Prediction on Interaction of Biuret Molecule on Urea Crystal by Using Molecular Modelling Technique

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Abstract—**In this study, the morphology of urea as well as its interaction with biuret is the subject of interest. The objectives of this study are to examine the morphology of urea crystal by using molecular modelling (HABIT98) and to assess the surface interaction between urea and biuret molecule on urea faces. By using HABIT 98, the energies of urea crystals, which include lattice energy and attachment energy of urea crystal are calculated. Upon obtaining these values, the morphology of urea crystal is visualized by using SHAPE. Material Studio is also use in order to visualize the functional group of urea for every faces. Systematic Grid-Based Search is then utilized to evaluate the highest interaction energy between urea and biuret molecule to urea faces by taking into account four faces of urea which are (001), (110), (111), and (-1-1-1). From the findings, it can be observed that (001) face is the fastest growing face whereas (110) face is the slowest growing face. The prediction also shows that the interaction of urea and biuret molecule both favor (001) and (-1-1-1) faces.**

Keywords*— *HABIT 98, morphology of urea, surface interaction urea to biuret molecule, Systematic Grid-Based Search.

I. INTRODUCTION

Crystallization is a process that is widely being applied in pharmacology and chemical industry. It is a process occurred when the solubility of a compound in a solvent is low or limited at a certain temperature or pressure. However, a compound is able to crystallize in various shapes. Hence, the study of morphology allows us to have a deeper knowledge on the structure of the crystals. Controlling the process of crystallization is important in order for the product to be manufactured for variety of purposes as the sizes and the shapes of the crystals have a direct impact on the efficiency of the product. The morphology is very crucial as it is able to influence the fundamental properties of the material, including the stability in storage, rate of dissolution and compressibility [1]. Thus, understanding the structure and shape of the crystals allow the optimization of the performance for meeting the desired interest. Problems will occur especially in the downstream production processes such as in particle flow, filtration, agglomeration, fragmentation and attrition

It is theoretically known that urea crystals will grow into a needle-like shape [2]. The needle-like shape of the urea crystals are the result of different growth speed of two relevant faces (001) and (110), which are known to grow fast and slow respectively [3]. The appearances of needle crystals are unwelcomed due to the problems that it may creates. The needle-like morphology of urea is hard to be handled especially during the downstream processes such as solid-liquid filtration and powder flow as it may be easily break. However, the growth of the crystal are able to be controlled either by acting on microscopic operative condition or by employing additive that have the ability to hinder the growth of the crystal at the molecular scale [3]. In this study, the focus is to add the additive in order to allow the interaction of the urea faces with the additive, which is biuret molecule. The effect of the interaction of the shape controlling inhibitor as biuret with the urea faces is the selective enhancement or discouragement of the growth on specific faces. In other words, biuret works by slowing down the growth of one face relative to another. This will then reduce the differences in growth rates of individual crystal face and hence reduce the anisotropic growth [3].

Many methods had been used to predict the morphological structure of crystals. The simplest method is to assume that the slowest growing face which is also the largest crystal faces have the largest interplanar spacing, d_{hkl}. This reflect the weakest interactions between the face and the net growth layer. This is the basis of BFDH [4]. Molecular modelling is conducted to allow a better understanding on the manners of the interaction of atoms and molecules. It produces a quicker and higher throughput compared to the experimental testing. In this study, the molecular prediction of the crystal is done by programs that are able to calculate a wide range of surface properties. The programs that are used are HABIT98 and Systematic Grid-Based Search. By using these programs, not only the morphology of urea can be examined , but it also allows the assessment of the surface interaction between biuret molecule and the primary faces of urea which are (001), (110), (111) and (-1-1-1)

II. METHODOLOGY

A. Materials

The two main materials that are involved in this study are urea and biuret. Urea is an organic compound with molecular formula of $CO(NH_2)_2$. As shown in Fig.1, it consists of a carbonyl functional group and two amide functional group. Urea, also known as carbamide is colourless, odourless and has a very high solubility in water. It is a commodity, non- toxic chemicals. The simple structure of urea has intrigued many researchers to choose this compound as model in the study of polar organic molecules. Besides that, of all the compounds that are available, urea is the only example, which the structure involves a single carbonyl oxygen atom engaged with four hydrogen bonds. It will crystallizes into simple tetragonal shape with $P\text{-}42_1m$ space group (Fig.2) and two molecules in the unit cell with dimensions of a=5.565Å and c = 4.684Å [1]. Urea is produce from the exothermic reaction between ammonia and carbon dioxide. It is mainly use in the agricultural, more specifically to produce fertilizers. It is also use in the production of plastics. It is known that when crystallize from water, it will produce a needle like shape of crystal. Urea develops a steady state shapes which normally dominated by (0 0 1), (1 1 0) and (1 1 1) faces [3]. However, urea has polar faces which are (111) face and (-1-1-1) face. The polarization of (111) face and (-1-1-1) face is due to the anomalous growth of these faces. The anomalous arises from the relaxation of the surface.

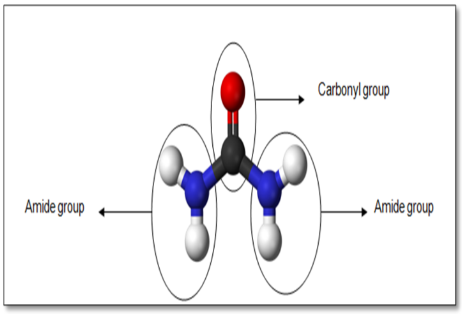


Fig. 1 :Molecular structure of urea

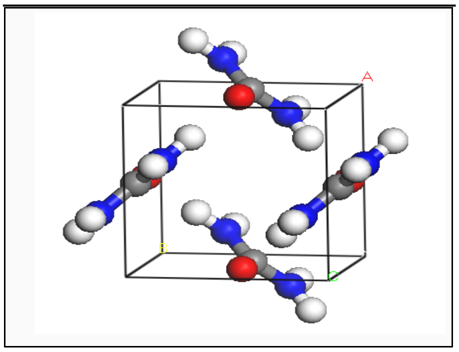


Fig. 2: Unit cell of urea

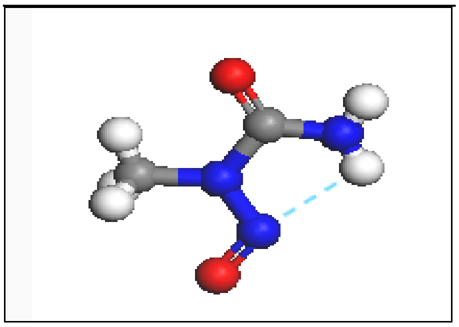


Fig. 3: Molecular structure of biuret

Biuret is formed when two molecules of urea is condensed and combined together and at the same time eliminate one molecule of ammonia. In other words, it is a dimer of urea, which forms during the synthesis reaction [5]. Biuret with molecular formula of $C_2H_5N_3O_2$, (Fig.3) is white in color when in solid state. It is also odorless and dissoluble in water, especially in hot water. In this study, biuret will act as the additive where it will change the morphology of the urea. Biuret acts by selectively binds to the fast growing face of the urea crystal but did not acts or may give a very little impact on the slow growing face of urea [3].

B. Computational Modelling methods

Morphology Prediction Using HABIT98

The morphological of urea crystal is predicted by using HABIT98. By using HABIT98, it will help to calculate the energies of urea crystals such as attachment energy, slice energy and lattice energy. Through Cambridge Structure Database (CSD), the Crystallographic Information File (CIF file) of urea crystal is obtained. The energies are also calculated by taking into account both bonded and non-bonded forces in molecule as well as all the atomic interactions that occur in the unit cell. The limiting radius of the sphere is set up to 30Å. The total interaction energy is the lattice energy of the crystal (E_{latt}). The lattice energy is the summation between slice energy (E_{sl}) and attachment energy (E_{att}).

$$E_{latt} = E_{sl} + E_{att} \tag{1}$$

Through HABIT98, (LATT) mode is used to calculate the lattice energy, (FULL) mode is used to analyze the bonding of atom-atom interactions, (POLR) mode is used to obtain the attachment energy of each face of urea crystal due to the polarity of the urea [8], [9]. and Hagler-Lifson is use as the force-field. As urea is a polar compound, both bulk charges and isolated charges is also taken into account. The charges obtained from Docherty, 1989 [2] using crystal, calculated again using Lifson & Hagler potential set and scaled charges for the isolated charges

Material Studio SHAPE

Basically, these programs help to visualize the crystal as HABIT98 can only able to calculate the energies. By using SHAPE, it enables for the morphology of the urea to be visualized by giving the input of the attachment energy data that had been calculated in HABIT98.

Surface Energy Prediction

Equation (2) below [7] is used to calculate the surface energy of (hkl) face. The attachment energy that is required in the equation is the attachment energy obtained from HABIT98 calculation.

$$\gamma_{hkl} = \left(\frac{E_{att} \cdot d_{hkl}}{Z.N_A.V_{cell}}\right) \tag{2}$$

Where,

γ_{hkl} = surface energy of (hkl) face, (kcal/m
E_{att} = attachment energy of the (hkl) face, (kcal/mol)
d_{hkl} = interplanar spacing of (hkl) plane, (Å)
Z = number of molecule in unit cell
N_A = Avogadro number
V_{cell} = cell volume of the crystal, m^3

Molecule to Surface Interactions Using Systematic Grid-Based Search

To understand into details the particle-particle interaction, the orientation of particles is predicted using Systematic Grid-Based Search method. This program enables evaluation of the interaction energy of molecule to the surface at its preferred orientation and location. Besides that, through this program, the solvent binding sites to the growing surface of the crystal is also able to be predicted. Summation of atom-atom pair potential is use to calculate the interaction energy of atom-atom pair interaction. In this study, this software is use to evaluate the highest energy between urea surfaces to biuret molecule [10]. Four surfaces of urea is considered for the evaluation include (001), (110) and another two polar faces which are (111) and (-1-1-1).

III. RESULTS AND DISCUSSION

A. Prediction on morphology of urea

From Habit98, the calculated lattice energy for urea is -22.57 kcal/mol, which is in good agreement as the lattice energy obtained from the work and experimental by Docherty [2]. It is important to ensure that the value of the predicted lattice energy is close to the known experimental sublimation enthalpy for urea [7]. The findings on the attachment energy of each faces of urea are as shown in Table 1. By obtaining these values of the attachment energy, it is possible to visualize the morphology of urea (Fig. 4) using SHAPE. Prediction of the urea crystal shape is observed to be elongated at the c direction, exhibiting faces (001), (110), and (111).

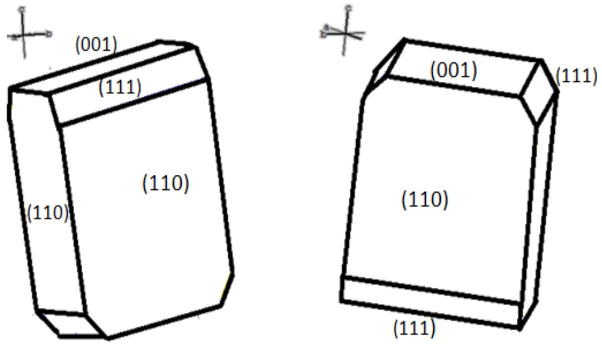
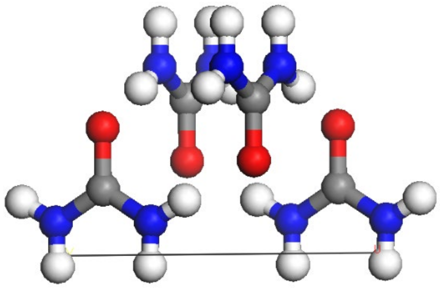
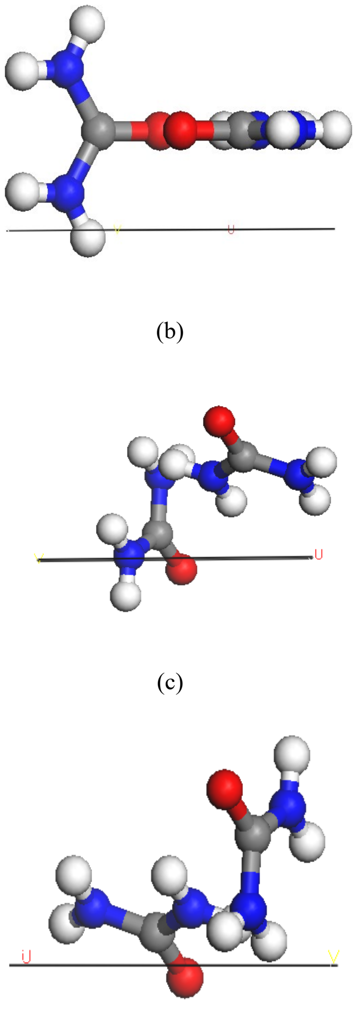


Fig. 4: The morphology of urea visualize using SHAPE

The slice and attachment energy of a given face is complementary to each other. E_{att} is the energy released for every mol of molecule when a new layer having thickness d_{hkl} is attached to the surface of the crystal. Growth rate is directly proportional to the attachment energy, but inversely proportional to the morphological importance [6]. In other words, faces with highest attachment energy will grow faster and have a lower morphological important. This explains why face (-1-1-1) do not appear in the urea morphology as it is the fastest growing face. Face (110) has the lowest attachment energy. This shows that it is the slowest growing face and hence has the largest face compared to other faces. The morphology of urea, which is elongated, is the result of different growth rates of the faces of urea.



(a)



(b)

(c)

(d)

Fig. 5: Cleave surfaces of urea for (a) 001 face, (b) 110 face (c) 111 face (d) -1-1-1 face

Fig. 5 shows the hydrogen bonding interaction for four important faces of urea. For Fig. 5 (a), which is at (001) face, it can be observed that the hydrogen atoms exposed at the surface, whereas the carbonyl oxygen shows up to the surface. The position of carbonyl oxygen at (001) face will allows the hydrogen bonding to the incoming molecule at the surface and hence, it has the highest possibility of having the strongest interaction to occur [7]. As for (110) face, by examine the packing diagram in Fig. (b), it can be seen that hydrogen atoms from amide also exposed to the surface. However, the carbonyl groups are located at the centre. This arrangement is not favorable as it will cause blocking for hydroxyl groups to bind at this face, and hence will retard the the growth of (110) face [2]. For another two faces which is the polar faces (111) and (-1-1-1) from Fig. 5 (c) and (d), both have carbonyl oxygen exposed at the surface, but hydrogen amides at (111) face also exposed at the surface.

B. Prediction on interaction

Interaction on urea molecule with urea faces

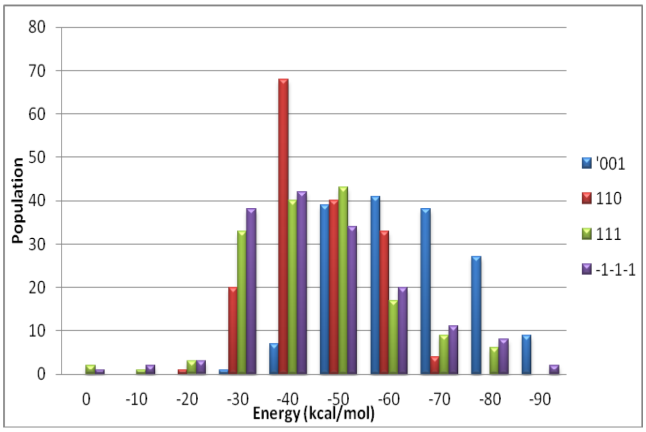


Fig. 6: Graphs showing the binding energy of urea molecule with urea faces at 001 face,110 face, 111 face and -1-1-1 face

Fig. 6 shows the result of the binding energy on urea molecule at 4 faces of urea. This was run by introducing one molecule of urea to urea faces. By referring to Fig.6 for (001) face, it is observed that at the class (-60 to -69) kcal/mol, it possesses the highest population of which urea molecule will bind at this face. The highest population of which urea molecule will bind at urea face (111), is at the range of (-50 to -59) kcal/mol. Whereas, for both (110) face and (-1-1-1) face, the highest population is at (-40 to -49) kcal/mol. These highest populations for each faces show that it is the energy where the interaction between the urea molecule will likely to occur at the faces. However, when comparing between these faces, (001) face has the lowest energy value which is in the range of (-60 to -69) kcal/mol. The lowest energy is where the strongest interaction will occur. This shows that of all four faces of urea, the strongest interaction between urea molecule will occur at (001) face.

However, the lowest energy where the interaction occurs between the urea molecule and each faces of urea also need to take into consideration. From Fig. 6, it can be observed that between the urea faces, the lowest energy occur at (001) face and (-1-1-1) face at the range of -90 kcal/mol. From this observation, it can be assumed that the interaction of urea molecule might occur at (001) face and (-1-1-1) face.

Interaction on biuret molecule with urea faces

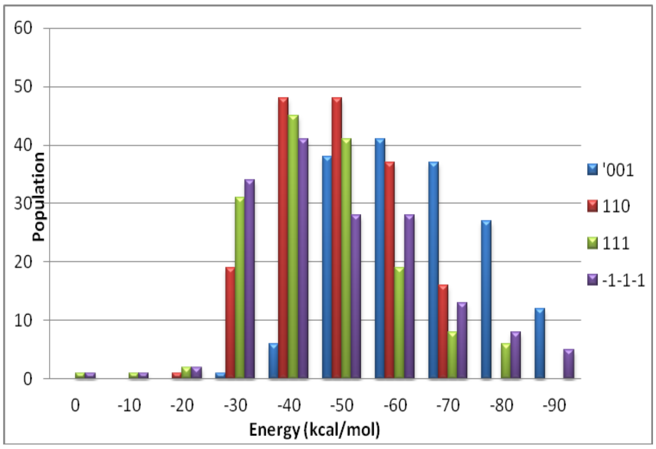


Fig. 7: Graphs showing the binding energy of biuret molecule with urea faces at 001 face,110 face, 111 face and -1-1-1 face

Fig. 7 shows the result of the binding energy on one molecule of biuret to 4 faces of urea. From Fig.7 the highest binding energy at (001) face is at the class of (-60 to -69) kcal/mol, (-40 to -59) kcal/mol for (110) face, (-40 to -49) kcal/mol for (111) face and (-50 to -59) kcal/mol for (-1-1-1) face. This binding energy is deemed as the 'highest' by observing the highest occurrence of biuret molecule that interact at urea faces in that particular range of energy. When comparing this faces, (001) face has the lowest energy value, meaning that the biuret molecule will tend to interact at this face. This is because biuret is a dimer of urea [5], hence one molecule of biuret will replace two adjacent molecule of urea. Biuret molecule favors (001) face more than (110) face due to the arrangement of molecule at (001) face. The (001) face would not differentiate a biuret molecule from two urea molecules when the urea is replaced. However, the next layer of urea molecules depositing on top of the biuret would find insufficient NH_2 groups at the surface to satisfy all the hydrogen bonding linkages. This would reduce the growth rate [2]. It can be seen that when comparing the interaction of urea and biuret molecule to urea faces, both show that the strongest interaction will occur at (001) face.

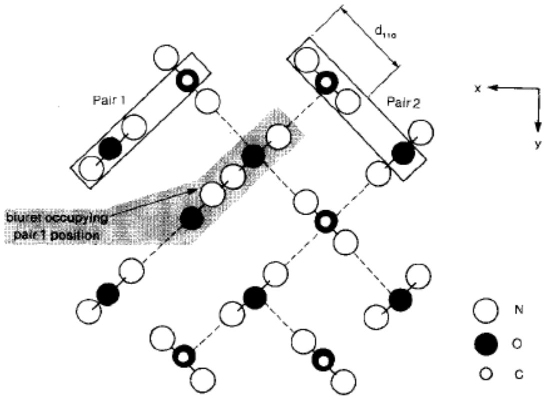


Fig. 8: Crystal structure projected onto (001) [5].

However, when looking at the most stable energy between the urea faces from Fig. 7, the lowest energy occur at (001) face and (-1-1-1) face at the range of -90 kcal/mol. From this observation, it can be assumed that the interaction of biuret molecule might occur at (001) face and (-1-1-1) face, the same that can be concluded on the interaction of urea molecule to urea faces. The values of the binding energies for both urea and biuret molecule is tabulated in Table 1.

Surface Energy Prediction

Surface energy indicates the disturbance of the intermolecular bonding that occurs during the formation of new surface. In other words, it can be defined as the energy required for building a new area of a particular surface. High surface energy means that strong molecular attractions occur on that particular surface, whereas low surface energy indicates that a weaker interaction will occur. The morphological importance can also be determined by predicting the surface energy. The morphological importance is inversely proportional to the surface energy [4]. Table 1 summaries the prediction energy of urea.

Table 1: Summary of prediction surface energy of urea

Face	E_{att} (kcal/mol)	Binding energy (kcal/mol)		Surface energy (kcal/mol)
		Urea	Biuret	

		molecule	molecule	
(001)	-10.481	-95.65	-96.90	0.3384
(110)	-9.005	-76.38	-79.20	0.2443
(111)	-12.001	-89.04	-87.50	0.2493
(-1-1-1)	-14	-96.73	-97.50	0.2908

Based on the data above, it can be seen that (001) face exhibits the highest surface energy, followed by (-1-1-1) face. Hence, it can be said here that (001) face and (-1-1-1) face of urea have the highest tendency for the interaction of the urea and biuret molecule to occur.

IV. CONCLUSION

In conclusion, we are able to examine the morphology of urea from the values of attachment energy calculated from HABIT98. The morphology in this work is correctly predicted as the known morphology of the urea. From the method of Systematic Grid Search, it is observed that the interaction of both urea and biuret molecule favor (001) face and (-1-1-1) face of urea as both give the smallest binding energy values which is in the range of -90kcal/mol. This is also supported by the values of the surface energy calculated which indicate (001) face, followed by (-1-1-1) face, are the faces of urea which have the highest tendency for the interaction of the urea and biuret molecule to occur. It can be concluded here that the higher the interaction energy, the higher the surface energy, hence resulted in a lower morphological importance of the urea faces.

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