

Solvent effects on the beta-cyclodextrin inclusion complexes with m-cresol and dynamic hydrophobicity: molecular dynamics

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Abstract:

Three systems included 1:1 beta-cyclodextrin inclusion complex with *m*-cresol in vacuum, nano water drop and nano acetone drop have been studied using molecular dynamics with pcff force field and without periodic boundary condition. Solvent effects have been discussed. The pre-equilibrated modelling inclusion complex in nano water drop and acetone drop contained two water and two acetone molecules respectively, and during the simulation one water molecule was observed to dissociate from the host in water drop while no dissociation was observed in acetone case. This result well validates the dynamic hydrophobicity of the beta-cyclodextrin. Many analytical results indicate that solvent has an important effect on the stability and dynamic structure of the beta-cyclodextrin inclusion complex.

Keywords: β -Cyclodextrin; *m*-cresol; inclusion complex; molecular dynamics; hydrophobicity; solvent effect

2. Experimental Part

2.1 Simulation Method

Molecular dynamics (MD) simulations were carried out using the MATERIALS STUDIO 2.2 software package (Accelrys Co.). PCFF (Polymer Consistent Force Field) which is in conjunction with the SPC water model [Brenndesen H. J. C. et. al 1987] and well suitable for organic substances was applied in the simulation. The equations of motion were solved with velocity verlet algorithm. The time step of integration was held 0.5 fs in water case and 1 fs in other cases. The summation methods for van der Waals and Coulomb are all atom based (no cutoff). The simulation ensemble was set to *NVE* microcanonical in which number of atoms, volume and energy of system are all kept constant during the simulation. No boundary condition was used for MD run. The system temperature was set to 298 K. After the MD trajectory of one system being collected, analysis was made by the Analysis module in the package and/or our analysis programs compiled by Fortran 90.

2.2 Modelling and simulation

Three systems were modeled for MD simulation. In all system, the host is β -cyclodextrin and the guest is *m*-cresol which is a common chemical agent, and the initial configuration of the inclusion complex is uniformly as shown in fig. 1.

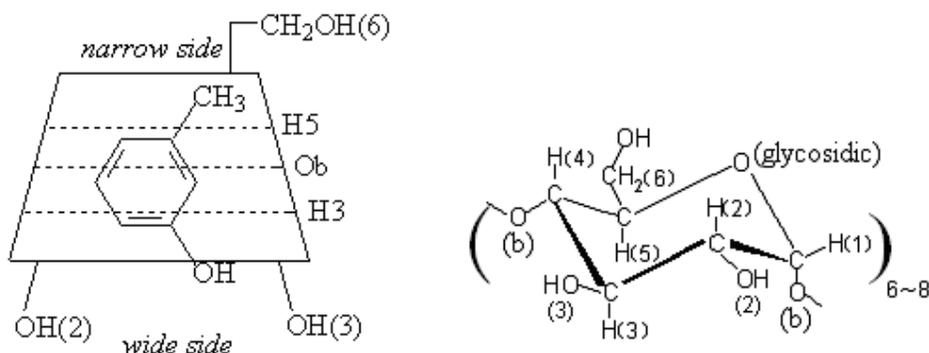


Fig.1 The initial configuration of β -CD inclusion complex (left) in all systems and oligosaccharide unit of CD

In system I, there is no solvent molecule, so the β -CD inclusion can be seen as in the vacuum. After energy minimizing, the system was pre-equilibrated for 500 ps at 298 K by MD simulation which ensemble was *NVE* (the MD within *NVE* ensemble usually be called classical MD) and step time was 1 fs. Then finally classical MD was carried out at 298 K. Iteration step time was chosen as 1 fs, trajectory was saved every 50 fs (0.05 ps), that can also be said sampling time was 50 fs, and 200 ps trajectory in total was collected for the analysis.

In system II, the solvent is water. First, we modeled an energy-minimized nano water drop contained 427 H₂O (the aim we modeled nano drop not periodic system is to save the CPU time) and pre-equilibrated it by the classical MD at 298 K for 200 ps with 0.5 fs step time. Choosing smaller step time – 0.5 fs for water was based on the higher vibrating frequencies of O-H bonds in water. Second, we soaked the β -CD inclusion into the nano water drop and minimized the system's energy to reduce the high energy which arose from the overlap of atoms. Third, we pre-equilibrated the system by the classical MD at 298 K for 500 ps with 1 fs as time step. This well relaxed system is shown in fig. 2. Finally, a classical MD run was made at 298 K with 0.5 fs as time step. Total 100 ps trajectory with every 50 fs as sampling time was collected for the analysis.

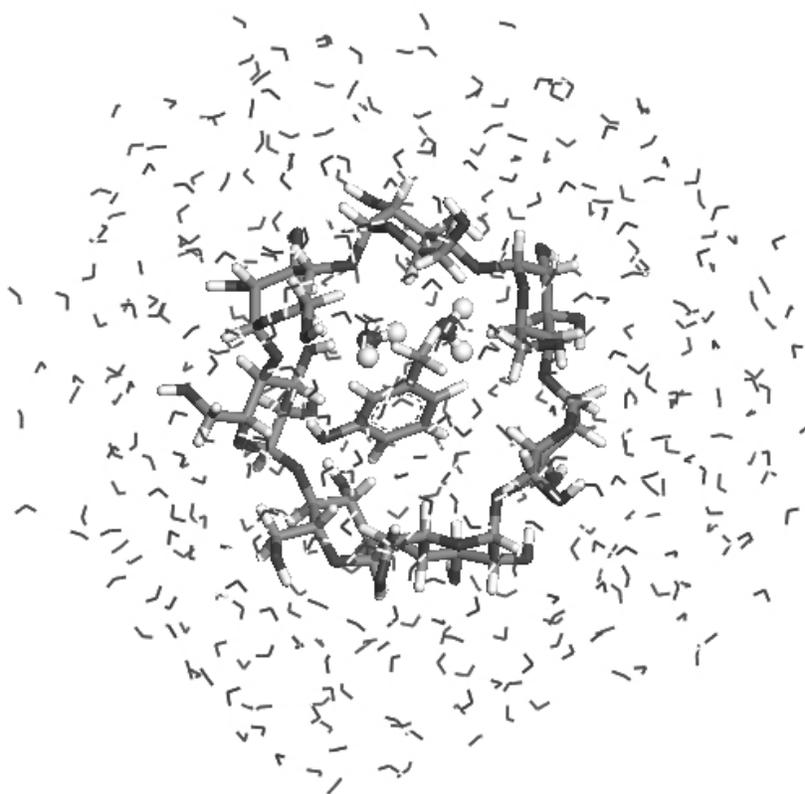


Fig.2 The well relaxed structure of system II

In system III, we select a common organic solvent — acetone. Similar modelling and pre-equilibration process to system II were made but the number of acetone was 238 and the step time was chosen as 1 fs. The finally classical MD run was performed on this nano acetone drop at 298 K with 1 fs as time step and total 100 ps trajectory with every 100 fs sampling was collected for the analysis.

3. Results and discussion

3.1 Solvent effects on the stability of β -CD inclusion complexes--hydrophobicity

After pre-equilibration, the β -cyclodextrin inclusion complex in system II was found including two inside water molecules named w1 and w2 (shown in fig. 2 by 'ball and stick' display style) near the wide side of β -CD, while in system III two acetone molecules named a1 and a2 were found complexing with β -CD near the narrow side of β -CD. In comparison with the two complexed acetone molecules, an uncomplexed acetone molecule near the wide side of β -CD named a3 was chosen as an example. To track the moving trajectories of two water molecules (w1 and w2) or three acetone molecules (a1, a2 and a3) during the final MD, the distances r_{om} between the mass center of Ob plane and the oxygen atoms of w1 and w2 in system II and/or the mass centers of a1, a2 and a3 in system III at every sampling time was calculated and shown in fig.3 and fig.4.

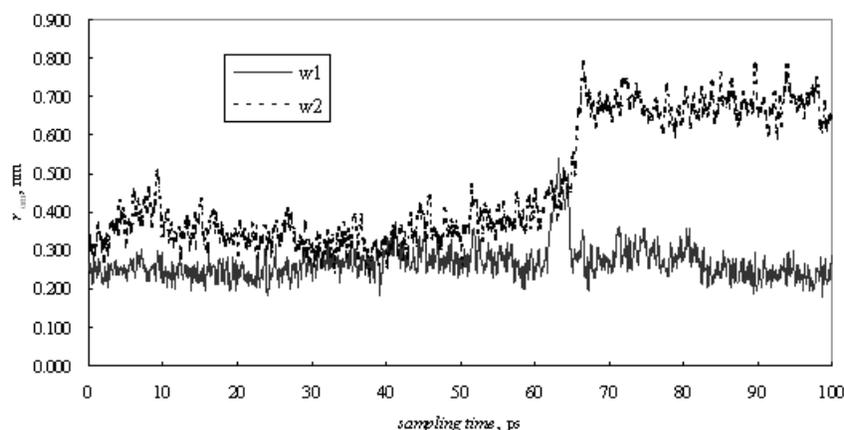


Fig.3 Trajectories of the distances r_{om} between the mass center of Ob plane and oxygen atoms of w1 and w2

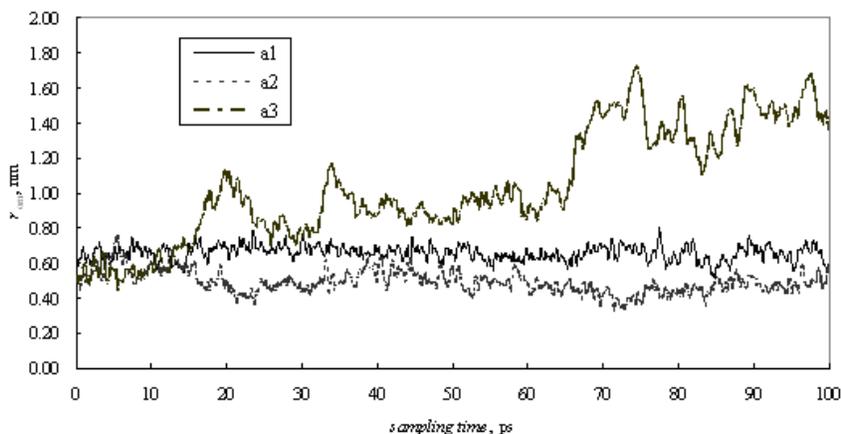


Fig.4 Trajectories of the distances r_{om} between the mass center of Ob plane and those of a1, a2 and a3

In fig.3, w2 molecule was observed to dissociate from the host β -CD at the sampling time about 68 ps while w1 molecule showed a fairly stability complexed by the host during whole simulation time period. This means that host β -CD can form a fairly stable inclusion complex with two guest molecules – one *m*-cresol and one water molecule, and this complex was found from the β -CD complexes with *m*-cresol in aqueous solution which crystal structure had been reported by K. H. Jogun *et al.* [Jogun K. H. et. al 1979].

It can be found from fig.4 that neither of the complexed acetone molecules a1 and a2 was observed to dissociate from the host β -CD during the MD time period. As a comparison, the uncomplexed acetone a3 was found moving away from the host β -CD with process of the simulation time. This shows that β -CD can complex one *m*-cresol and another two acetone molecules in acetone drop comparing with only another one water molecule in water drop case. The size of acetone is bigger than water molecule, but its number of complexation is two. This may be attributed to hydrophobicity of the inner cavity of β -CD as well as acetone as a non-aqueous solvent. The simulation result in this work well validates the hydrophobic property of the inner cavity of β -CD which had been validated by different experimental means [Onda M. et. al 1988].

3.3 Solvent effects on the dynamic structures of β -CD

As mentioned in section 2.3, there are seven bridged oxygen atoms $O(b)$ inside the cavity of CD, and the seven-member $O(b)$ ring had been approximately treated as a plane. In the crystal of pure β -CD, the distance $r_{b,i}$ ($i = 1\sim 7$) between the mass center of $O(b)$ plane and one bridged oxygen atom is 508, 518, 491, 498, 515, 512, 486 pm respectively [Tong L. H. 2001]. Once β -CD complexed a guest, the shape of this seven-member ring would change accordingly [Damodaran K. V. et. al 2001 and Yin K. L. et. al 2003], that agreed with the principle so called 'geometric matching' in supramolecular system. Table 1 lists the average values of $r_{b,i}$ over whole simulation time in three systems. In contrast with pure β -CD, the seven-member $O(b)$ ring of complexed β -CD in system I, II or III was found to deform to different extent. With the increase of number and size of complexed solvent molecule(s) from system I to system III, the deforming extent of the $O(b)$ ring increased. The shapes of $O(b)$ ring in two solvent systems II and III are similar to some extent but different from the non-solvent system I which shape of $O(b)$ ring is approximately normal heptagonal. These results show that solvent has an important effect on the dynamic structure of host β -CD. Besides these solvent effects, the difference between the shapes of $O(b)$ ring in three systems is inevitable also due to the principle of 'energetic and geometric matching' of which the flexible frame or cavity of CD would auto-adjust its structure to adapt the shape and/or movement of guest molecule(s) so as to decrease energy and increase the stability of β -CD complex.

In section 3.1, we had mentioned one water molecule w2 was observed to dissociate from the host β -CD after about 68 ps from fig. 3. While w2 leaving the cavity of CD, the shape of $O(b)$ ring would adjust automatically to produce or adapt this movement. Fig. 6 gives the trajectories of the distance r_b between the mass center of $O(b)$ ring and three of seven bridged oxygen atoms vs. sampling time. After time about 68 ps, obviously, one of r_b

increased, one decreased and another one almost kept constant. The fact that the O(*b*) ring changed its shape after 68 ps, on the other hand, confirmed the dissociation of w2.

Table 1 $r_{b,i}$ (pm) averaged over whole simulation time in systems I, II, III and in β -CD crystal

system	$r_{b,1}$	$r_{b,2}$	$r_{b,3}$	$r_{b,4}$	$r_{b,5}$	$r_{b,6}$	$r_{b,7}$
I	506.2	506.0	511.8	512.3	513.8	511.8	511.8
II	519.8	508.5	525.5	520.4	483.6	490.5	498.5
III	536.6	529.0	528.0	505.4	485.5	490.1	500.1
β -CD	515	512	486	508	518	491	498

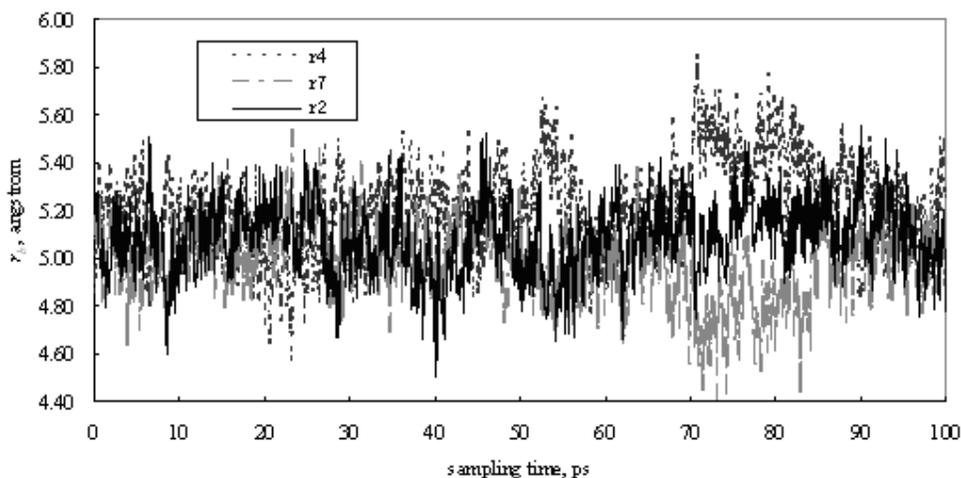


Fig.6 Trajectories of the distance r_b between the mass center of O(*b*) ring and three of seven bridged oxygen atoms of O(*b*) ring vs. sampling time

4. Conclusions

Solvent effects on the β -CD inclusion complexes of *m*-cresol in vacuum, in nano water drop and in nano acetone drop have been studied by molecular dynamics simulation with PCFF force field. In nano water drop (system II), one of the two initial complexed water molecules was observed to dissociate from β -CD after 68 ps. This validates the hydrophobicity of the cavity of host β -CD. While in nano acetone drop (system III), two initial complexed acetone molecules were found stable in the cavity during the simulation time period. The researches on the movement of guest molecules, the dynamic structures of host β -CD and the time average configurations of the inclusion complexes indicated that solvent has an important effect on the stability and dynamic properties of β -CD inclusion complex.

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