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Molecular simulation of ursolic acid/γ-cyclodextrin host-guest inclusion compounds under ultra high pressure

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ABSTRACT

Ursolic acid (UA) is a triterpenic acid compound a wide range of biological activities, but it has a very low water solubility. γ-cyclodextrin (γ-CD) can be used in order to increase water solubility of UA. To study the water solubility improve mechanism of UA and γ-cyclodextrin (γ-CD) inclusion compounds. Host-guest simulation system of UA and γ-CD under ultra high pressure is firstly investigated using molecular simulations. The results indicated that the most stable conformation is carboxyl of UA forward to smaller cavity of γ-CD and hydroxyl of UA to bigger cavity of γ-CD. In the inclusion compound, hydrogen bonds were formed between UA and γ-CD. In water environment, total energy and potential energy in 500 MPa is smaller than under normal pressure in 500MPa, the density is less than under normal pressure for that increased pressure can compress system volume. These demonstrate that ultra high pressure is a useful method for improve solubility of UA and γ-CD inclusion compounds.

KEYWORDS

Ursolic acid; γ-cyclodextrin; Ultra high pressure; Inclusion; Molecular simulation.

INTRODUCTION

Ursolic acid (UA) is a well-known triterpenic acid which has a wide range of biological activities such as anti-diabetic activity, anti-inflammatory and anti-bacterial activities[1,2]. However, UA has a very low water solubility, which limits its applications[3]. In order to improve its water solubility, inclusion is a useful method.

Cyclodextrins (CDs) are cyclic oligosaccharides consist of α-D-glucoses with glycosidic linkages. CDs has many kinds, such as β-cyclodextrin(β-CD), γ-cyclodextrin (γ-CD) and α-cyclodextrin(α-CD). For pharmaceutical purposes, CDs have been used in order to increase solubility and stability of drugs by form host-guest inclusion complex[4,5]. So to study the water solubility improvement mechanism of UA and CDs inclusion compounds is very important. Usually, calculation method is a useful method to study of host-guest inclusion complex[6-8]. Zong etal studied the molecular recognition mechanisms by molecular simulation for UA and (β-CD) inclusion complex under ultra high pressure[9]. However, there is not molecular simulation for UA and γ-CD inclusion complex under ultra high pressure.

In this work, the object is to study the UA and γ-CD inclusion complexes conformation under ultra high pressure by molecular mechanics (MM) and molecular dynamics (MD) calculations.

MATERIALS AND METHODS

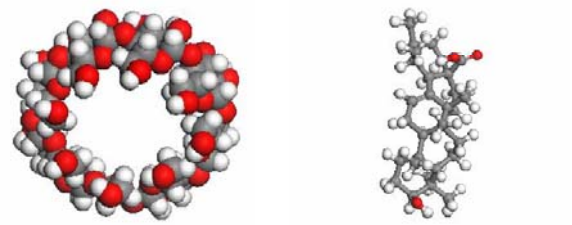
Test materials

This experiment mainly use materials studio software (Accelrys Co.Ltd., USA)

Test method

Establish of host and guest compound simulation

γ-CD compound simulation (Figure 1) was refer to organic crystal database and UA compound simulation (Figure 2) was drawn by materials studio software. Select force field: PCFF force field is applicable on CD inclusion complex system.



CD **UA**

Figure 1 : Compound simulationof CD and UA

Select possible construction phase of inclusion compounds

Accord the molecular structure of UA and CD, six initial construction phase were selected according the relative position of UA and CD.

Water environment model building

Using amorphous cell module of materials studio to form a amorphous type unit, the minimum energy conformation of inclusion compound was put in this amorphous type unit to imitate the inclusion course in water environment. The density of amorphous type unit was set as1.0g/cm^3.

Energy minimization

Using smart minimum method in discover module of materials studio to do energy minimization calculation. Convergence level set as medium. Maximum iteration set as 5000.

Select kinetic parameters

Using dynamics method in discover module of materials studio to do kinetic calculation. Ensemble set as NPT system. Temperature set as 298K. Pressure set as 0.1MPa, 100MPa, 300MPa and 600MPa. Number of steps set as 30000, Time step set as 1.0fs, Dynamics time set as 30.0ps. Trajectory save set as full trajectory save.

RESULTS AND DISCUSSION

Six initial structures of inclusion comple

The position of UA maybe has six conformations in the cavity of γ-CD as shown in Figure 2. The conformation 1: hydroxy end upward and carboxyl end down of UA through the cavity of γ-CD. The conformation 2: hydroxy end upward and carboxyl end down of UA carboxyl terminal in the cavity of γ-CD. The conformation 3: hydroxy end upward and carboxyl end down of UA hydroxyl terminal in the cavity of γ-CD. The conformation 4: carboxyl end upward and hydroxy end down of UA through the cavity of γ-CD. The conformation 5: carboxyl end upward and hydroxy end down of UA, carboxyl terminal in the cavity of γ-CD. The conformation 6: carboxyl end upward and hydroxy end down of UA, hydroxyl terminal in the cavity of γ-CD.

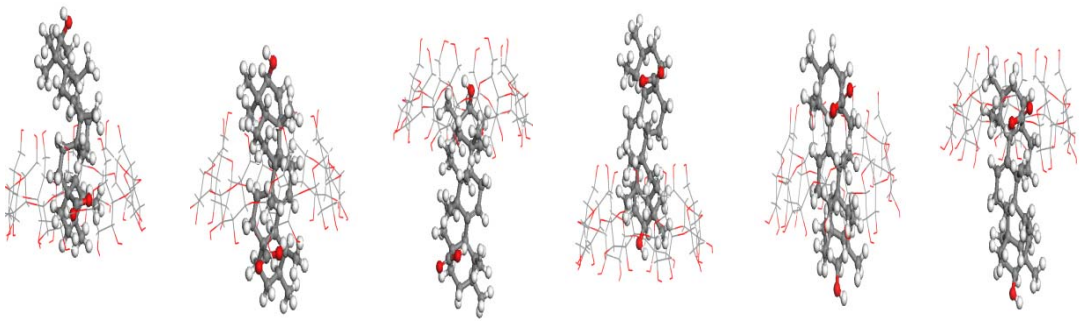


Figure 2 : The six initial structures complex

Minimum energy construction phase by energy minimization treatment

Using smart minimum method in discover module of materials studio to minimization treatment. The minimum energy construction phases were the most stable construction phase. The lowest energy list of the six initial structures of UA-γ-CD inclusion complex was in TABLE1.

From TABLE 1, we can see the minimum energy construction phase is phase 5. The construction phase is shown in Figure 3.

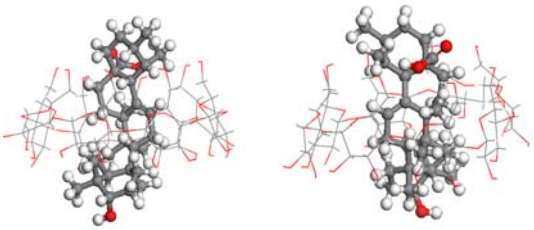


Figure 3 : The lowest energy structure of inclusion complex

TABLE 1 : The lowest energy list of the six initial structures of UA-γ-CD inclusion complex (Kcal/mol)

	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5	Phase 6
Total Potential energy	-114.04	-101.99	-93.89	-29.74	-131.44	-122.80
Internal	-22.69	-19.79	-19.64	-29.10	-34.55	-24.19
Bond	25.53	27.51	29.22	26.87	24.93	28.33
Angle	143.44	149.72	143.41	145.51	133.28	146.45
Torsion	-131.08	-131.25	-128.54	-137.67	-133.86	-136.18
Nonbond	-91.35	-82.21	-74.24	-0.64	-96.89	-98.61
Vdw	50.16	63.89	53.91	70.47	48.83	58.42
Electrostatic	-141.52	-146.10	-128.15	-71.11	-145.71	-157.03

Water environment model

In order to accurate simulation the solution environment, the simulation model which involve a certain number of water molecules must be built. The amorphous cell was built by amorphous cell module. It consist of lowest energy structure of inclusion compound and a certain number of water molecules. Figure 4a was the amorphous cell of the lowest energy structure of UA-γ-CD inclusion complex. Figure 4b was the amorphous cell including 600 water molecules. Figure4c was the amorphous cell of lowest energy including 600 water molecules.

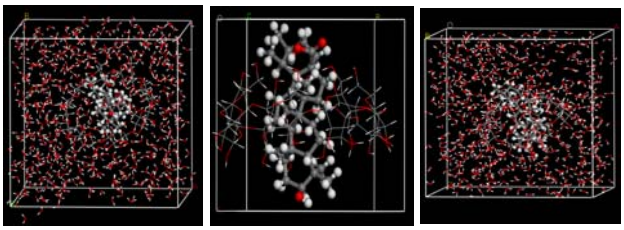


Figure 4 : Figure of water environment model ;(a: lowest energy structure of inclusion complex, b: amorphous cell including 600 water molecules, c:lowest energy including 600 water molecules)

Dynamics simulation in water environment

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 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.

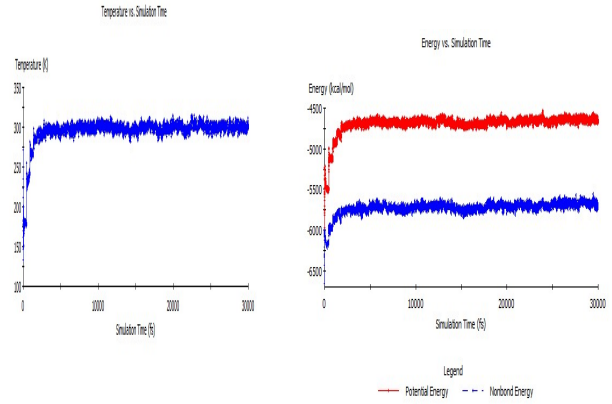


Figure 5 : The system energy and system temperature vs. simulation time at normal pressure ; (a: system energy vs. simulation time, b: system temperature vs. simulation time)

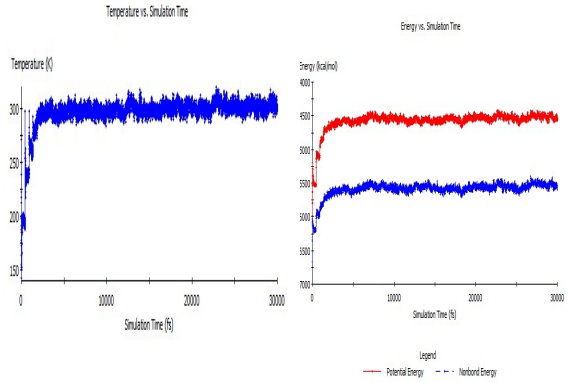


Figure 6 : The system energy and system temperature vs. simulation time at 500MPa; (a: system energy vs. simulation time, b: system temperature vs. simulation time)

The dynamic simulated data table which in water environment was shown in TABLE 2. Initial is the initial data of water environment model. Average is the average after dynamics simulation.

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

TABLE 2 : The data of dynamic simulation in water environment

	Initial	Average	
		0.1MPa	500MPa
Total energy (kcal/mol)	-4322.566	-2775.005	-2887.234
Potential energy(kcal/mol)	-6140.905	-4578.593	-4695.448
Kinetic energy(kcal/mol)	1818.340	1803.588	1808.213
Temperature (K)	298.000	295.582	296.340
Pressure (GPa)		0.000071	0.498332
Density (g/cm^3)	1.0003	1.0197	1.1925

In additions, when the simulation system in 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.

CONCLUSIONS

The most stable conformation is carboxyl of UA forward to smaller cavity of γ-CD and hydroxyl of UA to bigger cavity of γ-CD. In the inclusion compound, hydrogen bonds were formed between UA and γ-CD. In water environment, total energy and potential energy in 500 MPa is smaller than normal pressure. In 500MPa, the density is less than normal pressure. It shows that increased pressure can compress system volume.

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