | -89.33 |

The relative energy of di glucosamine(ethylene glycol) with water reaction can define in Figure 30.

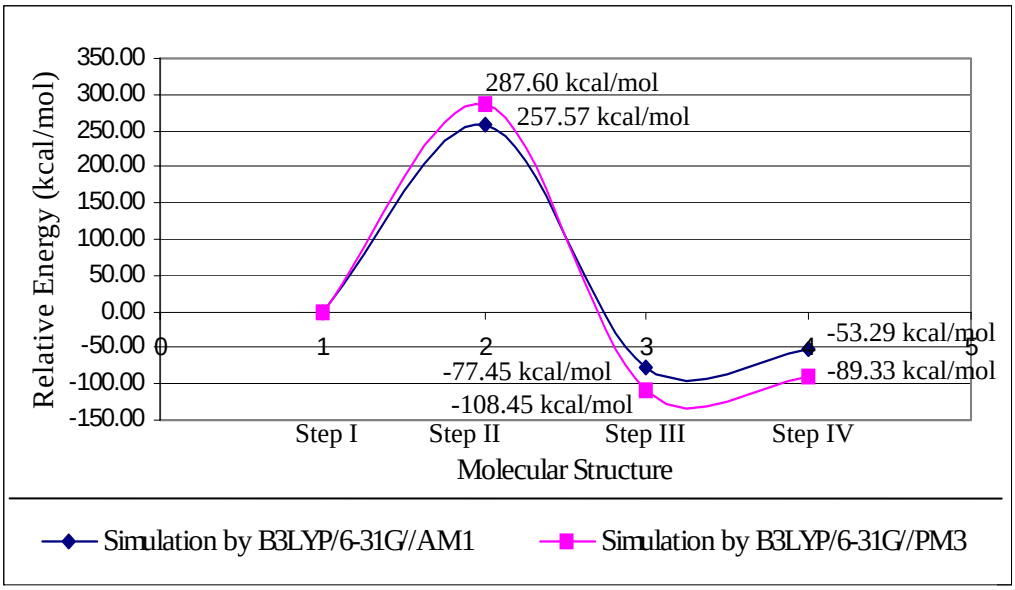



**Figure 30** Relative energy curve of reaction mechanism of di glucosamine (ethylene glycol) in base condition containing four steps in molecular structure:

1. Di glucosamine(ethylene glycol) is attracted by hydroxide ion.
2. Di glucosamine(ethylene glycol) forms complex with hydroxide ion.
3. Product complex contains glucosamine(ethylene glycol), and glucosamine (ethylene glycol) anion.
4. Total energy of product such as glucosamine(ethylene glycol), and glucosamine(ethylene glycol) anion.

Table 9 shows the relative energy in the reaction step. In the transition step, the relative activated energies are 257.57 and 287.60 kcal/mol from B3LYP/6-31G//AM1 and B3LYP/6-31G//PM3 methods, respectively. The relative energy of product is considered from two structures. The first structure is product complex containing with two molecules of glucosamine(ethylene glycol). The relative energies are -77.45 and -108.43 kcal/mol, respectively. The second structure is the noninteraction glucosamine(ethylene glycol) molecules. This relative energy is -53.29 and -89.33 kcal/mol from B3LYP/6-31G//AM1 and B3LYP/6-31G//PM3 methods, respectively.

From this simulation, the transition state needs the high activated energy. The reaction is difficult to occur, and then the glucosamine(ethylene glycol) might not break polymer bond in base solution. According to interaction of electron, the electron of

hydroxide ion and oxygen atom make hydroxide molecule difficult to attract oxygen atom at polymer bond.

**Hydroxide ion attracts H of ethylene glycol group in glucosamine(ethylene glycol)**

The reaction of di glucosamine(ethylene glycol) in base condition was interacted by the hydroxide ion with hydrogen of ethylene glycol in di glucosamine(ethylene glycol) molecule. The reaction mechanism of di glucosamine(ethylene glycol) in normal condition is shown in Figure 31.

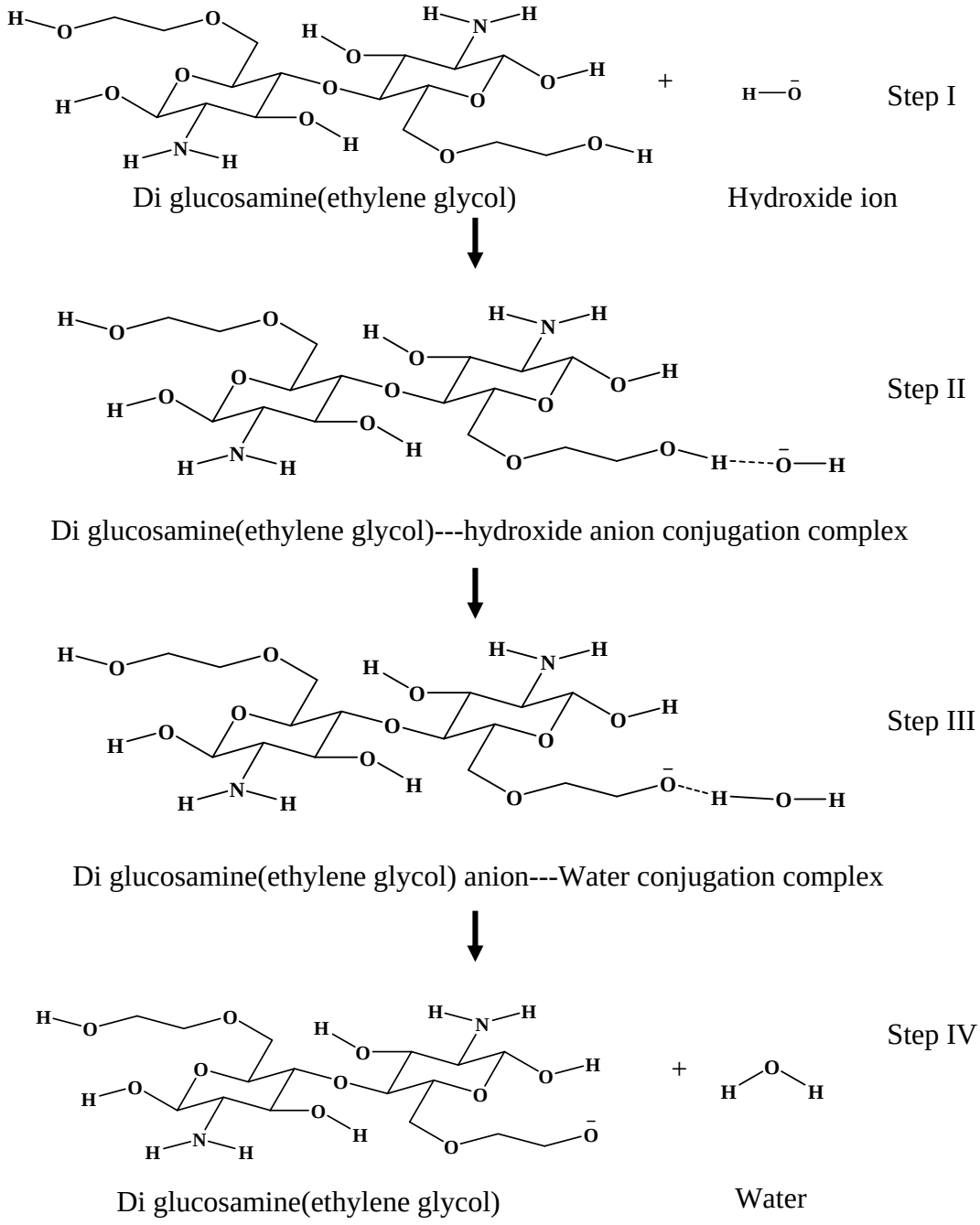



**Figure 31** Reaction mechanism of di glucosamine(ethylene glycol) in normal condition; reaction with ethylene glycol

This reaction contains four steps. In the first step, the $OH^-$ molecule attracts di glucosamine(ethylene glycol) at the polymer bond. In the second step called “Transition state”, the oxygen atom of hydroxide ion interacts with the hydrogen of ethylene glycol in di glucosamine(ethylene glycol). The molecules of di glucosamine(ethylene glycol) and $OH^-$ form complex structure. In the third step, this reaction generates the

glucosamine(ethylene glycol) anion and water in complex formation. In the last step, the di glucosamine(ethylene glycol) anion and water do not interact to each other. The relative energy of di glucosamine(ethylene glycol) in base solution is shown in Table 10.

**Table 10** Relative energy of di glucosamine(ethylene glycol) in base solution

| **Substances in reaction** | **Relative energy (kcal/mol)** | |
|---|---|---|
| | **B3LYP/6-31G//AM1** | **B3LYP/6-31G//PM3** |
| Di glucosamine(ethylene glycol) + $OH^-$ | 0.00 | 0.00 |
| Di glucosamine(ethylene glycol)--- $OH^-$ | -47.84 | -78.83 |
| Di glucosamine(ethylene glycol) anion---Water | -78.33 | -82.64 |
| Di glucosamine(ethylene glycol) anion +Water | -38.62 | -62.01 |

The relative energy of di glucosamine(ethylene glycol) with water reaction can define in Figure 32.

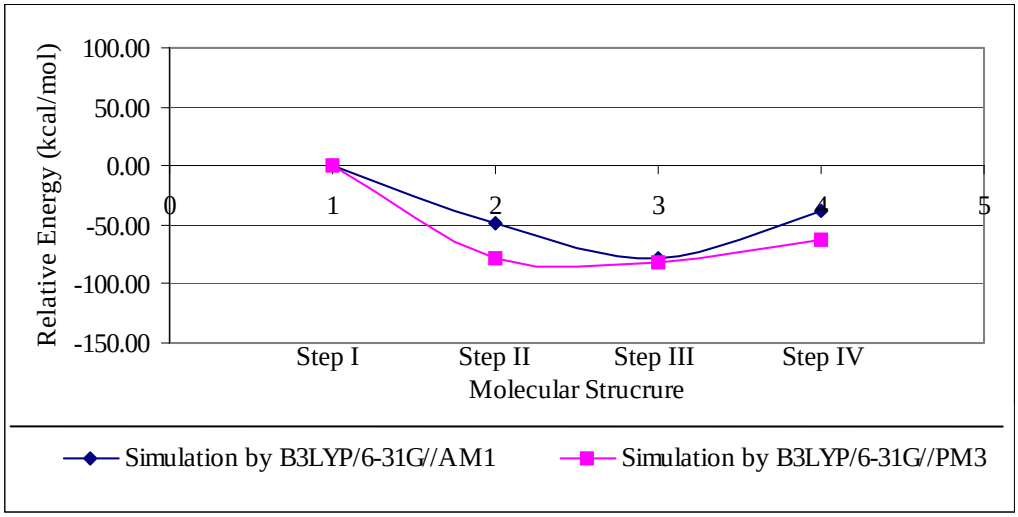



**Figure 32** Relative energy curve of reaction mechanism of di glucosamine (ethylene glycol) in base condition containing four steps in molecular structure:

1. Di glucosamine(ethylene glycol) was attracted by hydroxide ion.
2. Di glucosamine(ethylene glycol) forms complex with hydroxide ion.
3. Product complex contains glucosamine(ethylene glycol), and glucosamine ethylene glycol) anion.
4. Total energy of product such as glucosamine(ethylene glycol), and glucosamine(ethylene glycol) anion.

Table 10 shows the relative energy in the reaction step. In the transition step, the relative activated energies are -47.84 and -78.83 kcal/mol from B3LYP/6-31G//AM1 and B3LYP/6-31G//PM3 methods, respectively. The relative energy of product is considered from two structures. The first structure is a product complex containing glucosamine(ethylene glycol) anion and water molecule. The relative energies are -78.33 and -82.64 kcal/mol. The second structure is the glucosamine(ethylene glycol) molecules which do not interact between molecules. The relative energies are -38.62 and -62.01 kcal/mol, respectively.

**Condition effect to drug releasing from capsule polymer**

The relative energies in transition state and complex product from the reactions in acid, normal, and base conditions show an effect on breaking polymer bond of di glucosamine(ethylene glycol) because the reaction in solution needs activated energy to

generate reaction. If the activated energy is low, reaction is easy. For product, the possibility of reactions is studied from relative energy of complex product because the product molecules have significant distance to form an interaction. If complex product has lower relative energy, the molecule is more stable.

These simulations show the relative energy from Tables 7 to 10. In acid condition, hydronium ion can attract the polymer bond of di glucosamine(ethylene glycol) and break bond of polymer to make drug released from capsule glucosamine(ethylene glycol). In normal solution, water can attract the polymer bond and break bond as the study of activated energy. From this simulation, the relative energies of transition state in acid and normal conditions are closely. However, the relative energy of product complex in normal condition is higher than in acid condition which the polymer bond can be broken in acid easier than normal condition. This simulation agrees with (Oungbho *et al*. 1997) that drug release from chitosan in acid is better than normal condition. In base condition, hydroxide ion can attract hydrogen better than oxygen in polymer bond. Hence, capsule glucosamine(ethylene glycol) cannot release the drug in base condition.

## Micelle formation

From the charge structure, the molecules of glucosamine(ethylene glycol) and doxorubicin can form the micelle structure. The micelle formation of glucosamine(ethylene glycol) and doxorubicin molecules is the drug delivery by ethylene glycol as a carrier. The molecule of poly(ethylene glycol) can be used in block co-polymer in micelle delivery. Then, the ethylene glycol chain may help the glucosamine(ethylene glycol) on micelle formation with doxorubicin. After study micelle formation, the molecular energy of glucosamine(ethylene glycol) is studied by varying the ethylene glycol chain for estimation in micelle formation.

### Effect of amount of ethylene glycol in the glucosamine(ethylene glycol) oligomers

This section studies the chain effect of the ethylene glycol from 1, 2 and 3 monomers and 5 monomer for poly(ethylene glycol). From estimation, the length of ethylene glycol in glucosamine(ethylene glycol) molecule affects the micelle formation

because of stability of glucosamine(ethylene glycol) from increasing of molecular energy in Table 11. If length of poly(ethylene glycol) increases, the molecular energy will decrease. The lower molecular energy, the higher molecular structure can be obtained. The structure of poly(ethylene glycol) in glucosamine(ethylene glycol) is shown in Figure 33.

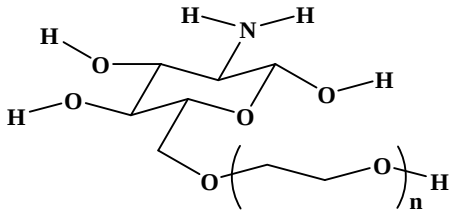


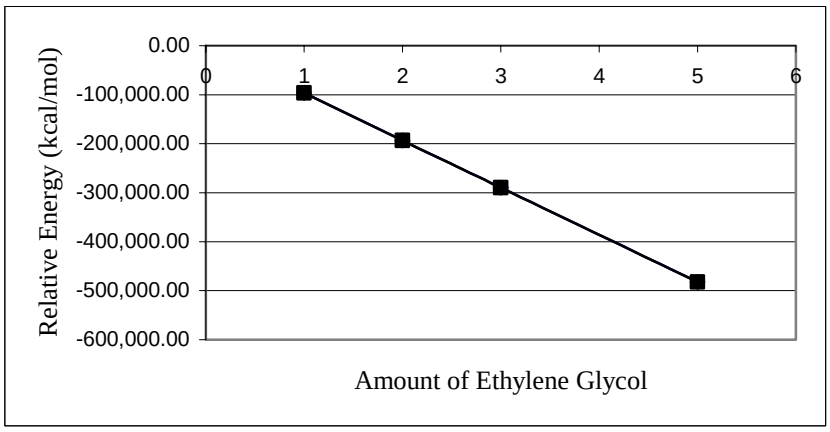
**Figure 33** Structure of poly(ethylene glycol) in glucosamine molecule
where n is amount of ethylene glycol group.

From molecular simulation, the molecular energy of glucosamine(ethylene glycol) relates with amount of ethylene glycol group. The relative energy of micelle formation is shown in Table 11.

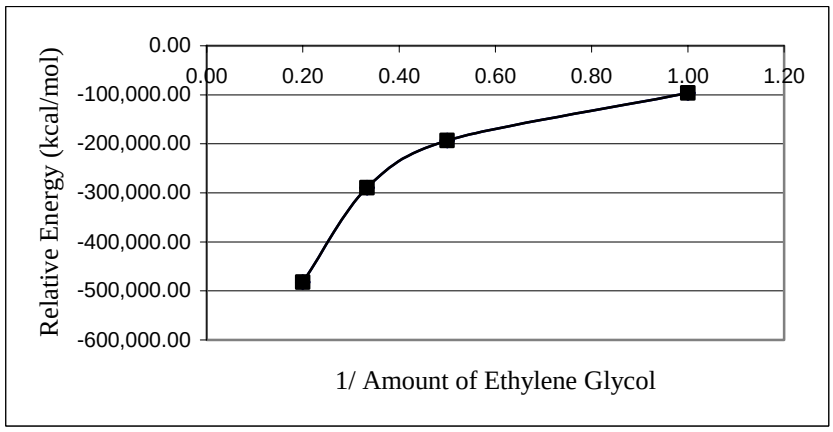
**Table 11** Relative energy of poly(ethylene glycol) in glucosamine molecule

| Amount of ethylene glycol | 1/(Amount of ethylene glycol) | Relative energy (kcal/mol) | |
|---|---|---|---|
| | | B3LYP/6-31G//AM1 | B3LYP/6-31G//PM3 |
| 0 | - | 0.00 | 0.00 |
| 1 | 1.00 | -96,496.48 | -96,516.09 |
| 2 | 0.50 | -192,989.80 | -193,001.03 |
| 3 | 0.33 | -289,493.77 | -289,494.65 |
| 5 | 0.20 | -482,490.93 | -482,490.93 |

From Table 10, the relative energy of glucosamine(ethylene glycol) is shown in Figure 34.




(a)




(b)

**Figure 34** Relative molecular energy of glucosamine(ethylene glycol) relate with ethylene glycol group

From molecule of glucosamine(ethylene glycol) simulation, if length of ethylene glycol chain increases, the molecular energy of glucosamine(ethylene glycol) decreases because of molecular stability. From this simulation, the ethylene glycol chain can help glucosamine(ethylene glycol) on micelle formation with doxorubicin.

**Micelle formation mechanism**

From molecular structure of glucosamine(ethylene glycol) and doxorubicin from simulation, they can form complex structure of micelle formation by hydrogen bonding linkage between glucosamine(ethylene glycol) and doxorubicin. The molecule of glucosamine(ethylene glycol) consists of hydrophobic and hydrophilic parts. Hydrophobic part is glucosamine and hydrophilic part is ethylene glycol molecule. In the part of

hydrophobic, the molecules of glucosamine catch doxorubicin by H-bond. On the other hands, the molecule of ethylene glycol can dissolve in water because of hydrophobic behavior.

The simulation of micelle formation was calculated by B3LYP/6-31G//PM3 in Appendix D. The PM3 method calculates the interaction with H-bond better AM1 method and uses computational time less than HF and B3LYP methods in molecular optimization. The micelle formation is considered from charge structure of doxorubicin and glucosamine(ethylene glycol). The doxorubicin and glucosamine(ethylene glycol) molecules are optimized by PM3 method as shown in Figure 35 and 36.

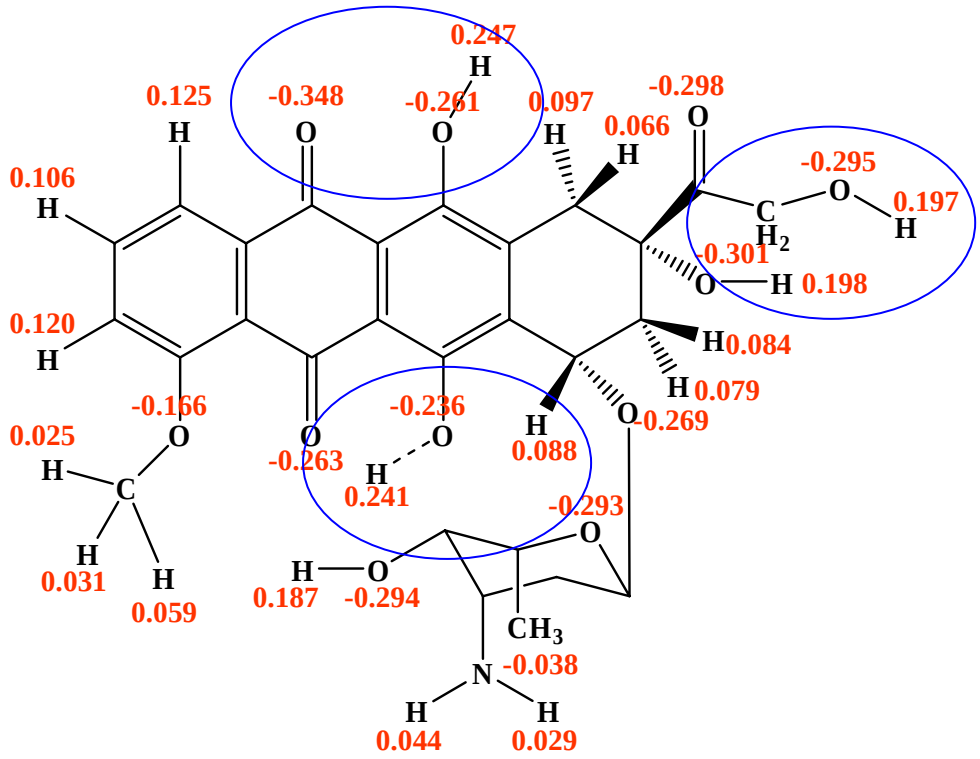



**Figure 35** Position of doxorubicin to micelle formation by H-bond with glucosamine (ethylene glycol) by semi-empirical PM3 method

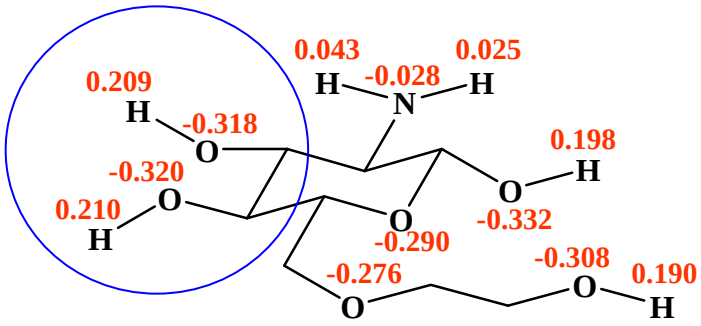



**Figure 36** Position of glucosamine(ethylene glycol) to micelle formation by H-bond with glucosamine(ethylene glycol) by semi-empirical PM3 method

The charge structure of doxorubicin has strongly negative charge. The H-bond can occur between doxorubicin and glucosamine(ethylene glycol) such as O-H and N-H hydrogen bond. This simulation calculates from electron density explained by charge structure. The negative charge at oxygen atoms in doxorubicin interacts with hydrogen atoms in glucosamine(ethylene glycol). The charge characteristics are calculated from high negative of doxorubicin and high positive of glucosamine(ethylene glycol) interaction, because the high electron density atom can share electron to the low electron density atom. The doxorubicin structure has three hi electron density position. The glucosamine(ethylene glycol) has hydrogen atom, which is low electron density. In this research, the micelle formation consists of amount of glucosamine(ethylene glycol) and chain of ethylene glycol. The amount of glucosamine(ethylene glycol) was studied by addition one by one of glucosamine(ethylene glycol) interact with doxorubicin one molecule. Chain of the ethylene glycol was studied by varying amount of ethylene glycol in the glucosamine(ethylene glycol) molecule. These molecules optimized by semi-empirical PM3 method can be shown in Figure 37.

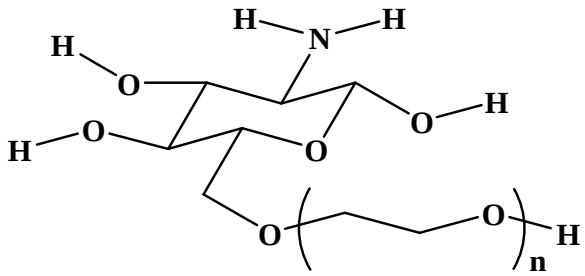



**Figure 37** Molecular structure of glucosamine(ethylene glycol)
Where n = 1; glucosamine-mono(ethylene glycol)
n = 2; glucosamine-di(ethylene glycol)
n = 3; glucosamine-tri(ethylene glycol)
n = 4; glucosamine-tetra(ethylene glycol)
n = 5; glucosamine-penta(ethylene glycol)

The micelle formation was calculated by B3LYP/6-31G//PM3 in order to find the relative energy of possibility of reaction. The relative energy of micelle formation was calculated from various amounts of glucosamine(ethylene glycol) molecule and ethylene glycol group in the glucosamine(ethylene glycol) as shown in Table 12.

**Table 12** Relative energy of micelle formation by B3LYP/6-31G//PM3 method calculation

| **monomer from capsule polymer** | **Relative energy of micelle formation (kcal/mol)** | | |
|---|---|---|---|
| | **1 monomer** | **2 monomer** | **3 monomer** |
| glucosamine-mono(ethylene glycol) | -6.99 | -12.65 | -15.32 |
| glucosamine-di(ethylene glycol) | -7.10 | -12.52 | -14.58 |
| glucosamine-tri(ethylene glycol) | -6.97 | -12.70 | -15.56 |
| glucosamine-penta(ethylene glycol) | -6.37 | -13.44 | -16.65 |

This micelle formation structure is related to the amount of glucosamine(ethylene glycol) and ethylene glycol group in glucosamine(ethylene glycol) molecule. The relationship between relative energy of micelle formation and amount of glucosamine(ethylene glycol) is shown in Figure 38.

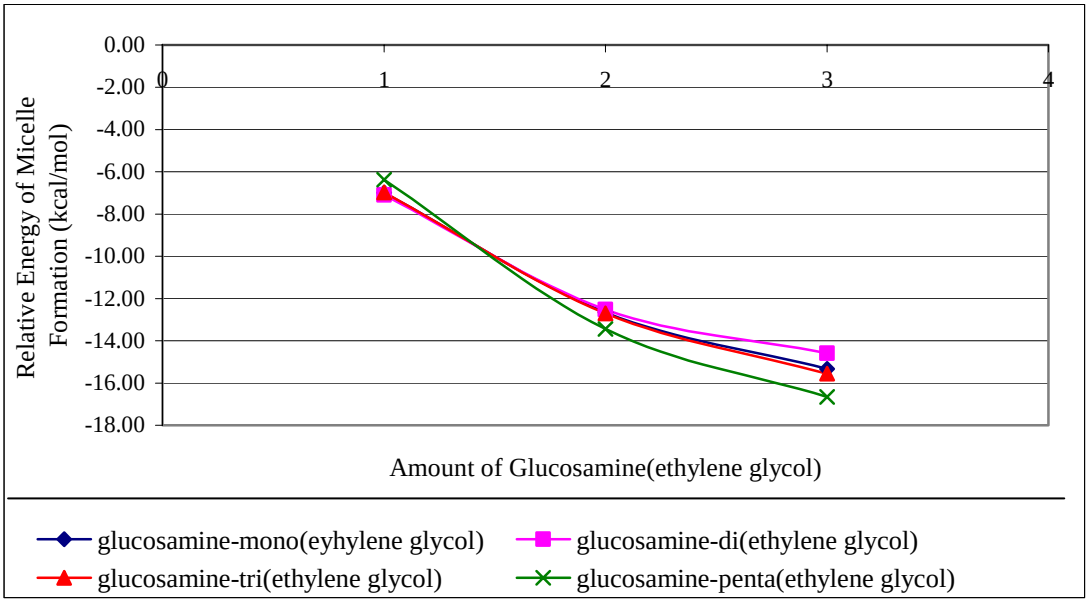



**Figure 38** Relationship between relative energy of micelle formation and amount of glucosamine(ethylene glycol)

One can see from this figure, that the amount of ethylene glycol in glucosamine(ethylene glycol) molecule induces doxorubicin and glucosamine(ethylene glycol) to form micelle structure by decreasing relative energy of micelle formation. Increasing the amount of ethylene glycol can make the micelle formation easier because the molecules in hydrophilic part increase. This part reduces the effect of water linkage with glucosamine in hydrophobic part. In case of increasing glucosamine(ethylene glycol), it can decrease the relative energy of micelle formation and molecule is more stable because of hydrogen bonding between doxorubicin and glucosamine(ethylene glycol). The effect of the amount of glucosamine(ethylene glycol) is more important than that of ethylene glycol molecules. The action of hydrogen bonding is to increase the hydrophilic part. The micelle formation from simulation is shown in Figure 39.

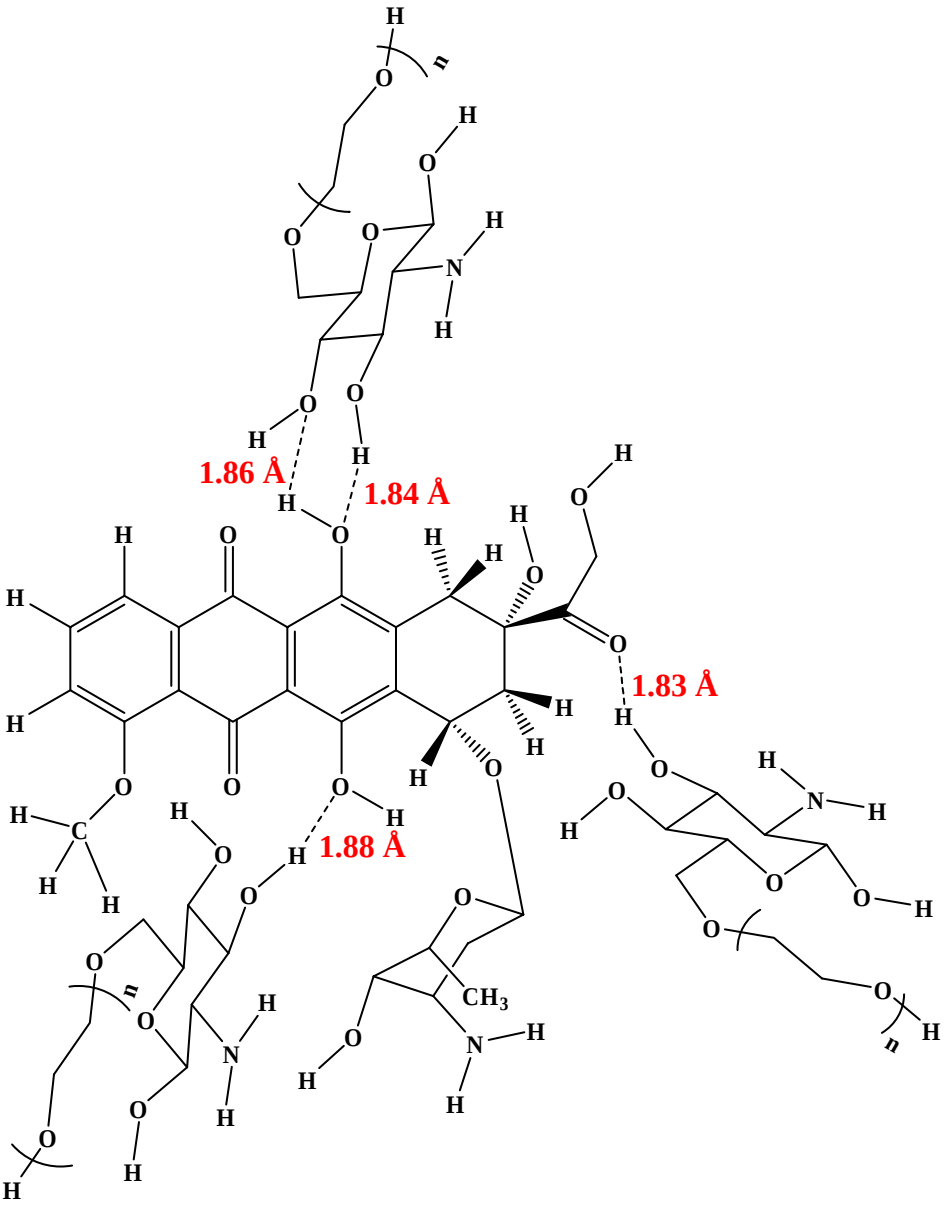



**Figure 39** Micelle formation from simulation by B3LYP/6-31G//PM3 method;

Where n = 1; glucosamine-mono(ethylene glycol)

n = 2; glucosamine-di(ethylene glycol)

n = 3; glucosamine-tri(ethylene glycol)

n = 4; glucosamine-tetra(ethylene glycol)

n = 5; glucosamine-penta(ethylene glycol)

**Effect of ethylene glycol to breaking bond of glucosamine(ethylene glycol)**

From micelle formation study, the ethylene glycol chain helps doxorubicin and mono glucosamine(ethylene glycol) on form micelle but the molecule of ethylene glycol has steric hindrance which affects the breaking bond of poly (ethylene glycol) glucosamine capsule. If the length of ethylene glycol chain in glucosamine(ethylene glycol) increases, the increasing of ethylene glycol chain can be broken in solution. This capsule is very good to protect drug and can form micelle in drug delivery. This result is researched by varying of the ethylene glycol chain in glucosamine(ethylene glycol) molecule for study polymer bond breaking of di glucosamine(ethylene glycol).

In this study, di glucosamine-mono(ethylene glycol) and di glucosamine-di(ethylene glycol) molecules were attracted by solution such as $H_3O^+$ in acid, $H_2O$ in normal, and $OH^-$ in base solution. The mechanism of reaction consists of four steps. In the first step, the reactants do not form the reaction because of the limitation of distance between them. The reactants can form complex to react between molecules in the second step. Following the third step, the reactants complex generates product molecules which have interaction (product complex). And the last step, the products have non-interaction between molecules. In simulation, the relative energy in each step can be calculated related to reactant step (first step).

The relative energies of reaction in acid, normal and base solutions are shown in Tables 13, 14 and 15, respectively.

**Table 13** The relative energy of di glucosamine-mono(ethylene glycol), di glucosamine-di(ethylene glycol), and di glucosamine-tri(ethylene glycol) in acid solution

| Molecular structures | Relative energy (kcal/mol) | |
|---|---|---|
| | **B3LYP/6-31G//AM1** | **B3LYP/6-31G//PM3** |
| **Di glucosamine-mono(ethylene glycol) + $H_3O^+$** | | |
| Di glucosamine-mono(ethylene glycol) + $H_3O^+$ | 0.00 | 0.00 |
| Di glucosamine-mono(ethylene glycol)---$H_3O^+$ | 176.58 | 145.51 |
| Glucosamine-mono(ethylene glycol)---Glucosamine-mono(ethylene glycol)cation---Water | -49.46 | -92.61 |
| Glucosamine-mono(ethylene glycol) + Glucosamine-mono(ethylene glycol)cation + Water | 18.58 | -7.29 |
| **Di glucosamine-di(ethylene glycol) + $H_3O^+$** | | |
| Di glucosamine-di(ethylene glycol) + $H_3O^+$ | 0.00 | 0.00 |
| Di glucosamine-di(ethylene glycol)---$H_3O^+$ | 119.13 | 119.13 |
| Glucosamine-di(ethylene glycol)--- Glucosamine-di(ethylene glycol)cation---Water | -58.36 | -27.20 |
| Glucosamine-di(ethylene glycol)--- Glucosamine-di(ethylene glycol)cation---Water | -31.48 | -19.70 |
| **Di glucosamine-tri(ethylene glycol)+ $H_3O$+** | | |
| Di glucosamine-tri(ethylene glycol)+ $H_3O^+$ | 0.00 | 0.00 |
| Di glucosamine-tri(ethylene glycol)---$H_3O^+$ | 111.73 | 135.02 |
| Glucosamine-tri(ethylene glycol)--- Glucosamine-tri(ethylene glycol)cation---Water | -49.48 | 78.24 |
| Di glucosamine-tri(ethylene glycol)---$H^+$---Water | - | -47.96 |
| Glucosamine-tri(ethylene glycol) + Glucosamine-tri(ethylene glycol) cation + Water | -20.81 | -18.30 |

**Table 14** The relative energy of di glucosamine-mono(ethylene glycol) and di glucosamine-di(ethylene glycol)in normal solution

| Molecular structures | Relative energy (kcal/mol) | |
|---|---|---|
| | **B3LYP/6-31G//AM1** | **B3LYP/6-31G//PM3** |
| **Di glucosamine-mono(ethylene glycol) + $H_2O$** | | |
| Di glucosamine-mono(ethylene glycol) + $H_2O$ | 0.00 | 0.00 |
| Di glucosamine-mono(ethylene glycol)---$H_2O$ | 166.60 | 135.78 |
| Glucosamine-mono(ethylene glycol)--- Glucosamine-mono(ethylene glycol) | -9.62 | -17.16 |
| Glucosamine-mono(ethylene glycol) + Glucosamine-mono(ethylene glycol) | -0.25 | -19.93 |
| **Di glucosamine-di(ethylene glycol) + $H_2O$** | | |
| Di glucosamine-di(ethylene glycol) + $H_2O$ | 0.00 | 0.00 |
| Di glucosamine-di(ethylene glycol)---$H_2O$ | 184.22 | 153.37 |
| Glucosamine-di(ethylene glycol)--- Glucosamine-di(ethylene glycol) | -19.75 | -13.80 |
| Glucosamine-di(ethylene glycol) + Glucosamine-di(ethylene glycol) | -7.24 | -13.94 |

**Table 15** The relative energy of di glucosamine-mono(ethylene glycol) and di glucosamine-di(ethylene glycol) in base solution

| Molecular structures | Relative energy (kcal/mol) | |
|---|---|---|
| | **B3LYP/6-31G//AM1** | **B3LYP/6-31G//PM3** |
| **Di glucosamine-mono(ethylene glycol)+ $OH^-$** | | |
| Di glucosamine-mono(ethylene glycol) + $OH^-$ | 0.00 | 0.00 |
| Di glucosamine-mono(ethylene glycol)---$OH^-$ | 257.57 | 287.60 |
| Glucosamine-mono(ethylene glycol)--- Glucosamine-mono(ethylene glycol) | -77.45 | -108.43 |
| Glucosamine-mono(ethylene glycol) + Glucosamine-mono(ethylene glycol) anion | -53.29 | -89.33 |
| **Di glucosamine-di(ethylene glycol) + $OH^-$** | | |
| Di glucosamine-di(ethylene glycol) + $OH^-$ | 0.00 | 0.00 |
| Di glucosamine-di(ethylene glycol)---$OH^-$ | 322.68 | 318.19 |
| Glucosamine-di(ethylene glycol)---Glucosamine-di(ethylene glycol) anion | -66.58 | -84.08 |
| Glucosamine-di(ethylene glycol) + Glucosamine-di(ethylene glycol) anion | -64.09 | -85.41 |

From the Table 13, the reaction of glucosamine(ethylene glycol) in acid condition is simulated by varying ethylene glycol chain length in the glucosamine(ethylene glycol) molecule. In this simulation, the glucosamine(ethylene glycol) is used in the forms of di glucosamine-mono(ethylene glycol), di glucosamine-di(ethylene glycol). This simulation found that the relative energy in transition state decreased. Consequently, the polymer bond breaking of di glucosamine-di(ethylene glycol) can be broken easier than di glucosamine-mono(ethylene glycol). From micelle formation study, the length of ethylene glycol increases, the micelle formation is more stable. Next, di glucosamine-tri(ethylene glycol) was studied and found that the relative energy decreased form calculation by B3LYP/6-31G//AM1 but increased form calculation by B3LYP/6-31G//PM3. From theory in calculation, the calculation of interaction between molecules by PM3 method is better than AM1 method.

The relative activated energy of di glucosamine-di(ethylene glycol) is lower than di glucosamine-mono(ethylene glycol). This relative activated energy is calculated from the difference between transition state in molecular step II and the total reactant energy from molecular step I. This relative energy is activated energy. From acid interaction with di glucosamine-mono(ethylene glycol), the activated energies are 176.58 and 145.51 kcal/mol, respectively. From acid interaction with di glucosamine-di(ethylene glycol), the activated energies are 119.13 and 119.13 kcal/mol. For acid interaction with di glucosamine-tri(ethylene glycol), the activated energies are 111.73 and 135.02 kcal/mol. This calculation confirms that ethylene glycol will help glucosamine(ethylene glycol) to break polymer bond. The ethylene glycol with high electron density helps the hydronium ion in polymer bond to attract with oxygen atom. On the other hand, if the ethylene glycol chain is more than di(ethylene glycol), it will block and reduce breaking of the bond. From di glucosamine-tri(ethylene glycol) simulation by B3LYP/6-31G//PM3, the polymer bond is broken in step III to glucosamine-tri(ethylene glycol), glucosamine-tri(ethylene glycol) cation, and water complex, but the molecule is not stable. The complex product rearranges to form di glucosamine-tri(ethylene glycol) cation and water complex in molecular structure step IV. After the di glucosamine-tri(ethylene glycol) is broken polymer bond, the glucosamine-tri(ethylene glycol) and glucosamine-tri(ethylene glycol) cation can form to di glucosamine-tri(ethylene glycol) cation. Because the effect of ethylene glycol chain interacts with glucosamine of another molecule, the glucosamine-tri(ethylene glycol) and glucosamine-tri(ethylene glycol) come close together to form di glucosamine-tri(ethylene

glycol) cation. This effect reduces the potential of polymer bond breaking of di glucosamine-tri(ethylene glycol).

The relative energy curve from molecular simulation step of di glucosamine-mono(ethylene glycol), di glucosamine-di(ethylene glycol), and di glucosamine-tri(ethylene glycol) interacted by $H_3O^+$ in acid solution is shown in Figure 40.

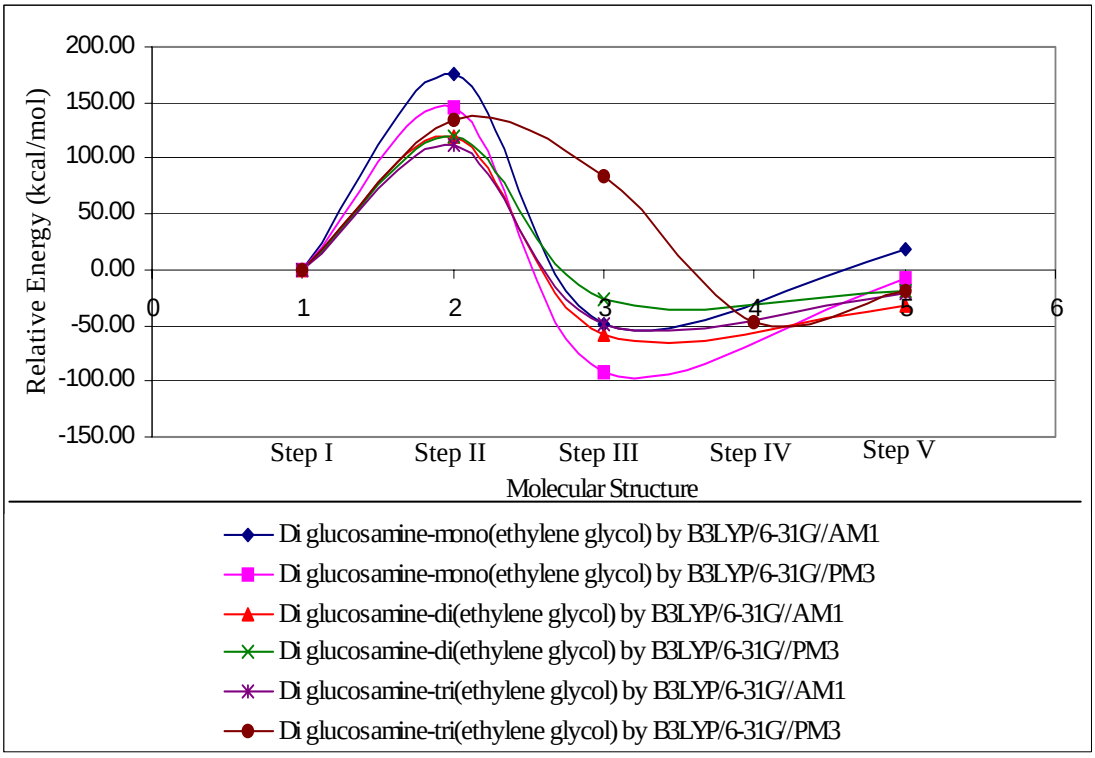



**Figure 40** The relative energy of acid interaction; di glucosamine-mono(ethylene glycol), di glucosamine-di(ethylene glycol), and di glucosamine-tri(ethylene glycol)

According to Table 14, the reaction of glucosamine(ethylene glycol) oligomers in normal condition is simulated by varying ethylene glycol chain in the glucosamine(ethylene glycol) molecule. Increasing ethylene glycol chain reduces the breaking of the polymer bond because of steric hindrance between ethylene glycol chain and $H_2O$ molecule. This effect obstructs hydrogen atom in water molecule to attract oxygen in polymer bond. Then, this reaction has a activated energy calculated from difference between transition state in molecular step II and the total reactant energy from molecular step 1 (in Figure 41). The water interactions with di glucosamine-

mono(ethylene glycol) and with di glucosamine-di(ethylene glycol) give the difference energy at 166, 135 kcal/mol and at 184.22, 153.37 kcal/mol, respectively. As a results, the length of ethylene glycol chain increases, the glucosamine(ethylene glycol) oligomers is more stable in water solution.

The relative energy curve from molecular simulation step of di glucosamine-mono(ethylene glycol) and di glucosamine-di(ethylene glycol) interacted with $H_2O$ in normal solution is shown in Figure 41.

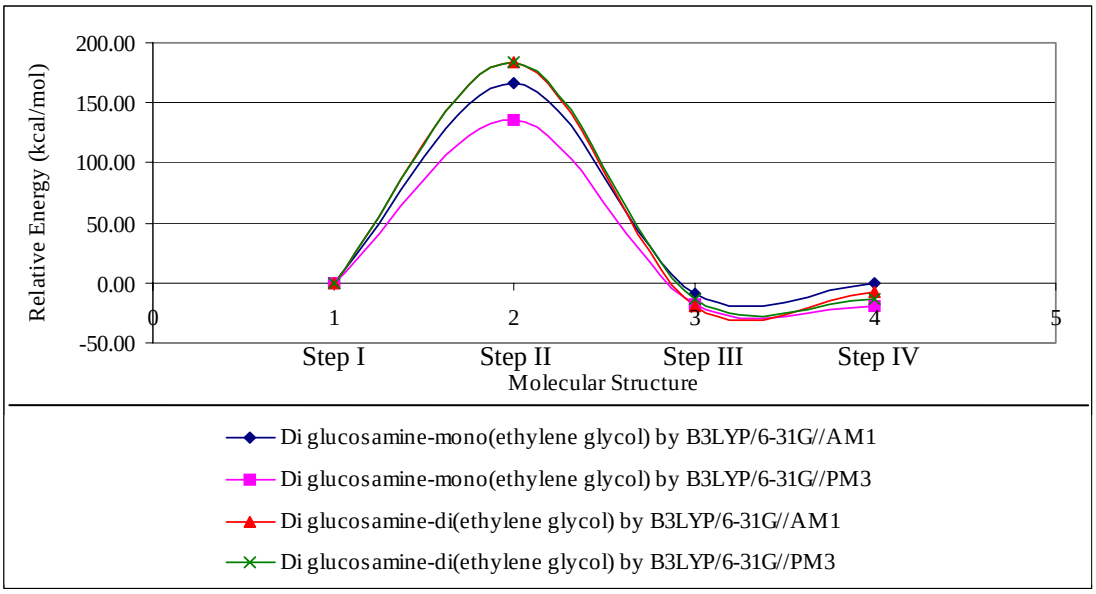



**Figure 41** The relative energy of water interaction; di glucosamine-mono(ethylene glycol) and di glucosamine-di(ethylene glycol) in normal solution

From Table 15, the reaction of glucosamine(ethylene glycol) oligomers in base condition is simulated by varying ethylene glycol chain in the glucosamine(ethylene glycol) molecule. Increasing ethylene glycol chain reduces breaking of the polymer bond because of steric hindrance between ethylene glycol chain and $OH^-$ molecule and, oxygen atom in the polymer bond. These effects draw back hydroxide ion molecule from attraction to the carbon next to the oxygen in polymer bond. This reaction must use the activated energy calculated from the difference between transition state in molecular step II and the total reactant energy from molecular step 1 (in Figure 42). From hydroxide ion interaction with di glucosamine-mono(ethylene glycol), the difference of energies are 257.57 and 287.60

kcal/mol. And hydroxide ion interaction with di glucosamine-di(ethylene glycol) has 322.68 and 318.19 kcal/mol difference energy by calculation. If the length of ethylene glycol chain increases, the glucosamine(ethylene glycol) oligomers are more stable in base solution.

The relative energy curve from molecular simulation step of di glucosamine-mono(ethylene glycol) and di glucosamine-di(ethylene glycol) interacted with $OH^-$ in normal solution is shown in Figure 42.

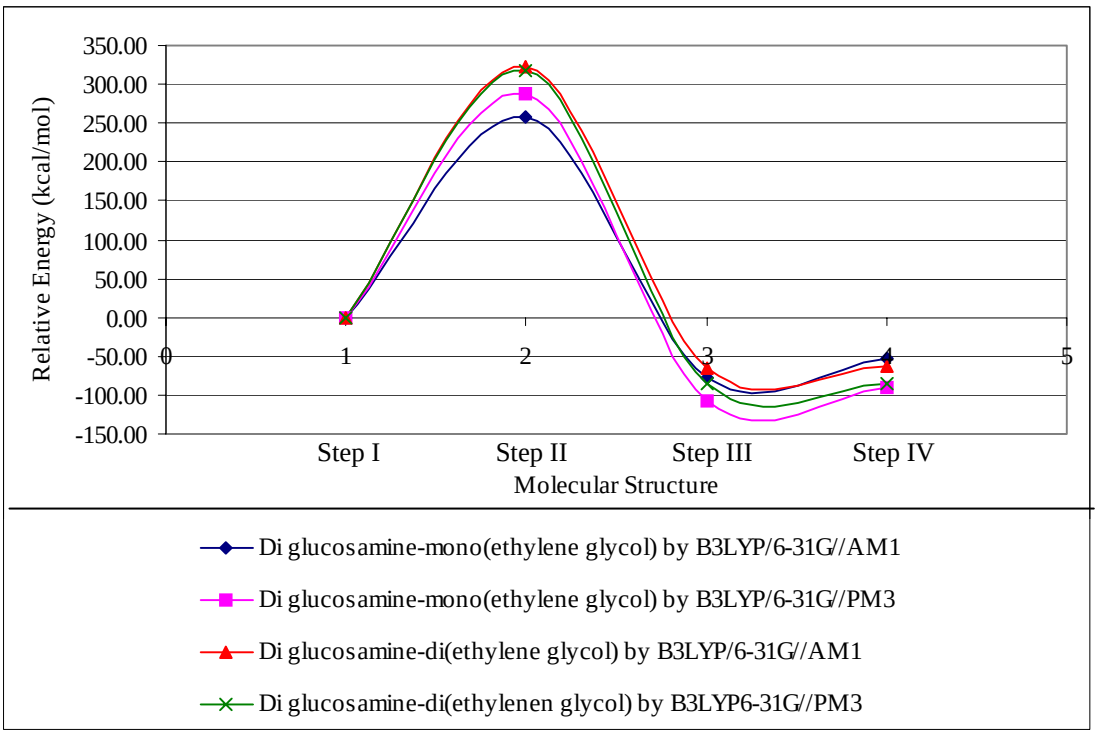



**Figure 42** The relative energy of hydroxide ion interaction; di glucosamine-mono (ethylene glycol) and di glucosamine-di(ethylene glycol) in normal solution

The study in effect of ethylene glycol to breaking bond of glucosamine(ethylene glycol) found that the glucosamine-di(ethylene glycol) can be used to be the capsule for delivery of doxorubicin. This glucosamine-di(ethylene glycol) can be broken in acid and form micelle structure with doxorubicin molecule better than glucosamine-mono(ethylene glycol). Moreover, glucosamine-di(ethylene glycol) is difficult to be broken in normal and in base conditions which this capsule can protect drug form moisture.