

Synthesis and Structure of Inclusion Complex of Cyclomaltoheptaose (β -Cyclodextrin) with *m*-Aminophenol

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The supramolecular compound, β -CD/*m*-aminophenol [$(C_{42}H_{70}O_{35}) \cdot (C_6H_7ON) \cdot (H_2O)_{7.5} \cdot CH_3OH$], was synthesized and characterized by X-ray diffraction analysis. It crystallizes in monoclinic system, $P2_1$ space group, with $a = 1.5122(4)$ nm, $b = 1.0335(4)$ nm, $c = 2.0915(3)$ nm, $\beta = 109.58(2)^\circ$, $V = 3.0798(3)$ nm³ and final $R = 0.0598$. The system belongs to "shallow inclusion" which is rarely found. In this supramolecule, the guest is located over the narrow rim of the host. There are so many hydrogen bonds that they build a dense hydrogen bond net. The hydrogen-bond interactions are the main force to form the whole system and keep the stability.

Keywords β -CD, *m*-aminophenol, synthesis, crystal structure

Introduction

Supramolecule is a kind of system with special structure depending on the weak molecular interactions (such as van der Waals, hydrogen bond, electrostatic and hydrophobic interactions). The weak interactions are related to biological processes, for example, the catalytic reactions of enzymes, the gene replication and mutation, the recognition of receptors.^{1,2} Micro-encapsulation of drug molecules in cyclodextrin (CDs) has been extensively used in the pharmaceutical industry to produce more stable drug preparations with improved bioavailability.³

Cyclodextrin (β -CD) consists of seven α -D glucose residues connected by 1 and 4 bonds of glucoside. Because the surface of the center cavity is formed by H

atoms bonded to C and glycoside O atoms, it is hydrophobic.⁴⁻⁸ To understand the role of the nature of the guest molecule in the structure of the CD complexes, several β -CD complexes have been synthesized.⁹⁻¹² Their crystal structures were determined, and the dynamic and molecular mechanism calculation were performed.

Experimental

m-Aminophenol (5 mmol) in 95% methanol was added dropwise to β -CD (5 mmol) in hot water at 60 °C. The reaction mixture was stirred and refluxed for 4 h, and then was put into a glass tube sealed with tin foil and wax. The glass tube was immersed in a container filled with 60 °C water. Ten days later, colorless crystals were formed but not stable in air. The molecular formula of the title compound is $(C_{42}H_{70}O_{35}) \cdot (C_6H_7ON) \cdot (H_2O)_{7.5} \cdot CH_3OH$, $M_r = 1411.27$. ¹H NMR (D_2O , 400 MHz), δ : 5.06 (s, 1H, H₁), 3.64 (d, 1H, H₂), 3.92 (d, 1H, H₃), 3.57 (d, 1H, H₄), 3.78—3.86 (m, 3H, H₅ and H₆); IR (KBr) ν : 3372, 2927, 1680, 1604, 1520, 1416, 1157, 1029 cm⁻¹. Anal. calcd for the title compound: C 41.70, H 6.86, N 0.99; found C 41.78, H 6.83, N 0.98. The chemical shifts of the β -CD complex of H₁, H₂ and H₅ are close to the free β -CD molecule, but those of the H₃ and H₅ move to the higher field, because the H₃ and H₅ atoms are located at the inside of the cavity, near the guest molecule.

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A single crystal with dimensions of $0.35 \times 0.35 \times 0.55 \text{ mm}^3$ was sealed in a glassy capillary tube with solution to prevent the loss of the crystallized water. The crystal was mounted on a MACD P2030 image diffractometer with graphite monochromatized MoK_α radiation ($\lambda = 0.071073 \text{ nm}$) using ω -scan, $1.2^\circ/\text{min}$ scan rate, 2θ from $4.16\text{--}41.90^\circ$ (h : $0 \rightarrow 14$, k : $0 \rightarrow 10$, l : $-21 \rightarrow 19$). A total of 3206 reflections were collected, of which 3146 reflections with $I \geq 2\sigma(I)$ were considered as observable. The complex crystallized in the monoclinic system, space group $P2_1$, with $a = 1.5122(4) \text{ nm}$, $b = 1.0335(4) \text{ nm}$, $c = 2.0915(3) \text{ nm}$, $\beta = 109.58(2)^\circ$, $V = 3.0798(3) \text{ nm}^3$, $Z = 4$, $D_c = 1.522 \text{ g/cm}^{-3}$, $Z = 0.136 \text{ nm}^{-1}$, $F(000) = 1506$.

The structure refinement was carried out using the coordinates of complex β -CD with benzalcohol¹³ (except for the guest and water molecules). By the difference Fourier calculation, the positions of the other non-H atoms (*m*-aminophenol molecule, methanol and water molecules) were fixed. The structure was allowed to refine anisotropically (but the *m*-aminophenol molecule was isotropically) by full matrix least squares technique. The positions of H atoms of host molecule were defined by the molecular geometrical calculation added to the structural factor calculation. The refinements of the β -CD molecules were preceded smoothly. For disordered O(66) and O(67) primary hydroxyl groups, the sum of oxygen occupation factors was fixed at one. In the complex of β -CD with *m*-aminophenol, four disordered water molecules (Ow6, Ow7, Ow8 and Ow9) were found. The final cycle of refinement included 841 variable parameters was converged to $R_1 = 0.0598$ and $wR_2 = 0.1611$ with $w = [\sigma^2(F_o)^2 + (0.1294P)^2 + 2.6941P]^{-1}$ for 3146 [$F_o > 4\sigma(F_o)$] reflections, $P = (F_o^2 + 2F_c^2)/3$, $\Delta/\sigma_{\text{max}} = 0.214$, $S = 1.073$. The maximum and minimum peaks in the final differences Fourier map were 494 e/nm^3 and -324 e/nm^3 , respectively. All calculations were performed on a PC computer using SHELX-97 program¹⁴ with WINGX package.¹⁵

Results and discussion

An ORTEP presentation of the β -CD complex and part of the numbering schemes are shown in Fig. 1. The coordinations of the non-H atoms are deposited in the Cambridge Crystallographic Date Center (No. 155151).

The average bond lengths, bond angles and intra-hydrogen bond distances are listed in Tables 1 and 2, respectively.

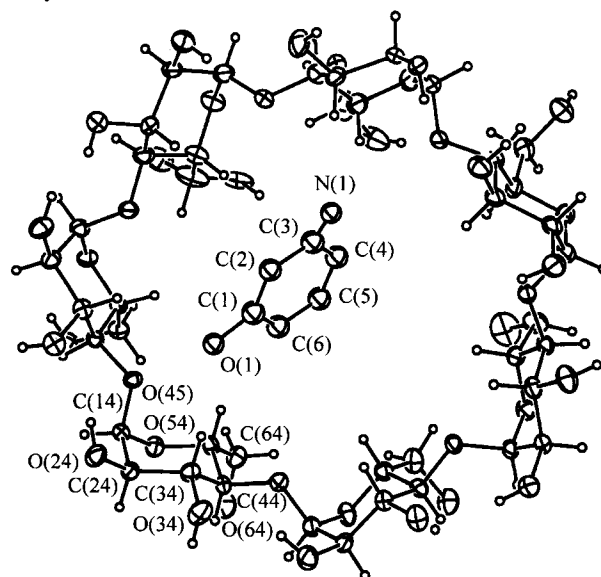


Fig. 1 ORTEP view of β -CD-*m*-aminophenol complex.

The X-ray analysis indicates that the complex consists of one β -CD molecule, one *m*-aminophenol molecule, 7.5 water molecules and one methanol molecule. Molecule β -CD is in the shape of a truncated heptagonal cone. The $\text{O}(4n)\text{--O}(4n+1)$ distances between the adjacent glucose residues are in the range of $0.4241\text{--}0.4502 \text{ nm}$ (average distance 0.4382 nm) and the angles of $\text{O}(4n-1)\text{--O}(4n)\text{--O}(4n+1)$ are in the range of $125.4^\circ\text{--}131.5^\circ$ (average angle 128.3°). Above case is close to the demands of regular heptagon. The endocyclic torsion angles are defined as *gauche-gauche* and *gauche-trans* conformations which can show the structure of β -CD.¹⁶ The primary hydroxyl groups (G2, G6 and G7A) show *gauche-trans* conformations while the others are in the *gauche-gauche* conformations which influence the formation of hydrogen bonds.¹⁷ The secondary hydroxyl groups formed intramolecular $\text{O}(mn)\text{--H}(mn)\text{---O}(m+1n+1)$ hydrogen bonds, which maintain the round structure of the β -CD.

The guest *m*-aminophenol molecule is partly enclosed within the host cavity and trapped in the lattice external to the cyclodextrin cavity. The system belongs to "shallow inclusion" which is rarely found,^{18,19} and the guest is located over the narrow rim of the host molecule. Normally, in the absence of polar groups, the guest molecules can not form H-bonding with host molecules, show-

Table 1 Mean bond lengths (nm) and angles ($^{\circ}$) of β -CD*

Atoms	Mean	Average deviation	Atoms	Mean	Average deviation	Atoms	Mean	Average deviation
C(1m)—O(4m+1)	0.1411	0.014	C(2m)—O(2m)	0.1431	0.019	C(4m)—O(4m)	0.1435	0.011
C(1m)—C(2m)	0.1523	0.011	C(3m)—C(4m)	0.1516	0.017	C(5m)—O(5m)	0.1449	0.012
C(1m)—O(5m)	0.1408	0.093	C(3m)—O(3m)	0.1432	0.096	C(5m)—C(6m)	0.1488	0.014
C(2m)—C(3m)	0.1509	0.011	C(4m)—C(5m)	0.1523	0.097	C(6m)—O(6m)	0.1384	0.064
						C(6m)—O(6mA)	0.1384	0.064
C(1m)-C(2m)-C(3m)	110.5	0.414	C(3m)-C(4m)-O(4m)	106.8	0.571	O(5m)-C(1m)-C(2m)	110.3	0.786
C(1m)-C(2m)-O(2m)	110.3	0.471	O(4m)-C(4m)-C(5m)	109.7	0.343	C(1m)-O(4m+1)-C(4(m+1))	118.3	0.586
O(2m)-C(2m)-C(3m)	111.7	0.857	C(4m)-C(5m)-O(5m)	108.7	1.20	C(2m)-C(1m)-O(4m+1)	107.9	0.357
C(2m)-C(3m)-C(4m)	110.2	0.714	C(4m)-C(5m)-C(6m)	114.1	0.600	O(5m)-C(1m)-O(4m+1)	111.5	0.486
C(2m)-C(3m)-O(3m)	110.3	0.371	O(5m)-C(5m)-C(6m)	106.1	1.03	O(6m)-C(6m)-O(6mA)	106	1.95
O(3m)-C(3m)-C(4m)	110.4	0.985	C(5m)-C(6m)-O(6m)	115.2	6.41			
			C(5m)-C(6m)-O(6mA)	115.2	6.41			
C(3m)-C(4m)-C(5m)	111.3	1.28	C(5m)-O(5m)-C(1m)	114.5	0.757			

* Where $m = 7$, $m + 1 = 1$ **Table 2** Intrahydrogen bond distances (nm)

Atoms	Distances	Atoms	Distances	Atoms	Distances
O(21)—O(31)	0.2904(11)	O(24)—O(35)	0.2905(10)	O(26)—O(37)	0.2976(12)
O(21)—O(32)	0.2896(11)	O(24)—O(45)	0.2751(9)	O(27)—O(41)	0.2732(10)
O(22)—O(43)	0.2896(11)	O(25)—O(46)	0.2793(10)	O(27)—O(31)	0.2864(11)
O(22)—O(33)	0.2776(10)	O(25)—O(36)	0.2919(11)	O(67)—N(01)	0.330(4)
O(23)—O(44)	0.2798(10)	O(36)—O(46)	0.2834(9)	O(66)—O(20)	0.330(3)
O(23)—O(34)	0.2817(10)	O(26)—O(47)	0.2762(10)		

ing faintly high thermal motion (4-*tert*-butyltoluence),²⁰ and even can not be located at all (biphenyl).²¹ That is to say, the solvation of polar group is a very important factor of positioning and stabilizing of guests in β -CD cavities. The O(20) and N(01) atoms of the guest molecule with the oxygen from the β -CD molecule form two intrahydrogen bonding of O(20)---O(66) (0.330(4) nm) and O(67)---N(01) (0.330(4) nm), respectively. There are so many hydrogen bonds between the β -CD molecules and water molecules (see Table 2), which build a dense hydrogen bond net. The hydrogen-bond interaction is the main force to form the whole system and keeps the stability. In the crystal, the β -CD molecules are stacked along the *b* axis to form a typical cage structure with a herringbone-like packing pattern.

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