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# Molecular simulation of ursolic acid/β-cyclodextrin inclusion compound

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## ABSTRACT

To explore stable mechanism of ursolic acid/β-cyclodextrin inclusion compound under high pressure. Molecular mechanics (MM) and molecular dynamics (MD) were used to analysis the conformation of ursolic acid and β - cyclodextrin inclusion under high pressure and normal pressure. Moreover, the molecular interaction between subject and object was calculated. Molecular simulation results confirm: the most stable conformation of inclusion complexes is hydroxyl end up and carboxyl end down which of ursolic acid. the formation of hydrogen bonds between the ursolic acid and β – cyclodextrin. In the water environment, the dynamic equilibrium of simulation system is reached. Simulation system in the water environment, the total energy and the potential energy which under 500Mpa pressure are smaller than normal pressure. The system density of 500Mpa pressure is bigger than others.These demonstrate that the pressure can make the system more stable and reduce its volume.


## KEYWORDS

Ursolic acid;
β – cyclodextrin;
Inclusion compound;
Molecular simulation.

## INTRODUCTION

Cyclodextrin (Cyclodextrins, CDs) with special structure are inner hydrophobic and hydrophilic, therefore can form inclusion complexes with many small molecules. Because of this unique performance, CDs has been widely used in many fields of food, medicine and other..Inclusion compounds with β –cyclodextrins are widely used in chemistry and have often been employed in Pharmaceutical Chemistry for drug delivery[1]. Host-guest inclusion complex of calculation takes a great part in the study of cyclodextrin. Molecular simulation considers small size systems, at a typical scale of a few nanometers, and determines their behaviour from a careful computation of the interactions between their components[2]. The research in this area can be divided into the following categories[3]: (1) The calculation of a binding free energy,(2) the analysis of a conformation,(3) the analysis of a spectral characterization etc.

With the rapid development of quantum mechanics, some microscopic properties of molecules can be obtained by quantum mechanical calculations, including molecular structure, ionization potential, conformation etc. According to the spatial scale and the simulation time is different, the method of molecular simulation is divided into molecular mechanics and molecular dynamics simulations (MM&MD), quantum mechanics

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simulations (QM) and mesoscopic simulation.

Molecular mechanics(MM) simulation is a kind of simulation method which use the molecular to analyse the static properties. It uses the analytic experience function through the characterization of bond lengths, bond angles and dihedral angle changes, as well as the potential function of non-bonding interaction from the typical structural parameters and force to describe the change of stress or energy is caused by the molecular structure change. Treatment of biological macromolecular systems can use the simple potential function.

Molecular dynamics (MD)[4,5] simulation is an important tool to study the structure of biological macromolecules, kinetic and thermodynamic properties. The method can not only give the motion details of large biological molecules at the atomic level, but also can provide detailed information of position fluctuations and conformational changes for biological macromolecules.It can explain the experimental data at the micro level[6]. Compared with other simulation method, molecular dynamics simulation has the advantages of high precision, can simultaneously obtain the statistical data of system dynamics and thermodynamics, a wide range of applications etc.

Common molecular simulation software including Amber, Charmm, Gromacs, Material and studio, this article selects the Materials Studio software which be developed by Accelrys company of America. Materials Studio software can be optimized geometries, predicted the properties, calculated the quantum mechanics and molecular dynamics simulation, the researchers can get very high accuracy data through some simple operation.

Tabushi and Mizutani et al.[7] calculated the interaction energy of the inclusion with iodine aniline and nitrophenol molecule and ± - cyclodextrins. The study found in the inclusion of Van der Waals force as the main force in the molecular recognition process.

D.Thompson and other scholars[8] studied the molecular recognition mechanisms by molecular simulation for medicine and β - cyclodextrin inclusion complex. They mainly using molecular dynamics free energy simulations (MDFE) to describe the specific combination of drugs and β – cyclodextrin. Through the computer simulation to analyze the electrostatic interaction between the metal organic molecular. Determination of β - cyclodextrin is to identify organic guest molecules by Van der Waals force, the simulation results agree with the thermodynamic analyses[11].

The objective of this work is to explore stable conformation inside the inclusion complexes of ursolic acid and β – cyclodextrin from molecular mechanics (MM) and molecular dynamics (MD) calculations. At the same time to analyze the conditions of simulated system in water environment.

## SELECT SIMULATION PARAMETERS

This experiment mainly used Discover and Amorphous cell of Materials Studio. Discover using molecular mechanics and molecular dynamics. Amorphous cell can establish a representative model to complex systems based on the CVFF, PCFF, COMPASS etc.

### Select force field

A structure model of β - cyclodextrin was constructed by Visualizer of Materials Studio based on crystal data of β – cyclodextrin. Similarly for a structural model for ursolic acid. To construct a periodic amorphous unit by Construction of Amorphous cell for a ursolic acid and a cyclodextrin. The PCFF force field is a powerful force field to support polymer and organic material atomic simulation. The CFF91 force field focuses on the research of polymer and polymer materials[9]. As shown in Figure 1, PCFF force field is applicable on β - cyclodextrin inclusion complex system.

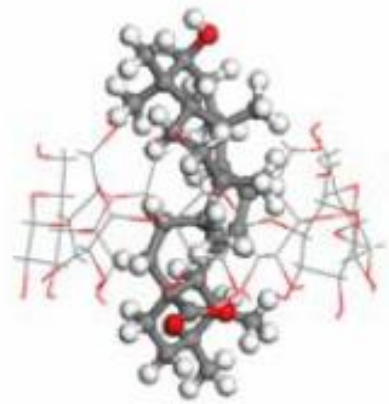

**Figure 1 : Structural simulation of the ursolic acid /β-cyclodextrin inclusi**

### Select Cut-off distance

Discover select the default values are Coarse,

Medium, Fine and Ultra-fine respectively for truncation distance, spline width and buffer width.

### Select parameter of dynamics simulation

Ensemble is set to NPT. Temperature selection of 298K, the choice of the force field focuses on the biochemical and molecular system simulation of the PCFF (including hydrogen bonding). Pressure was set as 0.0001 and 0.5GPa. The number of steps is set to 30000, the time step is set to LFS, dynamics time is 30.0ps. Record the full trajectories.

## SIMULATION AND MODELS

To find a lowest energy conformation from inclusion complexes of ursolic acid / β - cyclodextrin by the Smart Minimizer method of Material Studio. The lowest energy conformation is immersed in water environment simulation.The water environment simulation can build a amorphous periodic unit contains 600 water molecules through the Amorphous Cell of Material Studio,its density is 1.0g/cm$^3$. This study selects two kinds of simulation system:(1)the ursolic acid and β – cyclodextrin will be put in the water environment simulation contains 600 water molecules under atmospheric pressure and simulate the inclusion process;(2) Similarly under 500Mpa.

## RESULTS AND DISCUSSION

### Optimized conformation

The position of β – cyclodextrin is fixed as the smaller end upward and the bigger end downward.The ursolic acid maybe has six conformations in the cavity of β – cyclodextrin.As shown in Figure 2. The first conformation : hydroxy end upward and carboxyl end down of ursolic acid through the cavity of β – cyclodextrin.The second conformation: hydroxy end upward and carboxyl end down of ursolic acid, carboxyl terminal in the cavity of β –cyclodextrin.The third conformation: hydroxy end upward and carboxyl end down of ursolic acid, hydroxyl terminal in the cavity of β –cyclodextrin. The fourth conformation: carboxyl end upward and hydroxy end down of ursolic acid through the cavity of β – cyclodextrin.The fifth conformation: carboxyl end upward and hydroxy end down of ursolic acid, carboxyl terminal in the cavity of β – cyclodextrin.The sixth conformation: carboxyl end upward and hydroxy end down of ursolic acid, hydroxyl terminal in the cavity of β –cyclodextrin.

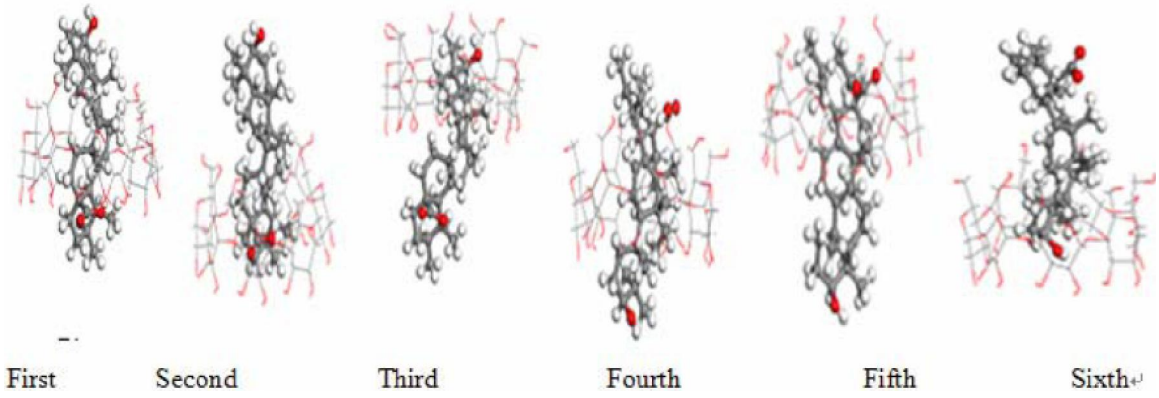


**Figure 2 : The six initial structures of the ursolic acid /β-cyclodextrin inclusion**

For energy minimization to the six kinds of conformations, the result is the specific energy values of the lowest energy conformation that be shown in TABLE 1. The first one as the lowest can be seen from TABLE 1.

Through the lowest energy conformation of inclusion complex to calculate hydrogen bond, results can be seen that the carboxyl of ursolic acid and the hydroxyl of β – cyclodextrin group. form hydrogen bond. As shown in Figure 3.

### Water environment model

The first conformation is immersed in water environment to establish the simulation model. Figure 4 (A) is the amorphous unit,which includes only the lowest energy conformation of the inclusion complex. Figure 4 (B) includes the lowest energy conformation and 600 water molecules of the inclusion complex. The inclusion

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**TABLE 1 : The lowest energy list of six structures of inclusion complexes**

| | First | Second | Third | Fourth | Fifth | Sixth |
|---|---|---|---|---|---|---|
| Total Potential energy/kJmol$^{-1}$ | -229.254 | -164.911 | -198.622 | -196.641 | -183.303 | -169.618 |
| Internal/kJmol$^{-1}$ | -120.186 | -120.895 | -130.823 | -101.125 | -119.944 | -132.477 |
| bond/kJmol$^{-1}$ | 35.10687 | 32.95465 | 28.31218 | 37.63021 | 34.94473 | 34.15739 |
| angle/kJmol$^{-1}$ | 128.9467 | 132.7825 | 123.0754 | 140.7557 | 126.8686 | 121.9324 |
| torsion/kJmol$^{-1}$ | -231.217 | -232.373 | -229.963 | -221.266 | -227.790 | -237.073 |
| out_of_plane/kJmol$^{-1}$ | 0.167723 | 0.265111 | 0.248937 | 1.889427 | 0.172785 | 0.174718 |
| cross/kJmol$^{-1}$ | -53.1907 | -54.5236 | -52.4967 | -60.1349 | -54.1408 | -51.6680 |
| nonbond/kJmol$^{-1}$ | -109.068 | -44.016 | -67.799 | -95.515 | -63.358 | -37.141 |
| vdW/kJmol$^{-1}$ | 68.47043 | 94.64051 | 100.36478 | 97.16308 | 105.70961 | 87.46060 |
| electrostatic/kJmol$^{-1}$ | -177.538 | -138.657 | -168.164 | -192.678 | -169.068 | -124.601 |

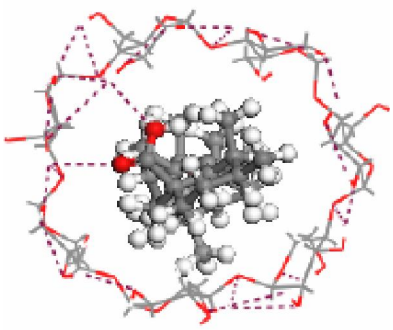


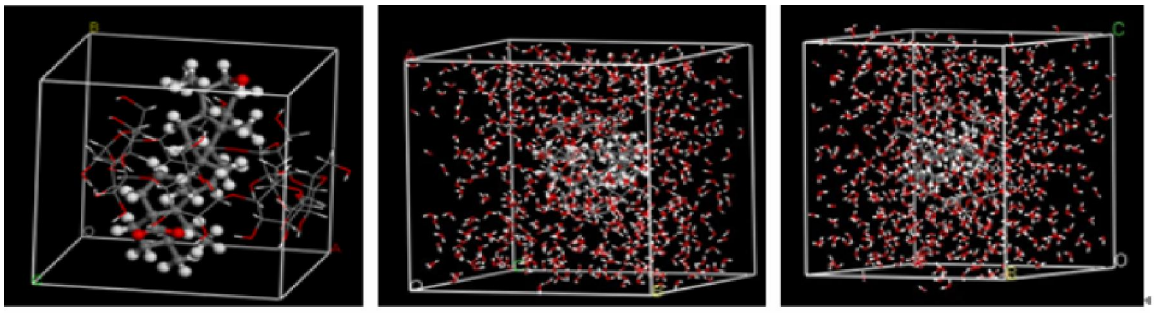
**Figure 3 : Schematic diagram of hydrogen bond**

complex was subjected to energy minimization, obtain amorphous unit, as shown in Figure4(C).

## Dynamics simulation

Using the Dynamics to carry out dynamics simulation for amorphous unit of the lowest energy. By changing pressure(0.1Mpa and 500Mpa) to obtain the diagram of energy and simulation time, temperature and simulation time, as shown in Figure 5 to 6.

The diagram above shows, energy value of



A B C

**Figure 4 : Water environment model**

simulation system is in small amplitude fluctuations with dynamics simulation, under the 0.1Mpa and 500Mpa. The temperature is in the set value 298K level fluctuation. It proved that simulation system achieve a balance.

The dynamic simulated data table which be in water environment shown in TABLE 2. Initial is the initial data of water environment model. Average is the average after dynamics simulation. Total energy (Etot) is the total energy. Potential energy (Epot) and Kinetic energy (Ekin) are potential energy and kinetic energy. The relationship between the three is Etot = Epot + Ekin.

See TABLE 2, simulation model after dynamic operation, the average temperature and pressure are basically reaches the set value0It proved that simulation system achieve a balance.

In addition, when the simulation system in the water environment, the total energy and the potential are smaller under 500Mpa pressure than it under 0.1Mpa. These demonstrate that the pressure can make the system more stable and reduce its volume.

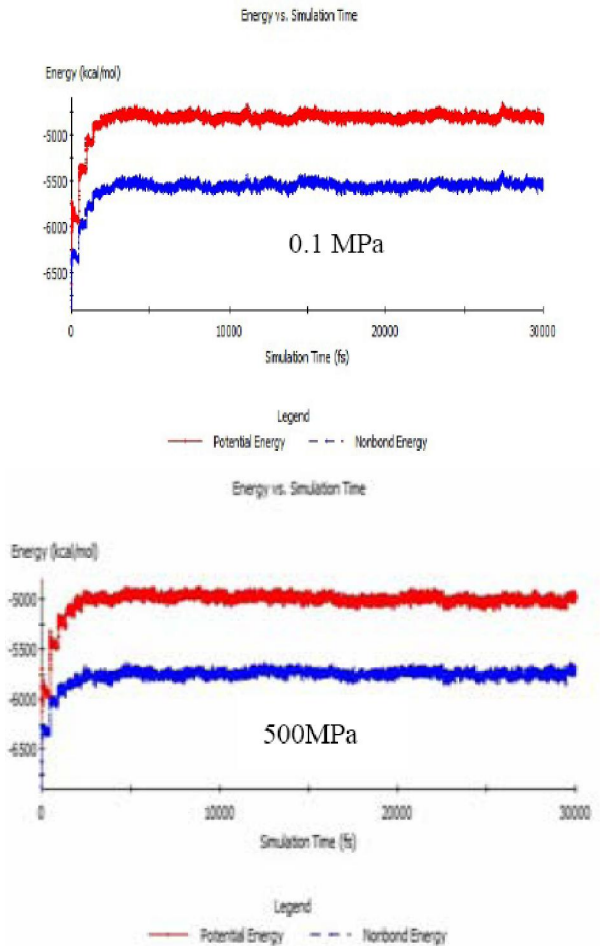



**Figure 5 : The energy variation vs simulation time**

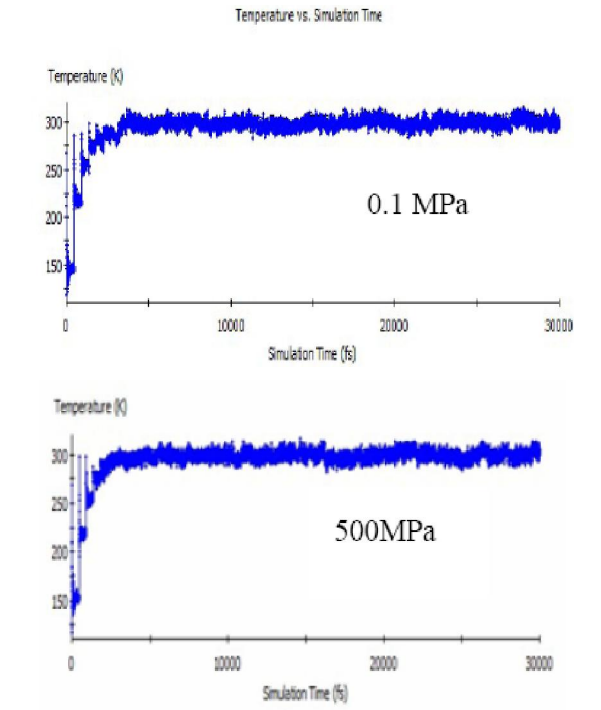



**Figure 6 : The temperature variation vs time**

**TABLE 2 : Motion dynamics data sheet**

| | Initial | Average | |
|---|---|---|---|
| | | 0.1Mpa | 500Mpa |
| Total energy (kcal/mol) | -5024.569 | -3063.216 | -3239.680 |
| Potential energy (kcal/mol) | -6824.263 | -4838.445 | -5017.769 |
| Kinetic energy (kcal/mol) | 1799.694 | 1775.229 | 1778.089 |
| Temperature (K) | 298.000 | 293.949 | 294.423 |
| Pressure (GPa) | _ | -0.000407 | 0.498579 |
| Density (g/cm$^3$) | 1.0003 | 1.0530 | 1.1735 |

## CONCLUSIONS

The most stable conformation of inclusion complexes is hydroxyl end up and carboxyl end down which of ursolic acid,it run through the cavity of β–cyclodextrin. In the inclusion compound, hydrogen bonds were formed between ursolic acid and β–cyclodextrin.When the simulation system in water environment, under the condition of 500 Mpa pressure,the total energy and potential energy is smaller than under normal pressure.It shows that increased pressure can make the system more stable. Under the same conditions, under 500Mpa pressure, the density is less than under normal pressure. It shows that increased pressure can compress system volume.

## ACKNOWLEDGMENT

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## REFERENCES

**[1]** D.A.McQuarrie; Statistical Mechanics,Harper and Collins,New York, **(1976)**.

**[2]** N.L.Pacioni, A.V.Veglia; Anal.Chim.Acta, **583**, 63 **(2007)**.

**[3]** S.Pricl, M.Fermeglia; Molecular simulation of host-guest inclusion compounds:an approach to the lactodendrimers case.Carbohydrate Polymers, **45**, 23-33 **(2001)**.

**[4]** N.D.Morelon, M.Bee; J.Combet.Molecular dynamics simulation of a channel type inclusion compound: comparison with neutron scattering

experiments.Chemical Physics, **261**, 75-88 **(2000)**.

**[5]** V.J.Smith, N.M.Rougier, R.H.Derossi, M.R.Caira, E.I.Bujan, M.A.Fernandez, S.A.Bourne, Carbohydr.Res., **344**, 2388 **(2009)**.

**[6]** O.Garcia-Arribas, R.Mateo, M.M.Tomczak, P.L.Davies, M.G.Mateu; Thermodynamic stability of a cold-adapted protein,type III antifreeze protein,and energetic contribution of salt bridges,Protein Sci., **16**, 227-238 **(2007)**.

**[7]** M.Fermeglia, M.Ferrone, A.lodi, S.Pricl; Host–guest inclusion complexes between anticancer drugs and β-cyclodextrin: computational studies. Carbohydrate Polymers, **53**, 15-44 **(2007)**.

**[8]** D.Thpmpson, J.A.Larrsson; Modeling ComPetitive Guest Binding to β-Cyclodextrin Molecular Printboards[J].J.Phys.Chem.B, **110**, 16640-16645 **(2006)**.

**[9]** Aiquan Jiao, Xing Zhou, Xueming Xu, Zhengyu Jin; Molecular dynamics simulational of cyclodextrin cumene hydroperoxide.Computational and Theoretical, **1013**, 1-6 **(2013)**.

**[10]** L.Natalia, B.Adriana, V.Alicia; Structural characterization of N-methylcarbamate: â-Cyclodextrin complexes by experimental methods and molecular dynamics simulations.Spectrochimica Acta Part A:Molecular and Biomolecular Spectroscopy, **103**, 319-324 **(2013)**.

**[11]** Li.Yang, Cong.Li, Tianhu.Yuan, Tianwei.Tan; Preparation of highly pure daidzin on oligo-â-Cyclodextrin sepharose HP and investigation of chromatographic behavior of isoflavones by molecular docking.Journal of Chromatography B, **879**, 1773-1780 **(2011)**.