β-Cyclodextrin—α-aminopyridine interaction: a DFT study

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The energy changes for two opposite complexation orientations of β-cyclodextrin (β-CD) and α-aminopyridine were calculated by the semiempirical PM3 method. The complexes with the lowest energies obtained by the PM3 method were further investigated by the density functional theory at the B3LYP/3-21G* level. The DFT results indicate that the complexation orientation, in which the amino group is located near the secondary hydroxyl rim of the β-CD cavity, is much more favorable, probably, due to effective hydrophobic interactions. The results of statistical thermodynamics calculations for $p = 1$ atm and $T = 298.15$ K suggest that the inclusion complexation processes of two different orientations are driven by enthalpy.

Key words: β-cyclodextrin, α-aminopyridine, complexation, quantum chemical calculations, PM3 method, density functional theory, interaction.

β-Cyclodextrin (β-CD) possessing the hydrophobic cavity could form host-guest or supramolecular inclusion complexes with a variety of guest molecules in solution[1—3] and in the solid state.[4] The weak non-covalent interactions (hydrogen bonding, hydrophobic and van der Waals interactions, *etc*.) are known as the main forces to drive the guest include into the β-CD cavity in the course of complexation process.[2] Although some powerful experimental techniques, such as microcalorimetric titration,[2] X-ray diffraction,[5] and 2D-NMR spectroscopy[6] can provide lots of important and valuable information for understanding the binding thermodynamics and structure features of the supramolecular complexes, the relevant energy changes concerning the complexation process are difficult to obtain. Meanwhile, precise quantum-chemical computations of the complexation process could offer the quantity, nature, and manners of the weak intermolecular interactions at the level of molecule, atom, and even electron.[7] In spite of the relatively large size and number of atoms containing in CD molecules, a series of computational methods were successively applied to β-CD-based systems to explain and/or predict some experimental phenomena.[8,9] The methods employed range from the molecular mechanics (MM), molecular dynamics (MD), and Monte Carlo simulations (MC)[10—12] to quantum chemistry (CNDO,[13] PM3,[14,15] AM1, and *ab initio*[14]). In our previous papers, we have systematically investigated the complexation behaviors of β-CD with typical guest molecules such as 4,4´-benzidine, *o*-tolidine (3,3´-dimethyl-(1,1´-diphenyl)-4,4´-diamine), and 4-methylpyridine by the semiempirical PM3 method[16] indicating that the van der Waals and hydrophobic interactions essentially contribute to the stability of the resulting complexes. Herein, we will continue to report on our density functional theory (DFT) investigations on the complexation of β-CD and α-aminopyridine. Our aim is to reveal the potential role of different noncovalent weak interactions (especially, hydrophobic interaction) in the complex formation by comparing the energy variations for two opposite complexation orientations.

Calculation Procedure

All theoretical calculations were carried out by GAUSSIAN 03 software package.[17] The geometry of β-CD was fully optimized by the PM3 method[18] without imposing any symmetry restrictions based on the available crystallographic data determined by X-ray diffraction analysis[5] and followed by harmonic frequency analysis to ensure that the stationary point located was the true minimum (all eigenvalues of the Hessian matrix were positive). α-Aminopyridine was constructed by the "Chem. 3D" package and fully optimized by the B3LYP/6-311G* method. The glycosidic oxygen atoms of β-CD were placed onto the XY plane and their center was defined as the origin of the Cartesian coordination system. The primary hydroxyl groups of β-CD are pointed to the positive direction of *Z*-axis. The longer dimension of the guest molecule was initially placed along the *Z*-axis, the relative position of β-CD and α-aminopyridine was measured by the distance from the center of the pyridine ring to the origin of the coordination system as shown in Fig. 1. The complexation process was simulated by entering the guest molecule from secondary hydroxyl rim of β-CD cavity and making it pass through β-CD cavity by steps. For each step, the geometry of the complex was fully optimized by PM3 without imposing any symmetrical restrictions to search for the local stationary point and further confirmed by vibrational frequency

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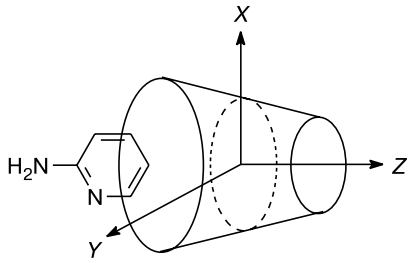

Fig. 1. The Cartesian coordinate system for the inclusion complex of β-CD with α-aminopyridine.

calculations. To gain more precise energy information, the PM3-optimized complexes with the lowest energy were fully optimized using DFT method with the B3LYP exchange-correlation functional[19] and 3-21G* basis set. Vibrational frequency analysis at the B3LYP/3-21G* level was carried out at the *Nankai Stars* supercomputer (Nankai University). The thermodynamic parameters at a pressure of 1 atm and $T = 298.15$ K were also calculated. In addition, the total energies of the complexes in aqueous solution were further computed using the Onsager continuum solvation model based on the self-consistent reaction field (SCRF) method.[20] All computations were performed at a Sun Java Workstation W2100z except those mentioned above.

Results and Discussions

The molecular structure of β-CD optimized at the B3LYP/3-21G* level exhibits an approximate 7-fold symmetry axis. Seven glycosidic oxygen atoms are nearly coplanar (maximum deviation is 0.36 Å) and form a heptagon with an average edge length of 431.4 pm and a radius of 494.3 pm. However, parameters of the H-bond ring formed by the secondary OH groups (four H-bonds are formed by the secondary OH groups of position 2 of the glucose residue with the oxygen atoms of the adjacent secondary OH groups in position 3, and the rest three H-bonds are formed by the secondary OH groups of position 3 of the glucose residue with the oxygen atoms of the adjacent secondary OH groups in position 2, see Fig. 2) are different from those reported by Avakyan *et al.*[21] According to our calculations, the O···O distances range from 265 to 287 pm, the H···O distances range from 169 to 191 pm and the O-H···O angles vary from 160 to 192°). All the primary hydroxyl groups of the narrow edge consistently point towards the exterior of the hydrophobic cavity.

Being a representative guest, the α-aminopyridine molecule has a hydrophilic amino group and hydrophobic aromatic moiety. Therefore, two binding orientations are possible during the complex formation process, namely, the amino group of the guest enters into the secondary side of the β-CD cavity (Am-orientation) firstly and the aromatic ring of α-aminopyridine preferentially embeds into the secondary side of β-CD (Ar-orientation). The energy changes for the two opposite inclusion

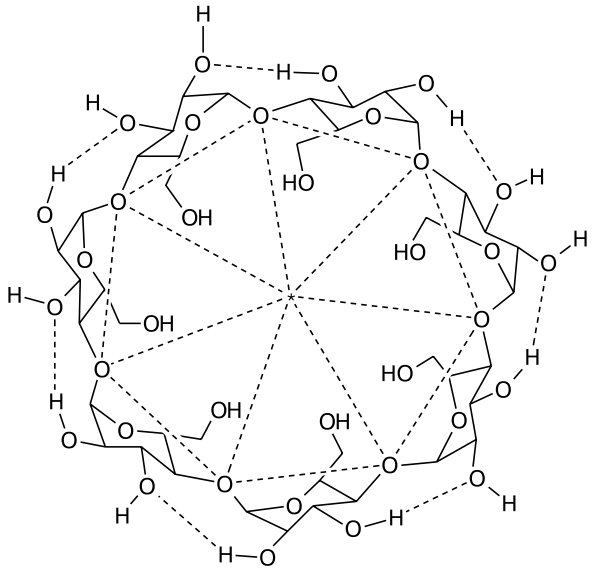

Fig. 2. β-CD molecule with the interglucose H-bonds and approximate 7-fold symmetry axis.

orientations calculated by the PM3 method are shown in Fig. 3.

The energy of the complex decreases as the guest molecule enters into the β-CD cavity (see Fig. 3), suggesting that weak intermolecular interactions cooperatively contribute to the stability of the complexes. When the distance between the centers of the pyridine ring and the plane of glycosidic oxygen atoms of β-CD is 285.4 pm (Ar-orientation), the HF energy of the system is minimal, thus indicating the formation of the supramolecular complex. For the Am-orientation, the distance corresponding to the minimal energy is 181.7 pm. When the guest molecule leaves the cavity by gradually moving from the primary side, the energy of the complex increases again with

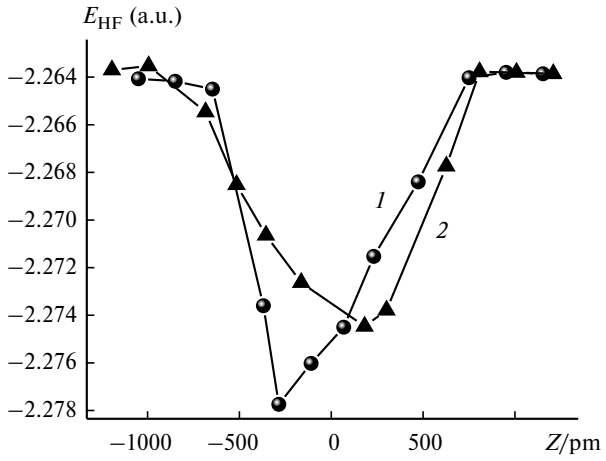

Fig. 3. Hartree—Fock energy (E_{HF}) of the complex plotted *vs.* Z coordinate of the pyridine ring center for the Ar- (*1*) and Am-complexation orientations (*2*).

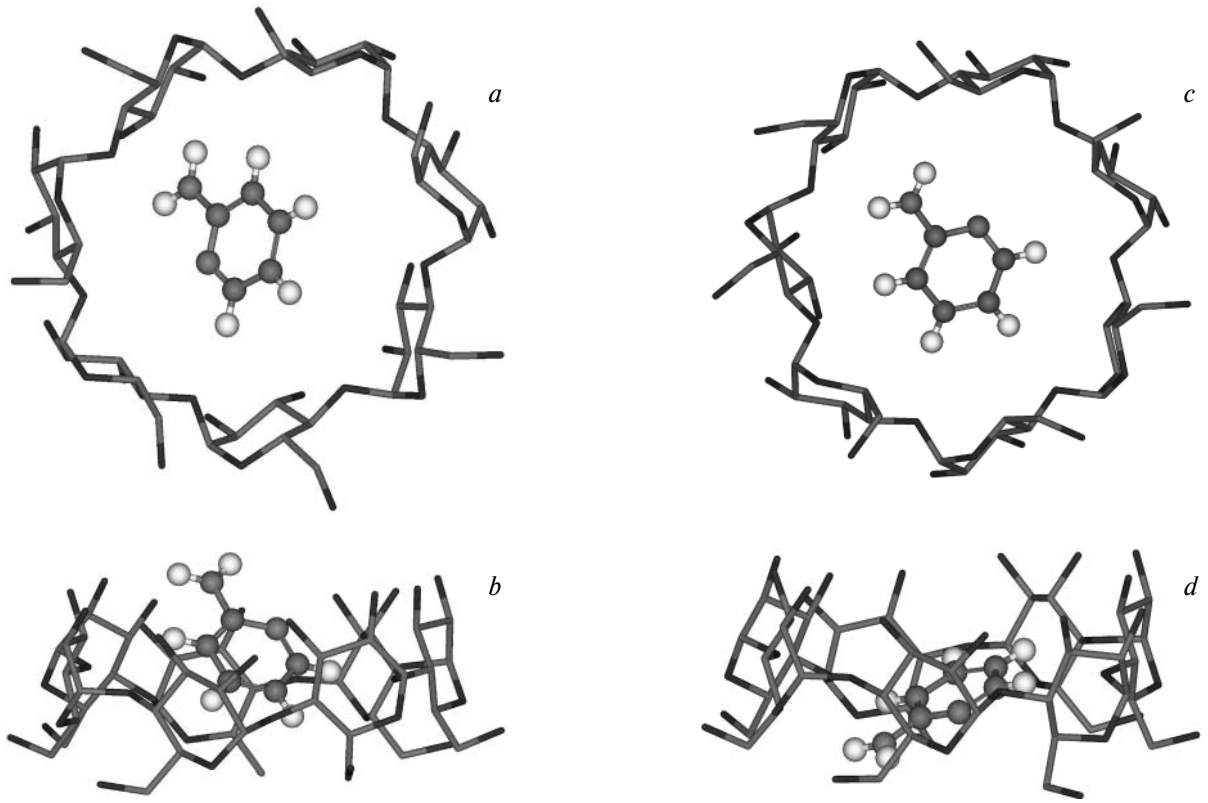

Fig. 4. The B3LYP/3-21G*-optimized structures of the lowest-energy complexes of β-CD with α-aminopyridine: Ar-orientation (*a*, *b*) and Am-orientation (*c*, *d*) seen from the primary hydroxyl rim of β-CD cavity (*a*, *c*) and from the β-CD wall (*b*, *d*). (The hydrogen atoms of β-CD were omitted for clarity).

the disappearance of the intermolecular interactions. It should be noted that, when α-aminopyridine is rather far from β-CD ($z < -750$ and $z > 750$ pm), the HF energies of the system for the two opposite complexation orientations were quite similar to each other.

To obtain the more precise information on the energy characteristics, the geometric parameters of the two complexes calculated by the PM3 method were taken as the starting points for full optimization at the B3LYP/3-21G* level. The optimized structures viewed from different angles are shown in Fig. 4 and their energies are listed in Table 1. Figure 4 reveals that the guest molecule can go freely through the hydrophobic β-CD cavity without any steric hindrances for both inclusion orientations, which is

Table 1. Energies, dipole moments, and thermodynamic parameters of β-CD, α-aminopyridine, and the inclusion complexes with the Ar- (**I**) and Am-orientation (**II**) in the gas phase and in aqueous solution (figures in parentheses)*

Compound	$-E_e$	E_{ZPE}	$-H_f$	$-G_f$	$-\Delta E$	$-\Delta H^\circ$	$-\Delta G^\circ$	$T\Delta S^\circ$	μ/D
	a.u.				kJ mol^{-1}				
α-Aminopyridine	301.97385	0.10619	301.86119	301.89665	—	—	—	—	2.0876
	(301.97541)								(2.7889)
β-Cyclodextrine	4251.81554	1.20837	4250.53356	4250.71189	—	—	—	—	13.4548
	(4251.82140)								(16.7914)
I	4553.82803	1.31815	4552.42980	4552.62361	92.0	92.0	39.6	52.5	10.9450
	(4553.83095)				(89.7)				(13.1951)
II	4553.81893	1.31806	4552.42029	4552.61228	68.4	67.1	9.8	57.2	17.0633
	(4553.82931)				(85.3)				(21.2848)

* Notations: E_e is the electronic energy, E_{ZPE} is the zero-point vibration energy correction; ΔE is the binding energy of the guest—host complex, $\Delta E = (E_e + E_{ZPE})_{compl} - (E_e + E_{ZPE})_{host} - (E_e + E_{ZPE})_{guest}$; $\Delta H^\circ = (H_f^\circ)_{compl} - (H_f^\circ)_{host} - (H_f^\circ)_{guest}$; $\Delta G^\circ = (G_f^\circ)_{compl} - (G_f^\circ)_{host} - (G_f^\circ)_{guest}$; $T\Delta S^\circ = \Delta H^\circ - \Delta G^\circ$.

determined by the relative size of the β-CD cavity and α-aminopyridine. At the energy minimum, the β-CD molecule has an approximate 7-fold symmetry axis and maintains the round shape of the macrocycle. Every glucose residue of β-CD adopts a chair conformation with $^4C_1$ symmetry and seven glycosidic oxygen atoms are coplanar within 1.50 Å. The α-aminopyridine molecule is completely included into the hydrophobic cavity of the host molecule, which favors stabilization of the complexes through van der Waals and hydrophobic interactions.[2] For the Ar-orientation, the distance from the center of guest´s aromatic ring to the *XY* plane of seven glycosidic oxygen atom of the β-CD molecule is 0.96 Å and the dihedral angle between the plane of the α-aminopyridine molecule and the *XY* plane is 47.5° (*cf.* 0.94 Å and 34.7°, respectively, for the Am-orientation).

In the case of Ar-orientation the electronic energy of the complex is 23.9 kJ mol^{-1} lower than that for the Am-orientation (see Table 1). When considering the zero-point energy correction (E_{ZPE}), the total energy ($E_T = E_e + E_{ZPE}$) difference between the two complexes reduced to 23.7 kJ mol^{-1}. Thus, the complex formed by the Ar-orientation is somewhat more stable than that formed by the Am-orientation. The total energies of both complexes are much lower than the sum of the energies of isolated host and guest molecules, suggesting that the resulting complex can be stable. The binding energy (ΔE) of the complex is calculated to be 92.01 kJ mol^{-1} for the Ar-orientation and 68.35 kJ mol^{-1} for the Am-orientation. The higher binding energy for the Ar-orientation suggests that this is the preferred orientation for the complexation of α-aminopyridine with β-CD. A possible reason is the more favorable hydrophobic interaction between the aromatic ring and the hydrophobic cavity of β-CD, which may substantially stabilize the complex.[2] It should be noted that the binding energies calculated by the B3LYP/3-21G* method are much higher than those reported earlier,[2,22] which is probably due to the fact that the inclusion of the long-range (electrostatic) interaction during the molecular geometry optimization is not straightforward within the DFT approach.[23] In addition, the change in the dipole moment upon complexation also confirmed the favorable hydrophobic interaction. The Ar-complexation orientation can cause the dipole moment of the originally highly polarized β-CD cavity to decrease to some extent. On the contrary, in the case of Am-orientation the dipole moment of the complex increased to 3.6085 D. On the other hand, the stability of the resulting complexes can be analyzed using the thermodynamic parameters (enthalpy, entropy, and Gibbs free energy changes) of the complexation process. The results of statistical thermodynamic calculations for $p = 1$ atm and $T = 298.15$ K (Table 1) suggest that the enthalpy changes for both inclusion orientations are negative, meaning that the complexation reaction is exothermic. Thermodynamically, the negative enthalpy changes result from the precise matching in size and shape between the host and the guest.[2] The calculated negative Gibbs free energy changes imply that complexation can occur spontaneously at room temperature. Based on the negative enthalpy and entropy, it can be concluded that the complexation of α-aminopyridine with β-CD is thermodynamically driven by enthalpy.

It is well known that most of inclusion complexations involving β-CD generally occur in aqueous solutions; therefore, the binding behavior of β-CD and α-aminopyridine in aqueous solution seems to be more important than their *in vacuo* behavior. Herein, the SCRF calculations in aqueous solution were performed to examine the potential influence of the solvation effect on the binding energy and the dipole moments of the complexes. The results of calculations listed in Table 1 suggest that the electronic energy of each species decreases to some different extent, which finally leads to reduction of the binding energy difference between two opposite complexation orientations from 23.90 kJ mol^{-1} *in vacuo* to 4.31 kJ mol^{-1} in aqueous solution. Contrary to this, the dipole moments of the complexes increase to some degree and the variation trend is the same as that obtained in the gas-phase calculations.

Two opposite complexation orientations for β-CD and α-aminopyridine were theoretically simulated by the semiempirical PM3 and the density functional B3LYP/3-21G* methods. The results obtained suggest that the inclusion complex with the Ar-orientation of the α-aminopyridine molecule is more stable. Thermodynamically, the stabilities of the two complexes mainly depend on the enthalpy change in the complexation reaction. These significant results may provide us more valuable information for better understanding of the inclusion process involving CDs.

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