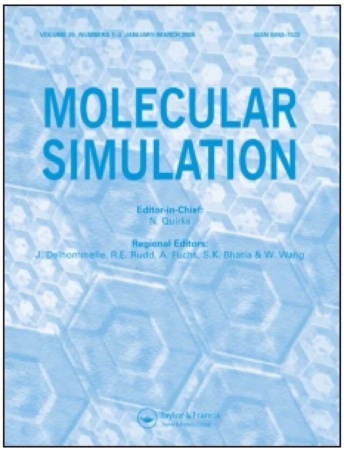

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Molecular simulation of β-cyclodextrin inclusion complex with 2-phenylethyl alcohol

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Molecular simulation of β-cyclodextrin inclusion complex with 2-phenylethyl alcohol

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The structures of β-cyclodextrin inclusion complexes with 2-phenylethyl alcohol in vacuum and aqueous solution have been investigated by using molecular dynamics simulation. The inclusion structures and the physicochemical stability of the complexes were also analysed, discussed and validated by ultraviolet spectrums and thermodynamic properties. The results of molecular dynamics simulation indicate that the A-type β-cyclodextrin inclusion complex with 2-phenylethyl alcohol in both vacuum and aqueous solution have better physical stability, and its chemical stability also has obvious promotion than that of free one. Therefore, the β-cyclodextrin can be used to control and regulate the release of the 2-phenylethyl in food.

Keywords: molecular dynamics simulation (MD); host–guest interaction; inclusion complex; 2-phenylethyl alcohol (PEA, guest); β-cyclodextrin (β-CD, host)

1. Introduction

β-Cyclodextrin (β-CD) formed by seven glucose units is quite important in the fields of molecular recognition and host–guest chemistry [1,2] because of its annular structure with hydrophobic cavity and hydrophilic surface. The molecular shape of β-CD is close to frustum of right circular cone as shown in Figure 1, in which seven axial hydrogen atoms (H3) form wide base and seven primary alcohol groups form narrow base. A great variety of guest molecules can be inserted into the annular structures of β-CD and form nano-sized host–guest inclusion complexes. Those host–guest complexes have many special functions, such as controlled release [2], targeting [3], enhanced solubility [4], chiral recognition [5], enhanced physicochemical stability [6] and so on. Therefore, β-CD has been applied to the pharmaceutical, food and cosmetic industries, etc. due to its special properties [1–4,6–11].

2-Phenylethyl alcohol (PEA) molecule has a popular flavour and is used commonly as crude rose oil and orange oil in food and cosmetics. The volatility of PEA is very high, especially when it is heated up in baking food. The present study is to investigate the stability of the β-CD inclusion complex with PEA, because it may be possible to use β-CD to control and regulate the release of PEA in food. Possible microstructures of the PEA–β-CD inclusion complexes were considered and studied in this work. Molecular simulations were performed to determine the structure of the most stable complex. Semi-empirical quantum chemistry calculations were also carried out to compare the theoretical result with experimental ultraviolet (UV) spectrum.

2. Theories and methods

In our simulation, the inclusion structure which the ethoxyl of PEA formed near the wide base (by primary alcohol) of β-CD is denoted as A-type complex, while the ethoxyl of PEA formed near the narrow base (by secondary alcohol) of β-CD is denoted as B-type complex as given in Figure 2, respectively. The initial configurations of these two inclusion complexes were constructed by docking PEA into β-CD using the chemical software ArgusLab v4.0.1 [12].

Molecular dynamics (MD) simulations of both A- and B-type complexes in vacuum were carried out by using Discover in commercial software Materials Studio® (Accelrys, Inc., San Diego, CA, USA). PCFF force field was adopted for the simulation [13].The cut-off distances for van der Waals and electrostatic force were 12.50 Å (precision as fine). To start the simulation, the potential energy of the system was minimised. After that, the system was equilibrated at 298.15 K by MD simulations. Then the production run was performed by using NVT ensemble for 200 ps. Temperature was maintained by the direct velocity scaling method. The trajectory was sampled every 20 fs and in total 10,000 structures were subject to the analysis.

For the MD simulation of the inclusion complexes in aqueous solution, the periodic boundary condition with an amorphous cell was applied. The complex was centred and soaked with 256 water molecules for the initial set-up and the system contained total atoms of 934. The amorphous cell parameters and density at 298.15 K were gained by pre-MD simulations at 298.15 K and 1 atm (NPT ensemble). Then, MD simulations of NVT ensemble were performed on this amorphous cell for

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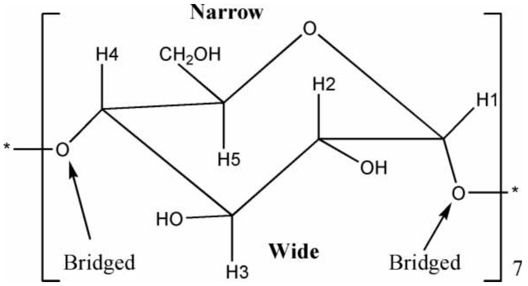


Figure 1. Structure of β-CD and its oligosaccharide unit.

2000 ps production run. The data trajectory was sampled every 200 fs and 10,000 structures were subject to analysis.

The semi-empirical quantum (Q.M.) chemistry calculations using PM5 was employed for the investigation of the thermodynamic stability of the inclusion complexes in vacuum and aqueous solution. The PM5 is a new semi-empirical Q.M. method provided in the MOPAC software original from the commercial software CAChe (Fujtsu limited Co., Tokyo, Japan), which is similar to PM3 but has faster computing speed and higher accuracy. In doing quantum mechanical PM5 calculation, the configurations of the complexes were derived from the averaged configurations in aqueous solution by MD simulation.

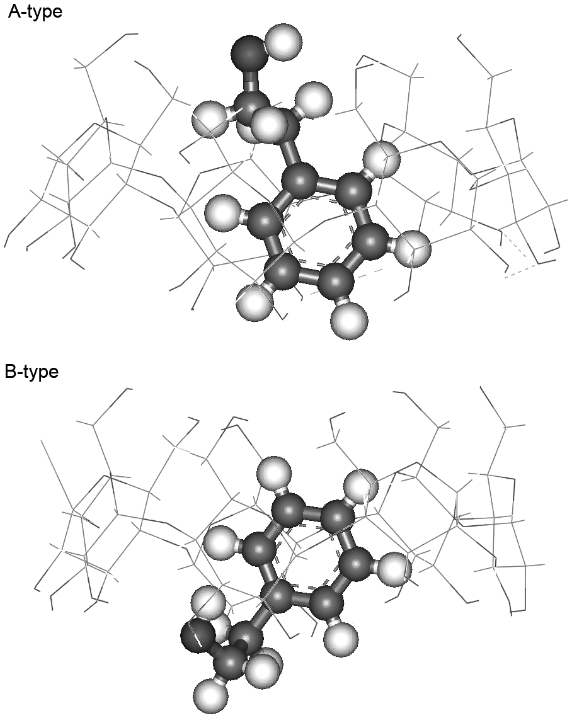


Figure 2. Structure of PEA–β-CD inclusion complex.

3. Results and discussion

3.1 Physical stability of the inclusion complexes

In order to investigate the physical stability of the inclusion complexes, molecular simulations of two kinds of inclusion complexes in vacuum and aqueous solution were performed.

3.1.1 Physical stability of the inclusion complexes in vacuum

The MD-simulated trajectories of the host and guest molecules in A- and B-type inclusion complexes are shown in Figure 3. In the figure, *r* is the radial distance from centroids of each atom group to the origin of the coordinate system. In both systems, *r* of the CH_2OH (narrow base) and H3 (wide base) of β-CD lay around 5.0 and 7.0 Å. In A-type complex, the ethoxyl group of PEA lies inside the interior of β-CD during the simulation. This indicates that PEA vibrated between narrow and wide base planes β-CD. However, in B-type complex, the trajectory analysis shows that PEA is more mobile. The figure shows that B-type complex converted to A-type complex during 25–50, 110–125 and 140–160 ps, respectively. At about 160 ps, the PEA molecule moved outside of β-CD. In comparison with these simulation results we found that A-type complex is more stable than B-type complex in vacuum.

3.1.2 Physical stability of the inclusion complexes in aqueous solution

In reality, inclusion complexes are usually prepared in aqueous solution and therefore the MD simulations of two

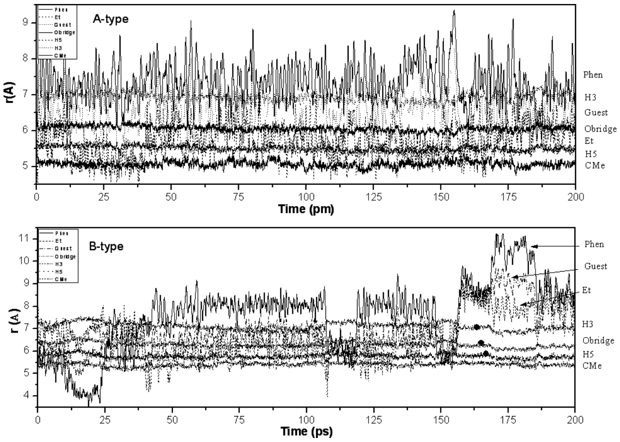


Figure 3. Movement trajectories of each centroid of the title inclusion complexes in vacuum. (CMe: $—CH_2OH$ in host; Et: $—CH_2CH_2—$ in guest; Phen, C_6H_5-ring).

kinds of inclusion complexes in aqueous solution were also carried out.

The trajectories of the host and guest molecules in two kinds of inclusion complexes in aqueous solution are shown in Figure 4. Unlike the result in vacuum, the atomic positions had no significant changes for both A- and B-type complexes during the simulation time range. This indicates that both A- and B-type complexes are stable in aqueous solution. The trajectory analysis showed that each type complex had completely different inclusion structure in aqueous solution than in vacuum.

For the A-type dynamic inclusion structure, the phenylene ring and ethoxy group of PEA are inserted into the cavity of β-CD, with the hydroxyl group of PEA at the edge of the narrow side of β-CD. This is due to the hydrophobic interaction between solvent and phenylene group and also hydrogen bond interactions between ethoxy group and β-CD.

For the B-type inclusion structure, the phenylene ring of PEA is outside of β-CD. This indicates that the hydrophobic effect between phenylene group and solvent is not significant. In addition to this, the hydroxyl group of PEA is near the wide side of β-CD. The distance between hydroxyl group of PEA and β-CD in B-type is larger than that in A-type complex. This indicates that the H-bond interaction between PEA and β-CD in B-type complex is weaker than that in A-type complex.

In summary, the A-type inclusion complex is more stable than the B-type inclusion complex due to the stronger hydrophobic effect and H-bond interactions.

3.2 H-bond and coulomb interactions between the guest and host

H-bond and coulomb interactions are two of the major driving forces for the formation of the title inclusion complex. In case of the similarity between the H-bond and coulomb interactions for O and H atoms, the formation of the H-bond can be defined with criterions that the hydrogen-acceptor distance is less than 2.5 Å and the donor–hydrogen–acceptor angle is larger than 120°.

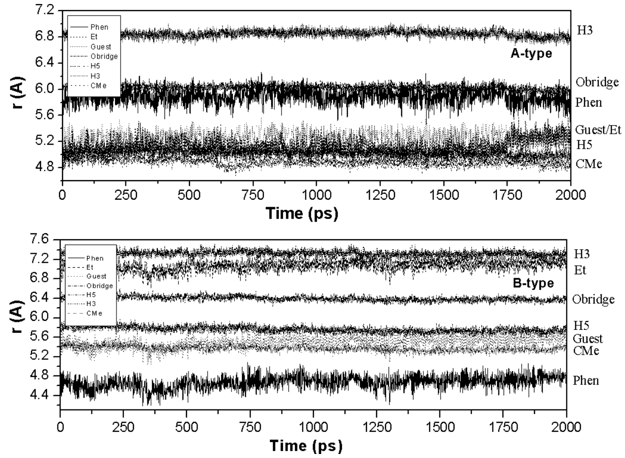


Figure 4. Movement trajectories of each centroid of the title inclusion complexes in aqueous solution. (CMe: $-CH_2OH$ in host; Et: $-CH_2CH_2-$ in guest; Phen, C_6H_5-ring).

3.2.1 H-bond and coulomb interactions between PEA and β-CD in vacuum

Given in Figure 5 are the calculated O—H distances between PEA and β-CD from MD simulations in vacuum. From Figure 5, it is shown that the hydrogen-acceptor distances in A-type complex are 2.25 Å with occurrence probability of 0.02245. The only H-bond was originated between H in PEA to O in β-CD. But there is not any

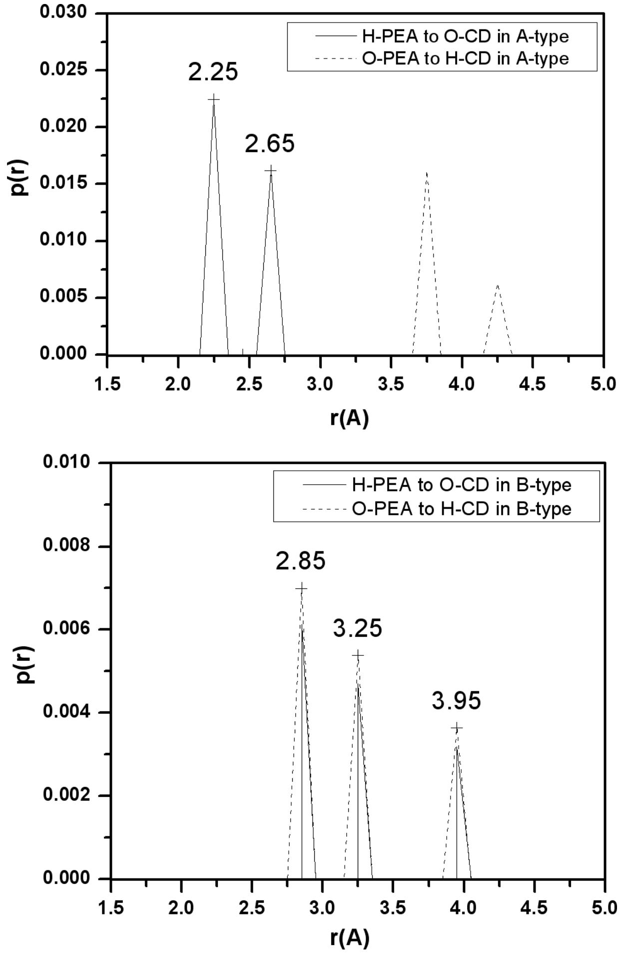


Figure 5. Hydrogen–acceptor distance distribution between PEA and β-CD original from the MD in vacuum. (In A-type inclusion complex, there is only one peak at r1 = 2.25 Å, which indicates that the formation of the H-bond and its hydrogen–acceptor distance is about 2.25 Å with the formation probability of 0.02245. In B-type inclusion complex, there is no peak which indicates the formation of the H-bond.).

H-bond in B-type complex. At the same time, it can be seen that the distances and formation probabilities of coulomb interaction in A-type are more favourable than those in B-type. Therefore, we can draw the conclusion that the A-type inclusion complex is more stable than the B-type one in vacuum due to the larger probability of forming an H-bond.

3.2.2 H-bond and coulomb interactions between the PEA and β-CD in aqueous solution

The PEA–β-CD complex in aqueous solution can form H-bonds between PEA and β-CD, PEA and water and β-CD and water. And the corresponding hydrogen-acceptor distances are shown in Table 1.

Table 1 shows that there is an H-bond interaction between PEA and β–CD in the A-type inclusion complex, but no H-bond interaction between PEA and β-CD in the B-type inclusion complex. Similarly, the distances and formation probabilities of coulomb interactions in A-type are more favourable than those in B-type. This indicates a stronger H-bond interaction between PEA and β-CD in the A-type inclusion complex than that in B-type complex.

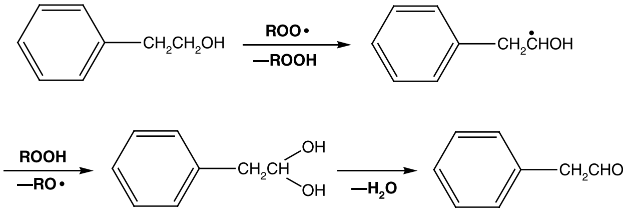
The table also shows that the H-bond and coulomb interactions between β-CD and water, PEA and water are stronger in the B-type inclusion complexes than those in the A-type inclusion complex. This result indicates that PEA in the B-type inclusion complexes can be pulled out easily from β-CD under the influence of water solvation in aqueous solution.

3.3 Effects of inclusion on the chemical stability of PEA

It is well known that the ethoxyl group on PEA can be autoxidised into acetaldehyde or acetoxy in actual aqueous solution (Graph 1). The first step of the autoxidisation is that the C—H on the hydroxymethyl group of PEA is oxidised into C—OH. Therefore, we may infer that the shorter C—H distance has lower chemical activity towards oxidation. Each normal distribution curve of the C–H bond distance was obtained by statistically analysing each C–H bond distance and its occurrence probability during the MD simulation. And the equilibrium length of C–H bond is the distance of the largest occurrence probability.

Table 1. The H-bond interaction between the guest and host in aqueous solution.

Complex	r (Å)	p (r)	Donor molecule	Acceptor molecule
A-type	2.45	0.01894	β-CD	PEA
	2.25	0.4110×10^{-4}	Water	β-CD
	2.45	0.694×10^{-4}	Water	β-CD
	2.45	2.4513×10^{-4}	β-CD	Water
B-type	2.15	3.1524×10^{-4}	Water	PEA
	2.35	3.6668×10^{-4}	PEA	Water
	1.85	1.0747×10^{-4}	β-CD	Water
	2.05	0.8750×10^{-4}	β-CD	Water
	2.15	0.4500×10^{-4}	Water	β-CD
	2.25	1.0899×10^{-4}	β-CD	Water
	2.45	1.5321×10^{-4}	β-CD	Water



Graph 1. The autoxidisation mechanism of PEA.

All equilibrium lengths of C–H in the hydroxymethyl of PEA in the inclusion complexes are listed in the Table 2. It is observed that the equilibrium C–H lengths in aqueous solution are always shorter than those in vacuum, which reveals that the complex has lower activity in aqueous solution due to solvent effect. The table shows that PEA in A-type complex is less active than that in B-type complex based on the same reason.

3.4 Thermodynamic properties and stability of the inclusion complexes

All the thermodynamic data of PEA, β-CD and their complexes calculated by PM5 method are shown in Table 3. In the table, $\Delta_f H$, S and $\Delta_r G$ are the formation enthalpy, entropy and Gibbs free energy change of the formation reaction, respectively. The results in the table reveal that A-type complex is more stable than B-type complex because both in vacuum and aqueous solution ($\Delta_r G(A)$) are less than zero. The $\Delta_r G(A)$ in vacuum and aqueous solution are − 10.105 kJ/mol and − 26.544 kJ/mol, respectively. The results indicate that the formation reaction of A-type complex is easier in the aqueous solution than that in vacuum. The $\Delta_r G(B)$ in vacuum and aqueous solution are both larger than zero: 3.146 kJ/mol and 2.146 J/mol, respectively. This indicates that forming of the B-type inclusion complex is

Table 2. Equilibrium lengths of bond C–H on the hydroxymethyl of the guest in inclusion complexes (Å).

Inclusion complexes	C—H $_1$	C—H $_2$	Equilibrium length	Length change
PEA	1.1032	1.1042	1.1037	Normal value
A type (vacuum)	1.1091	1.1083	1.1087	0.0050
B type (vacuum)	1.1059	1.1051	1.1055	0.0018
A type (aq)	1.0980	1.1038	1.1009	− 0.0028
B type (aq)	1.0946	1.1097	1.1022	− 0.0015

Table 3. Thermodynamic properties of the inclusion complexes and the host and guest molecules calculated using PM5 method.

			PEA-β-CD		$\Delta_r E(H/S/G)$	
T = 298 K	PEA	β-CD	A-type	B-type	A-type	B-type
$\Delta_f H_m^\theta$(gas)	− 137.003	− 6578.441	− 6780.202	− 6766.694	− 64.758	− 51.25
$\Delta_f H_m^\theta$(water)	− 160.373	− 6865.726	− 7069.651	− 7054.776	− 43.552	− 28.677
S_m^θ(gas)	393.599	1733.558	1941.177	1942.202	− 187.980	− 184.955
S_m^θ(water)	375.190	1520.623	1838.189	1792.014	− 57.624	− 103.799
$\Delta_r G_m^\theta$(gas)	–	–	–	–	− 10.105	3.146
$\Delta_r G_m^\theta$(water)	–	–	–	–	− 26.544	2.146

[*] The unit for S is J/mol·K; Then for H and G is kJ/mol.

difficult than A-type complex. Therefore, we may infer that A-type complexes must be the actual inclusion structure.

3.5 Validation of the actual inclusion structure by using UV spectrums

It was reported that there are two common transformations in UV spectrums after guests form inclusion complexes [14,15]. A transformation is that the maximum absorption peak of the complex has red shift or violet shift; the another transformation is that the absorbency of the maximum absorption shows the regularity of fluctuation at the various mole ratios of the host and guest, namely the inductive effect of UV spectrums [16].

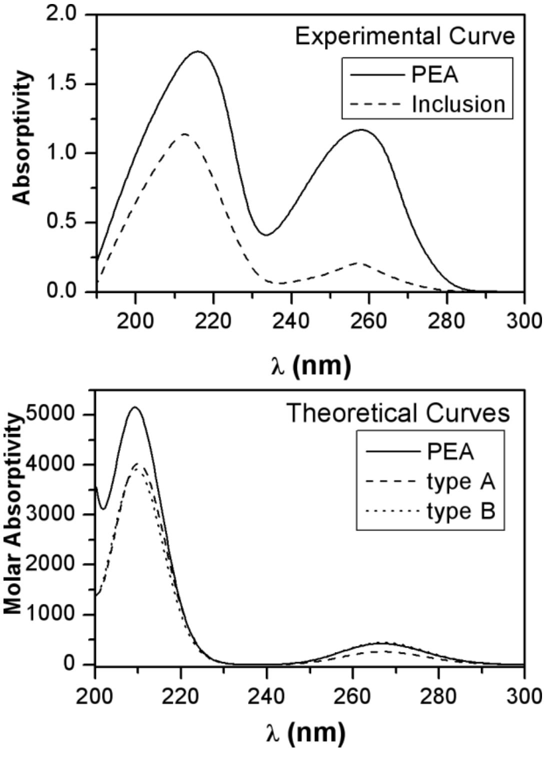


Figure 6. Experimental and theoretical UV spectrum of the inclusion complexes.

Table 4. Experimental and theoretical UV spectrum of the inclusion complexes.

	λ_{max1}/nm	λ_{max2}/nm
PEA(experimental)	206.5(208 nm[17])	259.0
PEA-β-CD	204.0	257.0
PEA(theoretical)	209.24	266.61
PEA–β-CD-A	209.08	266.93
PEA–β-CD-B	206.65	266.76

Given in Figure 6 and Table 4 are the calculated and experimental UV spectrum of the PEA-β-CD complex. The theoretical values of the absorption maximum wavelength of PEA and its inclusion complex are very close to experimental values. The absorbance of the experimental UV spectrum decreases after PEA formed inclusion complex with β-CD. The theoretical absorbance values of A-type inclusion complex are lower than that of the free PEA. On the other hand, for the B-type inclusion complex, the theoretical value of the first maximum absorption peak is lower but the second maximum absorption peak is higher than that of the free PEA. This comparison suggested that the structure of the PEA-β-CD inclusion complex may be A-type complex.

4. Conclusions

The structure, stability, thermodynamic properties and UV spectrum of the PEA-β-CD inclusion complex were investigated by MD simulation. The results of MD indicate that the A-type PEA-β-CD inclusion complex in both vacuum and aqueous solution had better physical chemical stability. Quantum mechanical method is also applied to calculate UV spectrum of the complex. The result supports the MD simulation that the A-type inclusion complex is more stable and it may be the real structure form in solution. The present research helps to design the β-CD inclusion complex that can be used to control and regulate the release of PEA in food.

Acknowledgements

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