



Structure of the β -Cyclodextrin-*p*-Hydroxybenzaldehyde Inclusion Complex in Aqueous Solution and in the Crystalline State*

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Abstract

β -Cyclodextrin (β -CD) and *p*-hydroxybenzaldehyde (*p*-HB) were studied by ¹H-NMR in deuterated aqueous solution and the stoichiometry of the resulting complex (1:1) was determined by the continuous variation method. Inclusion of *p*-HB in β -CD was confirmed by the observation of NMR shifts for the inside H5 protons of the β -CD cavity. In the solid state X-ray analysis was carried out and revealed the detailed structure of the inclusion complex. Two β -CDs cocrystallize with four *p*-HB and 9.45 water molecules [2(C₆H₁₀O₅)₇·4C₇H₆O₂·9.45H₂O] in the triclinic space group *P*1 with unit cell parameters: *a* = 15.262(2), *b* = 15.728(1), *c* = 16.350(1) Å, α = 92.67(1)°, β = 96.97(1)°, γ = 103.31(1)°. The anisotropic refinement of 1973 atomic parameters converged at an *R*-factor = 0.066 for 10157 data with $F_o^2 > 2\sigma(F_o^2)$. The 2:4 stoichiometry for the β -CD inclusion complex with *p*-HB in the crystalline state is different from that obtained in solution. β -CD forms dimers stabilized by direct O2(*m*)₁/O3(*m*)₁ ··· O2(*n*)₂/O3(*n*)₂ hydrogen bonds (intradimer) and by indirect O6(*m*)₁ ··· O6(*n*)₂ hydrogen bonds with one or two bridging water molecules joined in between (interdimer). These dimers are stacked like coins in a roll constructing infinite channels where the *p*-HB molecules are included. The *p*-HB molecules direct their polar CHO and OH groups into the nonpolar β -CD cavities and are hydrogen bonded to each other, yielding infinite, antiparallel chains. In addition, crystals of the complex were also investigated with thermogravimetry, vibrational spectroscopy (FTIR), and ¹³C CP-MAS NMR spectroscopy. The results obtained enabled us to structurally characterize the β -CD inclusion complex with *p*-HB.

Introduction

α -, β - and γ -Cyclodextrins (CDs) are cyclic oligosaccharides composed of 6, 7 and 8 D-glucose units linked by α -(1→4) glycosidic bonds. They have the shape of a truncated cone with a hydrophobic central cavity coated by nonpolar C–H groups and ether-like O4, O5 (see Figure 1) [1]. The rims of the cone are hydrophilic, lined by primary O6–H hydroxyl groups on the narrower side and secondary O2–H, O3–H hydroxyl groups on the wider side.

For years, CDs have been the subject of a large number of studies and industrial applications in different areas, e.g., agriculture, cosmetics, electronics, food industry, pharmaceutical sciences, toxic waste treatment [2, 3]. This is mainly due to their ability to form inclusion complexes with various guest molecules, from simple organic compounds [4] to pharmaceutical drugs [4, 5] and organometallic compounds

[6]. Still, their ability to include hydrophobic molecules or molecular fragments differs from guest to guest and the general trends of selective inclusion are not yet fully understood. Moreover, no general guidance lines are available to reliably predict host–guest interactions and stoichiometries in aqueous solution and in the crystalline state.

Previous studies have shown that monosubstituted benzene molecules have, in general, the right size to be totally included in the β -CD cavity [7, 8]. In this work, the interaction between the *p*-hydroxybenzaldehyde (*p*-HB) molecule (see Figure 1), selected as a representative guest, and β -CD, as a host molecule, is studied in aqueous solution and in the crystalline state by standard methods of structural chemical analysis. β -CD is known to form a stable complex with benzaldehyde [9], and the inclusion of a hydroxylated derivative was considered since the hydroxyl group is known to generally hinder complex formation [7].

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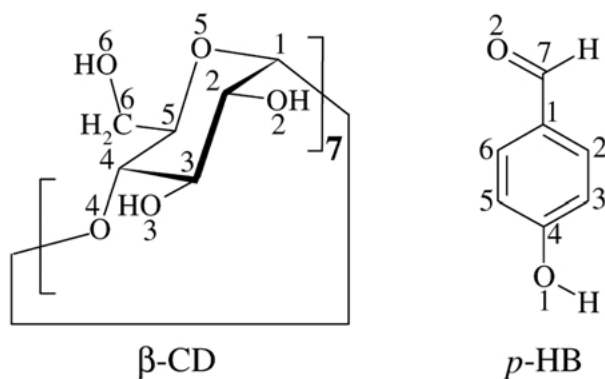


Figure 1. Chemical structures and atomic numbering of β -CD and p -HB.

Experimental

β -CD, kindly donated by Wacker-Chemie, München (Germany), was recrystallized prior to use, by cooling concentrated aqueous solutions in a Dewar flask from ca. 80 °C to room temperature. p -HB was obtained from BHD Chemicals and used as received. Distilled water and analytical grade ethanol and 1,4-dioxane were used as solvents for crystallization. Solutions for $^1\text{H-NMR}$ studies were prepared with deuterium oxide (99.9%) from Aldrich.

Inclusion complex stoichiometry in solution

The stoichiometry of β -CD· p -HB in deuterium oxide solution was determined using the continuous variation method or Job's method [10]. This method involves running a series of experiments varying the host to guest initial concentrations while keeping constant the sum of the initial molar concentrations of host and guest ($[\beta\text{-CD}]_0 + [\text{G}]_0$), at well defined r values ($r = [\beta\text{-CD}]_0 / ([\beta\text{-CD}]_0 + [\text{G}]_0)$). In particular, 10 mM fresh D_2O solutions of guest (G) and β -CD were mixed (i) to constant volume, i.e., the sum of the initial concentrations of β -CD and G remained equal to 10 mM ($[\beta\text{-CD}]_0 + [\text{G}]_0 = 10$ mM), and (ii) to defined values of r , where r took values from 1/10 to 9/10, in steps of 1/10. The stoichiometry was finally determined by plotting $\Delta\delta[\beta\text{-CD}]_0$ against r , where $\Delta\delta$ is the NMR shift of the H5 proton of β -CD, and finding the r value corresponding to the maximum of this distribution.

^1H -, $^{13}\text{C-NMR}$ and IR spectra

$^1\text{H-NMR}$ spectra were recorded on a Bruker AM X 300 spectrometer, with a working temperature of 19.5 °C. The water shift ($\delta = 4.63$ ppm) was used as internal reference.

Solid state ^{13}C CP-MAS NMR spectra were recorded at 100.62 MHz, on a 9.4 T Bruker Avance 400 spectrometer (25 °C, 4.5 μs ^1H 90° pulse, 2.0 ms contact time, 9 kHz spinning rate and 12 sec recycle delays). Chemical shifts are quoted in ppm from TMS (used as an external reference).

Infrared spectra were obtained on a Mattson 700 FTIR spectrometer using KBr pellets (resolution 2.0 cm^{-1} ; 32 scans per spectrum; atmosphere, air).

Thermogravimetric analysis (TGA)

TGA was performed on a Shimadzu TGA-50 thermogravimetric analyser. The analytical parameters were: sample mass about 5 to 10 mg; nitrogen atmosphere, flow rate 30 mL min^{-1} ; sample holder, 5 mm \varnothing platinum plate; heating rate, 1 °C min^{-1} .

X-ray diffraction

Single crystals of the β -CD inclusion complex with p -HB were prepared by dissolving the host and guest in stoichiometric proportion in water, water and ethanol (25%), and water and 1,4-dioxane (5%) mixtures. The resulting mixtures were heated at 40 °C, stirred for 6 hours and slowly cooled. Good crystals were obtained after several days. Ethanol and 1,4-dioxane were chosen as co-solvents since they are totally miscible with water, reduce the polarity of water in mixed solvents, and have little or no affinity to the β -CD cavity. These co-solvents helped dissolve the guest molecule, as the permittivities of the resulting solvent mixtures were lower than that of water. Although the water-dioxane mixture gave higher yields, larger crystals and improved growth rates, the crystals obtained from all mixtures had comparable quality when visually inspected with an optical microscope. However, only the crystals of the complex β -CD· p -HB grown from water-ethanol mixture were used for X-ray analysis.

A plate-like, light yellow crystal with dimensions of 0.3 \times 0.6 \times 0.8 mm^3 was mounted in a glass capillary for the X-ray diffraction experiment performed at RT with a Turbo-CAD4 diffractometer (Enraf-Nonius) using Ni-filtered $\text{CuK}\alpha$ radiation ($\lambda = 1.5418$ Å) from a rotating anode generator (Enraf-Nonius FR571) operating at 40 kV and 80 mA. A total of 10775 reflections were collected to a resolution of 0.89 Å ($2\theta = 120^\circ$). Data were corrected for Lorentz and polarization effects but not for absorption ($\mu = 0.97$ mm^{-1}), see the crystallographic data in Table 1.

The structure was solved by direct methods with the program SHELXS-97 [11], which revealed most of the non-hydrogen atom positions of two β -CD and four p -HB molecules. The remaining atoms including the water oxygen atoms were subsequently determined from the difference Fourier electron density maps aided by the graphic program XTALVIEW [13]. Anisotropic refinements were made by full-matrix least squares of F^2 for all non-hydrogen atoms with the program SHELXL-97 [12]. All hydrogen atom positions could not be determined and were calculated to ideal geometry according to the 'riding model' [12]. All O6-H hydroxyl groups are fully occupied except for that of glucose residue #1 of β -CD molecule #1 (denoted O61_1, see atomic numbering below) which is twofold disordered. The four β -HB molecules are fully occupied and located in the channel-like cavity formed by head-to-head stacking of β -CD molecules. They are refined without any restraints. The 9.45 water molecules are distributed over 28 positions in the interstices between β -CD molecules. The anisotropic refinement of 1973 atomic parameters against 10157 data with $F_o^2 > 2\sigma(F_o^2)$ converged at an R -factor = 0.066 (Table 1).

Table 1. Crystallographic data of 2 β -CD-4*p*-HB-9.45H₂O

Chemical formula	2(C ₆ H ₁₀ O ₅) ₇ ·4C ₇ H ₆ O ₂ ·9.45H ₂ O
Formula weight	2928.28
Crystal habit, color	Plate, light yellow
Crystal size (mm ³)	0.3 × 0.6 × 0.8
Crystal system	Triclinic
Space group	<i>P</i> 1
Unit cell dimensions	
<i>a</i> (Å)	15.262(2)
<i>b</i> (Å)	15.728(1)
<i>c</i> (Å)	16.350(1)
α (°)	92.67(1)
β (°)	96.97(1)
γ (°)	103.31(1)
Volume (Å ³)	3780.1(7)
<i>Z</i>	1
<i>D</i> _x (g cm ⁻³)	1.278
μ (mm ⁻¹)	0.97
<i>F</i> (000)	1554
Diffractometer	Turbo-CAD4 (Enraf-Nonius)
Wavelength, CuK α (Å)	1.5418
Temperature (°C)	20
θ range for data collection (°)	2.73 to 59.50 (0.89 Å resolution)
Measured reflections	10775
Unique reflections	10370
Index ranges	$-17 \leq h \leq 0, -17 \leq k \leq 16, -18 \leq l \leq 18$
Unique reflections [$F^2 > 2\sigma(F^2)$]	10157
Structure solution	Direct methods (SHELXS-97)
Refinement method	Full-matrix least-squares on F^2
Weighting scheme	$w = [S^2(F_o^2) + (0.1579P)^2 + 1.5832P]^{-1}$, where $P = (F_o^2 + 2F_c^2)/3$
Data/parameters	10775/1973
<i>R</i> [$F^2 > 2\sigma(F^2)$]	$R^a = 0.066, wR^b = 0.184$
<i>R</i> (all data)	$R^a = 0.071, wR^b = 0.190$
Goodness of fit	1.038
Highest peak/deepest hole (e Å ⁻³)	0.60/-0.27

$$^a R = \frac{\sum \|F_o\| - |F_c|}{\sum \|F_o\|}$$

$$^b wR = \frac{\sum \{w(F_o^2 - F_c^2)^2\}}{\sum w(F_o^2)^2}^{1/2}$$

A summary of crystallographic data, the geometrical parameter for the β -CD inclusion complex with *p*-HB, and the inclusion geometry of the *p*-HB molecules in the β -CD cavities are given in Tables 1, 2, and 3, respectively. The final fractional atomic coordinates and equivalent isotropic thermal displacement factors are deposited at the Cambridge Crystallographic Data Center [14]. The atomic numbering used is conventional for carbohydrates, i.e., the first number is the position in the glucose and the second number is the glucose number in the CD macrocycle. Additionally, the extra numbers 1 and 2 are used to indicate the β -CD molecules #1 and 2, respectively. For example C41_2 denotes C4 of glucose unit #1 of β -CD molecule #2 (see Figure 1). The letters A and B indicate the disordered atoms. For the guest molecules, similar atomic numbering is adopted and the letter P indicates the four *p*-HB molecules, e.g., C5P_3 stands for C5 of *p*-HB molecule #3 (see Figure 1).

Results and discussion

Inclusion complex in solution

The H3 and H5 protons of β -CD form two inner ‘crowns’ of hydrogen atoms, in the wider and narrower rims, respectively. These protonic ‘crowns’ have strategic positions for signaling host–guest interactions in the cavity. Both H3 and H5 are shifted upfield due to anisotropic shielding caused by encapsulated *p*-HB. However, while the H5 protons give rise to a relatively broad NMR peak and experience a larger shift, the H3 signal gives a multiplet and its shift was difficult to measure due to peak overlapping [15]. Hence, the H5 NMR signal was used for probing the host–guest interaction [16].

No distinct resonances for the free host and the host–guest species could be observed, and the chemical shifts changed monotonically as the β -CD:*p*HB molar ratio was varied. Hence, this system was considered to be in the NMR chemical shift fast exchange limit. Under these conditions, the frequency of a proton signal is obtained by averaging the

Table 2. Geometrical parameters of 2 β -CD-4*p*-HB-9.45H₂O (distances in Å and angles in °)

Residue	1	2	3	4	5	6	7
Q^a, θ^b	0.57, 2 0.55, 7ⁱ	0.57, 5 0.57, 4	0.56, 6 0.56, 3	0.57, 1 0.57, 6	0.55, 6 0.57, 7	0.56, 2 0.55, 4	0.55, 5 0.56, 5ⁱ
ϕ^c, ψ^c	115.2(5), 123.3(5) 116.1(5), 125.8(5)	112.4(5), 126.2(5) 112.7(5), 127.4(5)	117.2(5), 133.4(5) 112.5(5), 124.2(5)	114.1(5), 119.5(5) 117.0(5), 122.1(5)	108.7(5), 131.1(5) 119.3(5), 129.2(5)	118.8(5), 122.6(5) 112.9(5), 125.1(5)	111.2(5), 128.4(5) 112.3(5), 127.7(5)
Tilt angle ^d	9.4(4) 7.9(1)	6.2(1) 8.8(1)	7.1(1) 9.5(1)	13.3(2) 5.5(1)	2.8(1) 2.5(1)	11.4(1) 9.5(1)	7.4(1) 8.5(1)
O4 angle ^e	130.8(1) 130.3(1)	129.2(1) 130.2(1)	126.2(1) 126.7(1)	128.5(1) 127.5(1)	131.1(1) 127.5(1)	127.2(1) 128.9(1)	126.9(1) 125.5(1)
<i>Distances</i>							
O4 deviation ^f	-0.03 -0.04	0.01 -0.01	0.03 0.03	-0.04 -0.01	0.02 -0.03	0.00 0.02	0.01 0.03
O4(<i>n</i>)...O4(<i>n</i> - 1)	4.45(1) 4.31(1)	4.35(1) 4.46(1)	4.38(1) 4.37(1)	4.37(1) 4.35(1)	4.38(1) 4.36(1)	4.44(1) 4.44(1)	4.25(1) 4.37(1)
O3(<i>n</i>)...O2(<i>n</i> + 1)	2.77(1) 2.76(1)	2.76(1) 2.82(1)	2.87(1) 2.81(1)	2.82(1) 2.72(1)	2.81(1) 2.77(1)	2.80(1) 2.82(1)	2.81(1) 2.84(1)
O3(<i>n</i>) ₁ ...O2(<i>m</i>) ₂ ^g	3.19(1)	3.01(1)	3.06(1)	3.26(1)	3.03(1)	3.10(1)	3.08(1)
O3(<i>n</i>) ₁ ...O3(<i>m</i>) ₂ ^g	2.86(1)	2.77(1)	2.85(1)	2.95(1)	2.75(1)	2.85(1)	2.77(1)
O2(<i>n</i>) ₁ ...O3(<i>m</i>) ₂ ^g	3.15(1)	3.02(1)	3.08(1)	3.37(1)	2.98(1)	3.17(1)	3.05(1)
O2(<i>n</i>) ₁ ...O2(<i>m</i>) ₂ ^g	3.00(1)	3.03(1)	2.94(1)	3.17(1)	2.89(1)	3.08(1)	2.93(1)
<i>Torsion angle</i>							
C4-C5-C6-O6	-174.7(24) ^h 48.1(9) ^h 56.3(8)	55.5(6) 54.6(7)	60.5(8) 57.2(10)	59.3(9) 56.9(7)	60.5(6) 55.3(7)	50.7(8) 58.2(9)	58.3(9) 54.5(7)
O5-C5-C6-O6	64.9(24) ^h -72.3(8) ^h -65.7(8)	-65.9(6) -65.9(6)	-62.6(7) -63.8(9)	-61.9(8) -65.7(7)	-62.6(6) -67.0(6)	-72.7(7) -65.1(8)	-63.8(8) -68.2(7)

^aCremer-Pople puckering amplitude [24].

^bIndicates the deviation from the theoretical chair conformation (ideal value: $\theta = 0$; [24]).

^cTorsion angles ϕ and ψ at glycosidic O4, defined as O5(*n*)-C1(*n*)-O4(*n*)-C4(*n*-1) and C1(*n*)-O4(*n*)-C4(*n*-1)-C3(*n*-1), respectively [25].

^dTilt angles, defined as the angles between the O4 plane and the planes through C1(*n*), C4(*n*), O4(*n*) and O4(*n* - 1).

^eAngle at each glycosidic O4: O4(*n* + 1)-O4(*n*)-O4(*n* - 1).

^fDeviation of O4 atoms from the least-squares plane through the seven O4 atoms.

^gIntradimeric hydrogen bonds between O2, O3 of glucose unit *n* (β -CD #1) and of glucose unit *m* (β -CD #2).

^hValues for twofold disordered O6 with the occupancy factors 0.25, 0.75 for sites A and B, respectively.

ⁱBold numbers are the values of β -CD #2.

frequencies of the free host and host-guest species, weighted by their mole fractions [17]. From this relationship, one can easily arrive at $[C]/[\beta\text{-CD}]_0 = \Delta\delta/\Delta\delta_{\max}$, showing that $\Delta\delta$ provides a means for measuring the concentration of the host-guest species, [C] [16–20].

Plotting $\Delta\delta \cdot [\beta\text{-CD}]_0$ against *r* reveals a roughly symmetrical distribution with a maximum at $r \approx 0.5$ (Figure 2) pointing to a 1:1 host-guest association. In addition, since the appreciably shifted protons in β -CD (H3 and H5) point to the cavity interior, it can be inferred that the host-guest association is of the inclusion type.

The equilibrium for the inclusion process in aqueous solution involves hydrated forms of β -CD and G, and represents a substitution of water molecules in the β -CD cavity by the incoming guest molecule. Hence, the corresponding equilibrium constant is given by $K = K_{\text{app}} \cdot (a_{\text{H}_2\text{O}})^w$, where $a_{\text{H}_2\text{O}}$ represents the water activity, the exponent *w* is the amount of displaced water, and K_{app} is the appar-

Table 3. Inclusion geometry of the four *p*-HB molecules in the β -CD cavities (distances in Å and angles in °, more details see Figure 7)

<i>p</i> -HB	1	2	3	4
d^a	3.66(1)		3.78(1)	
η^b	20.8(1)		25.0(1)	
τ^c	86.2(2)	86.5(2)	87.9(2)	88.4(2)
χ^d	0.3		0.5	

^aCenter-to-center distances of the aromatic rings from *p*-HB #1 to #2 and #3 to #4.

^bAngle between the line *d* and the glycosidic O4 plane of β -CD.

^cAngle between the aromatic ring of *p*-HB and the glycosidic O4 plane of β -CD.

^dInterplanar angle between the aromatic rings of *p*-HB #1, 2 ($= |\tau_1 - \tau_2|$); #3, 4 ($= |\tau_3 - \tau_4|$).

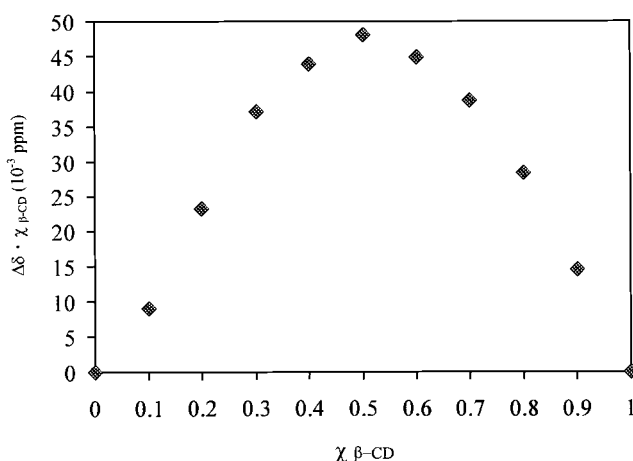


Figure 2. Job plot for the β -CD-*p*-HB complex in D_2O .

ent equilibrium constant which, in this case, measures the extent of inclusion. Introducing the initial concentration conditions (i.e., $[\beta\text{-CD}]_0 = [\beta\text{-CD}] + [C]$, $[G]_0 = [G] + [C]$) in the expression for K_{app} , and making use of $[C]/[\beta\text{-CD}]_0 = \Delta\delta/\Delta\delta_{max}$, one obtains [16]

$$1/\Delta\delta = 1/\Delta\delta_{max} + ([\beta\text{-CD}]_0 K_{app} \Delta\delta_{max})^{-1} \times ([G]_0/[\beta\text{-CD}]_0 - \Delta\delta/\Delta\delta_{max})^{-1}.$$

This equation, exact under the assumption of a single 1:1 association equilibrium, represents a linear dependence of $1/\Delta\delta$ vs. $([G]_0/[\beta\text{-CD}]_0 - \Delta\delta/\Delta\delta_{max})^{-1}$, with ordinate intercept given by $1/\Delta\delta_{max}$ and slope by $([\beta\text{-CD}]_0 K_{app} \Delta\delta_{max})^{-1}$; its mathematical solution calls for an iterative recurrence procedure. For the initial concentrations used in this work ($[\beta\text{-CD}]_0 = 0.5$ mM, $[G]_0 = 5.0, 6.0, 7.0, 8.0, 9.0, 9.5$ mM, see Figure 3), $[G]_0/[\beta\text{-CD}]_0$ takes defined values in the range 10–19, whereas $\Delta\delta/\Delta\delta_{max} < 1$. Hence, the iterative method as applied to the above equation was carried out by successive linear regressions of $1/\Delta\delta$ vs. $([G]_0/[\beta\text{-CD}]_0 - \Delta\delta/\Delta\delta_{max})^{-1}$, with the initial estimate for $\Delta\delta_{max}$ being obtained by neglecting $\Delta\delta/\Delta\delta_{max}$ near $[G]_0/[\beta\text{-CD}]_0$. The iterative convergence of $\Delta\delta_{max}$ to the 2nd decimal place was reached within 2–3 cycles. After performing three experiments, $K_{app} = 3\text{--}4 \times 10^2 \text{ M}^{-1}$ was obtained.

While a word of caution is necessary when comparing association constants obtained from different studies and eventually measured by distinct techniques, comparison of this association constant with that of benzaldehyde ($K_{app} = 17.2 \times 10^2 \text{ M}^{-1}$ [21]) suggests a somewhat weaker association for *p*HB in β -CD, as previously expected.

Inclusion complex in the crystalline state

(a) ^{13}C CP-MAS NMR

The solid state CP MAS ^{13}C -NMR spectrum of the β -CD inclusion complex with *p*-HB is shown in Figure 4. Also shown for comparison are the spectra of β -CD and pure *p*-HB. The spectrum of β -CD exhibits multiple resonances for each type of carbon atom, assigned to C_1 (101–104 ppm),

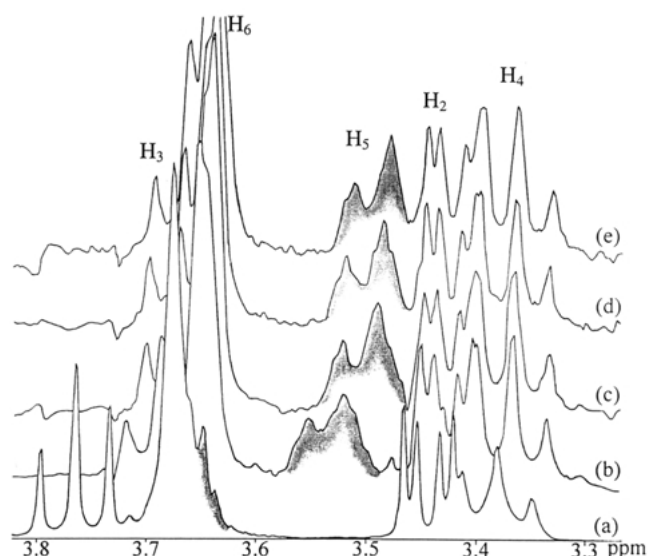


Figure 3. ^1H NMR spectra in heavy water of (a) β -CD 10 mM, and β -CD 0.5 mM with *p*-HB: (b) 5 mM, (c) 7 mM, (d) 8 mM, and (e) 9 mM. The peaks assigned to β -CD H5 protons are shaded. All the β -CD peaks are labelled except for the signal corresponding to H1 (not shown).

C_4 (78–84 ppm), $C_{2,3,5}$ (71–76 ppm) and C_6 (57–65 ppm) [22], see atomic numbering in Figure 1. The spectrum of *p*-HB shows one peak for the aldehyde carbon at 195 ppm and four peaks assigned to the aromatic carbons, C_1 at 165 ppm, C_4 at 138 ppm, $C_{2,6}$ at 127 ppm and $C_{3,5}$ at 116 ppm.

The β -CD spectrum reveals multiple resonances for all the carbon atoms of β -CD. These multiplicities become reduced in the inclusion complex spectrum, giving broader signals with much less structure, if any, thus suggesting a symmetry increase for the β -CD macrocycle upon inclusion. In contrast, in the region of *p*-HB resonances, this spectrum exhibits multiplets, as a result of the distinct environments for the included *p*-HB molecules.

These observations are consonant with the X-ray structure (see below) which shows that the *p*HB molecules in the inclusion compound are packed in pairs with parallel aligned aromatic rings, roughly in a head-to-tail arrangement (the carbonyl group is approximately facing the hydroxyl group of the neighbouring molecule). This spacial arrangement results in an asymmetric environment for the included guest molecules that may be responsible for the presence of multiplets in the ^{13}C CP/MAS NMR spectrum.

(b) Vibrational spectra

The FTIR spectrum of β -CD-*p*-HB was recorded and compared with those for free *p*-HB and a 1:1 physical mixture of β -CD and *p*-HB. The most relevant feature in the vibrational spectra was observed for the carbonyl stretch, see Table 4. The C=O stretching FTIR frequency shifted 20 cm^{-1} to higher frequency, from 1667 cm^{-1} in pure *p*-HB to 1687 cm^{-1} in the β -CD-*p*-HB complex. Since an increase in the $\nu\text{C=O}$ frequency is associated with an improved contribution of the non-polarised canonical form ($>\text{C=O}$) and, consequently, a decreased contribution of the polarised form ($>\text{C-O}^-$) in the resonance structure of the C=O bond, a pos-

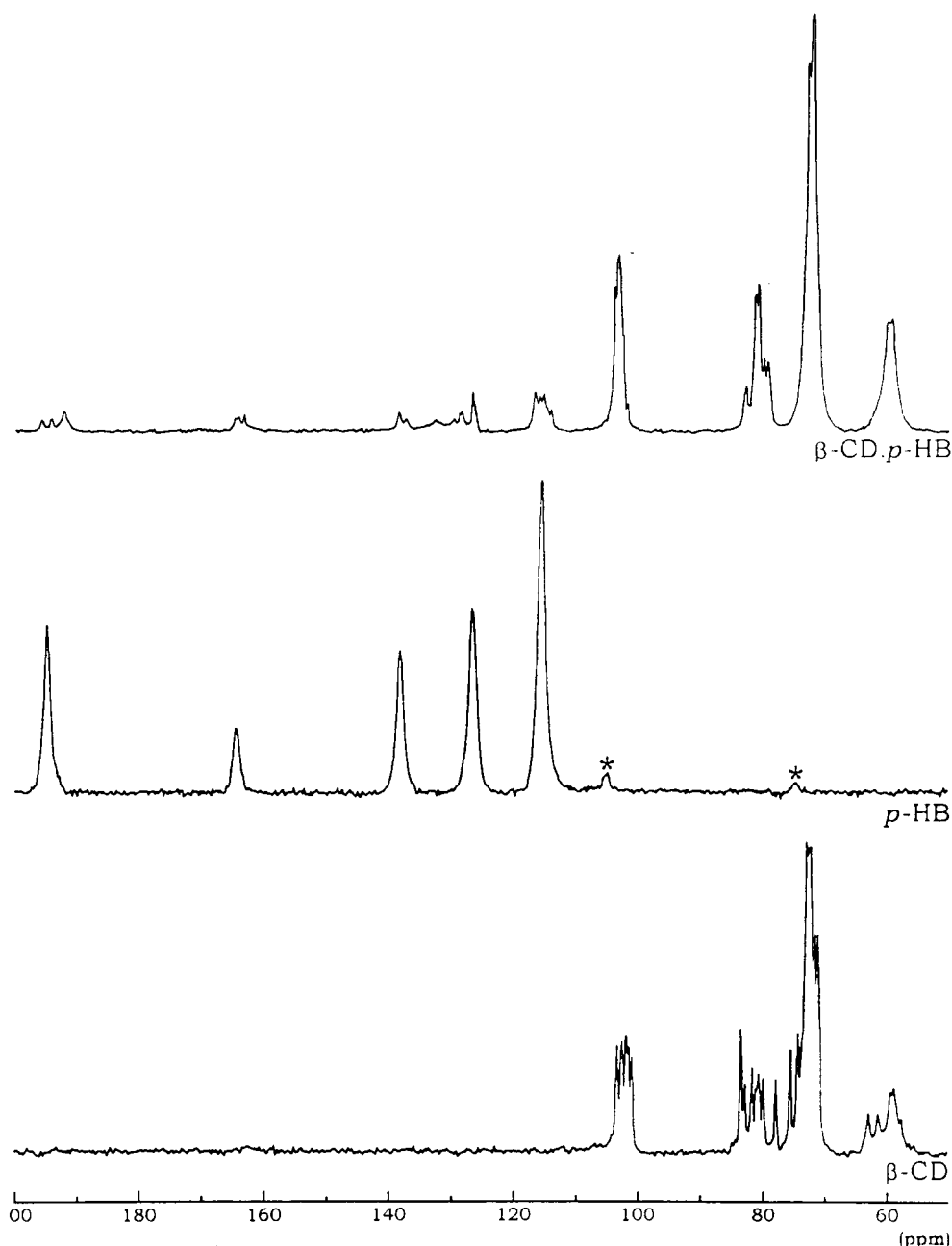


Figure 4. ^{13}C -NMR spectra for β -CD, p -HB, and β -CD- p -HB (the peaks marked * are spinning bands).

Table 4. Relevant vibrational frequencies (FTIR) for p -HB and its complex with β -CD

	Guest molecule	Physical mixture	Complex
$\nu\text{C}=\text{O}$	1667	1666	1687
$\nu\text{C}-\text{O}$	1218	1217	1214

itive $\nu\text{C}=\text{O}$ shift can be interpreted as suggesting a change towards a less polar environment for the $\text{C}=\text{O}$ oscillator, as a result of guest encapsulation.

The inclusion of benzaldehyde and vaniline in β -CD lead also to carbonyl frequency shifts to higher frequencies [9]. The $\text{C}=\text{O}$ frequency for the former shifted 6 cm^{-1} upon in-

clusion (1700 cm^{-1} for benzaldehyde and 1706 cm^{-1} for its β -CD complex) and for the latter the shift was 12 cm^{-1} (1668 cm^{-1} for benzaldehyde and 1680 cm^{-1} for its β -CD complex).

(c) Thermogravimetry

The thermograms of β -CD- p -HB, β -CD decahydrate and p -HB are shown in Figure 5. β -CD demonstrates a gradual loss of hydrated water from ambient temperature up to $77\text{ }^\circ\text{C}$ (13.5% mass loss corresponding to about 10 water molecules per β -CD molecule), exhibiting no further weight changes until $260\text{ }^\circ\text{C}$, where it begins to decompose [23]. The water loss occurs in two steps with different thermogravimetric slopes, a feature that may suggest two distinct

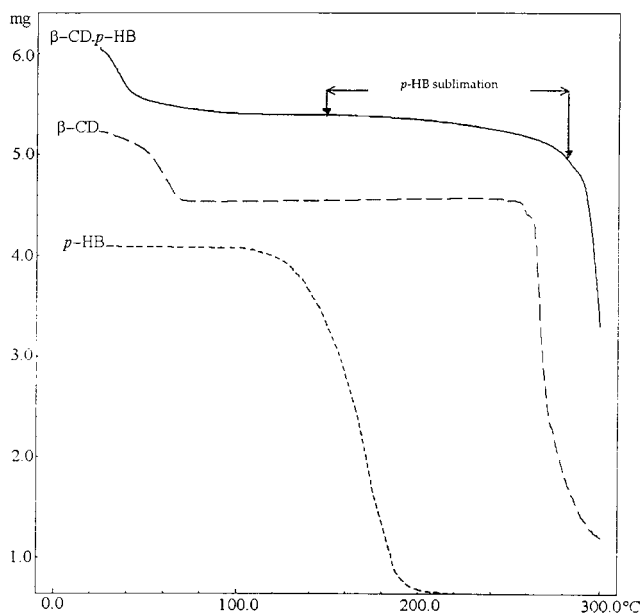


Figure 5. Thermograms for β -CD, p -HB, and β -CD· p -HB.

groups of water molecules concerning their interaction energies. In turn, p -HB starts to decompose thermally at 97 °C, proceeding up to approximately 220 °C, with a total weight loss of 87.5%.

Initially, the β -CD· p -HB thermogram presents two distinct features for dehydration (overall loss of 8.7%): one occurs from room temperature to ca. 40 °C and presents a sigmoid profile; another occurs from 40 °C to 100 °C, and exhibits a constant slope. At ca. 150 °C and up to 280 °C, decomposition occurs in a gradual and smooth way (arrows on Figure 5 show approximate interval of decomposition), with a 9% weight loss, suggesting the sublimation of p -HB. This process occurs at higher temperature than the oxidative decomposition of pure p -HB, thus suggesting that p -HB is more strongly held in the β -CD· p -HB lattice than in the pure compound. From 280 °C on, the inclusion complex thermogram exhibits an abrupt weight loss as a result of the onset of chemical decomposition of the β -CD macrocycle.

(d) X-ray analysis

- Molecular structure of the 2β -CD· $4p$ -HB· $9.45\text{H}_2\text{O}$ inclusion complex

There are two β -CD, four p -HB, and 9.45 water molecules in the asymmetric unit. The two β -CD molecules are isomorphous and can be superimposed with a small rms deviation of 0.25 Å (O6 atoms are excluded from the calculations). Their glucose units are in a regular 4C_1 chair conformation as shown with the glucose puckering parameters Q and θ [24] in the range of 0.55–0.57 Å and 2–7°, respectively (Table 2). The ‘round’ conformations of β -CD macrocycles are stabilized by the systematic intramolecular, interglucose $\text{O}3(n)\cdots\text{O}2(n+1)$ hydrogen bonds with $\text{O}\cdots\text{O}$ distances in the range of 2.76–2.87 Å (Table 2). This is also evidenced by the small fluctuation of the torsion angles about the glycosidic O4, ϕ and χ [25] in the ranges 108.7–119.3° and 119.5–133.4°, respectively, and by the

short span of the tilt angle 2.5–11.4° (Table 2). The well defined heptagons of the β -CD macrocycles are indicated by the deviation of the O4 atoms from their least-squares plane, by the $\text{O}4(n)\cdots\text{O}4(n-1)$ distances, and by the $\text{O}4(n+1)\cdots\text{O}4(n)\cdots\text{O}4(n-1)$ angles which are ≤ 0.04 Å, 4.25–4.45 Å, and 125.5–131.1°, respectively (Table 2). The orientation of the O6–H hydroxyl groups is described by the torsion angles $\text{C}4\text{--C}5\text{--C}6\text{--O}6$ and $\text{O}5\text{--C}5\text{--C}6\text{--O}6$ which show that all O6–H groups are directed ‘away’ from the β -CD cavities and are *-gauche* (50.7° to 60.5° and -61.9° to -72.7°). Except for O61_1–H which is doubly disordered, site A is *+gauche* (-174.7° , 64.9°) and site B is *-gauche* (48.1°, -72.3°).

The four p -HB molecules are not located in the β -CD cavities but in the channel-like cavity formed by alternative head-to-head and tail-to-tail stacking of β -CD molecules, viz, the p -HB #1, 2 at the interdimer region (head-to-head, $\text{O}6(m)\text{--O}6(n)_2(x, y, z+1)$), the p -HB #3, 4 at the intradimer area (tail-to-tail, $\text{O}2(m)_1/\text{O}3(m)_1\text{--O}2(n)_2/\text{O}3(n)_2$), Figures 6, 7, 8. The molecular axes of the p -HB molecules are almost parallel to those of the β -CD molecules as indicated by small deviations from 90° of the angles between the p -HB molecular axes and the glycosidic O4 plane (τ), Figures 7, 8 and Table 3. The p -HB #1, 3 and #2, 4 point their OH hydroxyl groups antiparallel – the former upward, the latter downward, see Figure 6 and arrow directions in Figure 7. The intermolecular $\text{O}\cdots\text{H}\cdots\text{O}$ hydrogen bonds formed between the OH and CHO groups ($\text{O}\cdots\text{O}$ distances 2.56–2.71 Å, Table 5) give rise to endless, antiparallel chains of guest molecules (see dashed-dotted lines in Figure 7, dashed lines in Figures 6, 8) as observed in the crystal structure of free p -HB [26]:

chain 1, OH ‘upward’: $\rightarrow \text{O}1\text{P}_3\text{--H}\cdots\text{O}2\text{P}_1, \text{O}1\text{P}_1\text{--H}\cdots\text{O}2\text{P}_3(x, y, z+1), \dots \rightarrow$

chain 2, OH ‘downward’: $\leftarrow \text{O}1\text{P}_2\text{--H}\cdots\text{O}2\text{P}_4, \text{O}1\text{P}_4\text{--H}\cdots\text{O}2\text{P}_2(x, y, z-1), \dots \leftarrow$

The four p -HB molecules form two dimers (#1, 2; #3, 4) and are aligned such that their aromatic rings are almost coplanar with the interplanar angles (χ) of 0.3° (p -HB #1, 2), 0.5° (p -HB #3, 4), see Figures 6, 7, and Table 3. The corresponding distances from center to center of the two aromatic rings (d) and the angles between the line d and the O4 plane (τ) of each dimer are 3.66 Å, 3.78 Å, and 20.8°, 25.0°, respectively (Figure 7, Table 3). This shows that the dimers of guest molecules are themselves stabilized by π – π interactions as observed in the crystal structure of free p -HB [26]. The p -HB molecules are maintained in positions by only a few hydrogen bond interactions between the p -HB hydroxyl group and the glycosidic O4 of β -CD, viz, $\text{O}1\text{P}_4\text{--H}\cdots\text{O}4_2$, $\text{O}1\text{P}_3\text{--H}\cdots\text{O}4_1$ with respective $\text{O}\cdots\text{O}$ distances of 3.44, and 3.29 Å (Figures 6, 8, Table 5).

The 9.45 water molecules are distributed over 28 positions in the intermolecular spaces between the β -CD molecules. They are severely disordered with an average oc-

Table 5. O–H···O hydrogen bonds in 2(β -CD)·4(*p*-HB)·9.45H₂O with O···O separation <3.5 Å^a

Interaction	Distance (Å)	Symmetry	Interaction	Distance (Å)	Symmetry
W1···W2	2.75(2)	<i>x, y, z</i>	W11···W24	2.40(4)	<i>x + 1, y, z + 1</i>
W1···W3	2.85(4)	<i>x, y, z</i>	W11···O61B_1	2.70(1)	<i>x + 1, y, z</i>
W1···W20	3.22(2)	<i>x, y - 1, z + 1</i>	W11···O65_1	2.65(1)	<i>x, y, z</i>
W1···O63_1	2.68(1)	<i>x, y - 1, z</i>	W11···O56_2	3.45(1)	<i>x + 1, y, z + 1</i>
W1···O66_1	2.76(1)	<i>x, y, z</i>	W12···W15	3.44(4)	<i>x, y, z + 1</i>
W1···O67_2	2.80(1)	<i>x, y, z + 1</i>	W12···O64_1	2.70(4)	<i>x, y, z</i>
W2···W21	2.76(2)	<i>x + 1, y, z + 1</i>	W12···O55_1	3.04(3)	<i>x, y, z</i>
W2···W22	2.83(2)	<i>x + 1, y, z + 1</i>	W12···O62_2	3.07(4)	<i>x, y, z + 1</i>
W2···W23	2.64(3)	<i>x + 1, y, z + 1</i>	W13···W15	2.70(4)	<i>x, y, z + 1</i>
W2···O51_2	3.08(2)	<i>x, y, z + 1</i>	W13···O64_2	2.81(2)	<i>x + 1, y, z + 1</i>
W2···O61_2	3.13(2)	<i>x, y, z + 1</i>	W14···O27_2	2.76(2)	<i>x + 1, y + 1, z</i>
W2···O63_2	2.70(2)	<i>x, y - 1, z + 1</i>	W15···O62_2	2.79(1)	<i>x, y, z</i>
W3···O54_1	3.07(3)	<i>x, y - 1, z</i>	W15···O53_2	3.40(2)	<i>x, y, z</i>
W3···O64_1	3.13(4)	<i>x, y - 1, z</i>	W16···O21_1	2.75(3)	<i>x + 1, y + 1, z</i>
W3···O63_2	2.85(3)	<i>x, y - 1, z + 1</i>	W17···W27	3.26(5)	<i>x + 1, y, z</i>
W4···W20	2.41(4)	<i>x, y - 1, z + 1</i>	W17···W28	3.07(5)	<i>x + 1, y, z</i>
W4···O54_1	3.43(3)	<i>x, y - 1, z</i>	W17···O21_1	3.26(3)	<i>x + 1, y + 1, z</i>
W4···O64_1	2.63(2)	<i>x, y - 1, z</i>	W17···O23_2	2.99(3)	<i>x, y, z</i>
W5···W6	2.69(5)	<i>x, y, z</i>	W18···O34_1	3.15(5)	<i>x, y, z</i>
W5···W9	2.79(2)	<i>x, y, z</i>	W18···O23_2	2.96(4)	<i>x, y, z</i>
W5···O56_1	3.47(2)	<i>x, y, z</i>	W19···O53_2	3.21(3)	<i>x, y, z</i>
W5···O66_1	2.64(2)	<i>x, y, z</i>	W19···O63_2	2.87(4)	<i>x, y, z</i>
W6···O51_1	3.48(4)	<i>x + 1, y, z</i>	W20···W21	2.94(2)	<i>x + 1, y + 1, z</i>
W6···O61B_1	2.74(3)	<i>x + 1, y, z</i>	W20···W22	3.06(2)	<i>x + 1, y + 1, z</i>
W7···W25	3.41(3)	<i>x + 1, y, z</i>	W20···W23	2.89(3)	<i>x + 1, y + 1, z</i>
W7···O31_1	2.86(1)	<i>x + 1, y, z</i>	W20···O51_2	3.45(2)	<i>x, y + 1, z</i>
W7···O26_1	2.72(2)	<i>x, y, z</i>	W20···O61_2	3.18(2)	<i>x, y + 1, z</i>
W7···O36_1	3.47(1)	<i>x, y, z</i>	W20···O63_2	2.55(2)	<i>x, y, z</i>
W7···O31_2	3.10(1)	<i>x, y, z</i>	W21···O51_2	2.58(3)	<i>x - 1, y, z</i>
W8···W25	2.95(4)	<i>x + 1, y, z</i>	W22···O51_2	2.60(1)	<i>x - 1, y, z</i>
W8···O31_1	3.20(4)	<i>x + 1, y, z</i>	W23···W24	3.39(4)	<i>x, y, z</i>
W8···O31_2	3.04(4)	<i>x, y, z</i>	W24···O61_2	2.45(4)	<i>x - 1, y, z</i>
W8···O26_2	2.77(4)	<i>x + 1, y, z</i>	W24···O56_2	3.08(3)	<i>x, y, z</i>
W8···O36_2	3.33(3)	<i>x + 1, y, z</i>	W25···O36_1	3.12(3)	<i>x - 1, y, z</i>
W9···W21	2.92(3)	<i>x - 1, y, z - 1</i>	W25···O21_2	2.27(2)	<i>x - 1, y, z</i>
W9···W22	3.09(2)	<i>x - 1, y, z - 1</i>	W25···O41_2	2.94(2)	<i>x - 1, y, z</i>
W9···O61_2	2.80(2)	<i>x, y, z + 1</i>	W25···O51_2	3.45(3)	<i>x - 1, y, z</i>
W9···O56_2	3.10(1)	<i>x + 1, y, z + 1</i>	W25···O22_2	3.42(2)	<i>x - 1, y, z</i>
W9···O66_2	2.80(2)	<i>x - 1, y, z - 1</i>	W26···O23_1	3.50(1)	<i>x, y, z</i>
W10···W21	2.64(6)	<i>x + 1, y, z + 1</i>	W27···O25_1	2.58(3)	<i>x - 1, y, z</i>
W10···W22	2.73(6)	<i>x + 1, y, z + 1</i>	W27···O32_2	3.12(3)	<i>x - 1, y, z</i>
W10···W23	3.44(4)	<i>x + 1, y, z + 1</i>	W27···O23_2	3.20(3)	<i>x - 1, y, z</i>
W10···O61_2	2.71(5)	<i>x, y, z + 1</i>	W27···O32_1	3.06(3)	<i>x, y, z</i>
W10···O66_2	3.37(6)	<i>x + 1, y, z + 1</i>	W27···O23_1	3.22(2)	<i>x, y, z</i>
W28···O23_1	3.39(3)	<i>x, y, z</i>	O21_2···O24_2	3.43(1)	<i>x, y - 1, z</i>
W28···O25_1	2.69(3)	<i>x - 1, y, z</i>	O62_2···O55_2	3.45(1)	<i>x + 1, y, z</i>
O61A_1···O66_2	3.26(3)	<i>x, y, z + 1</i>	O62_2···O65_2	2.82(1)	<i>x + 1, y, z</i>
O22_1···O22_2	2.72(1)	<i>x - 1, y, z</i>	O64_2···O67_2	2.92(1)	<i>x, y + 1, z</i>
O62_1···O55_1	3.25(1)	<i>x - 1, y, z</i>	O1P_1···O2P_3	2.70(1)	<i>x, y, z + 1</i>
O62_1···O65_1	2.82(1)	<i>x - 1, y, z</i>	O1P_2···O2P_4	2.65(1)	<i>x, y, z</i>
O63_1···O67_1	3.34(1)	<i>x, y + 1, z</i>	O1P_3···O2P_1	2.71(1)	<i>x, y, z</i>
O63_1···O67_2	3.45(1)	<i>x, y + 1, z + 1</i>	O1P_4···O2P_2	2.56(1)	<i>x, y, z - 1</i>
O65_1···O65_2	2.79(1)	<i>x + 1, y, z + 1</i>	O1P_3···O47_1	3.29(1)	<i>x, y, z</i>
O27_1···O24_2	2.79(1)	<i>x, y - 1, z</i>	O1P_4···O42_2	3.44(1)	<i>x, y, z</i>
O67_1···O53_1	3.48(1)	<i>x, y - 1, z</i>			

^aOccupancy factors of water sites are 1.0 (W1), 0.3 (W2), 0.25 (W3), 0.3 (W4), 0.35 (W5), 0.25 (W6), 0.4 (W7), 0.25 (W8), 0.3 (W9), 0.25 (W10), 0.5 (W11), 0.2 (W12), 0.3 (W13), 0.3 (W14), 0.3 (W15), 0.25 (W16), 0.25 (W17), 0.25 (W18), 0.25 (W19), 0.3 (W20), 0.35 (W21), 0.7 (W22), 0.3 (W23), 0.25 (W24), 0.3 (W25), 0.5 (W26), 0.25 (W27), 0.25 (W28).

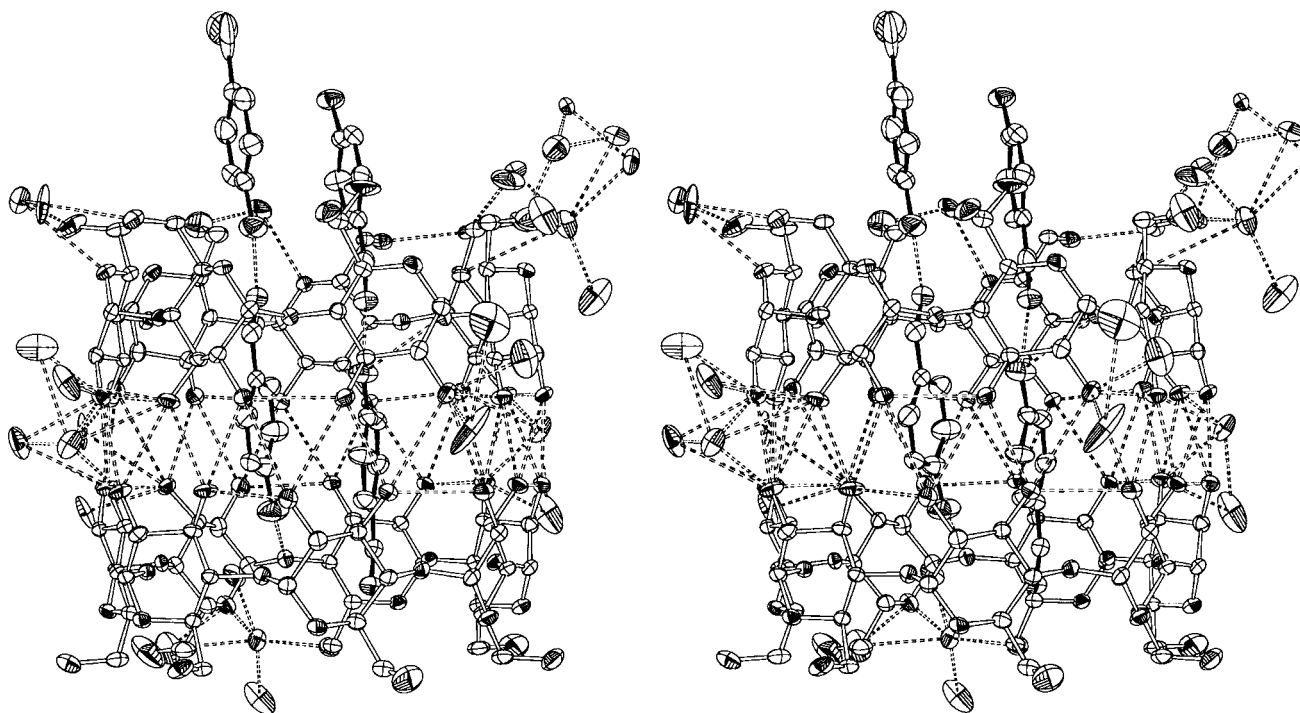


Figure 6. ORTEPIII [35] stereo plot of the $2\beta\text{-CD-}4p\text{-HB-}9.45\text{H}_2\text{O}$ inclusion complex drawn with thermal ellipsoid (30%) representation. Ellipsoids with and without octant shading are C_{CD} and O_{CD} , O_{w} , respectively; $\beta\text{-CD}$ bonds are represented by white sticks and $p\text{-HB}$ bonds are represented by black sticks. Dashed lines indicate possible $\text{O-H}\cdots\text{O}$ hydrogen bonds with $\text{O}\cdots\text{O}$ separation within 3.5 Å.

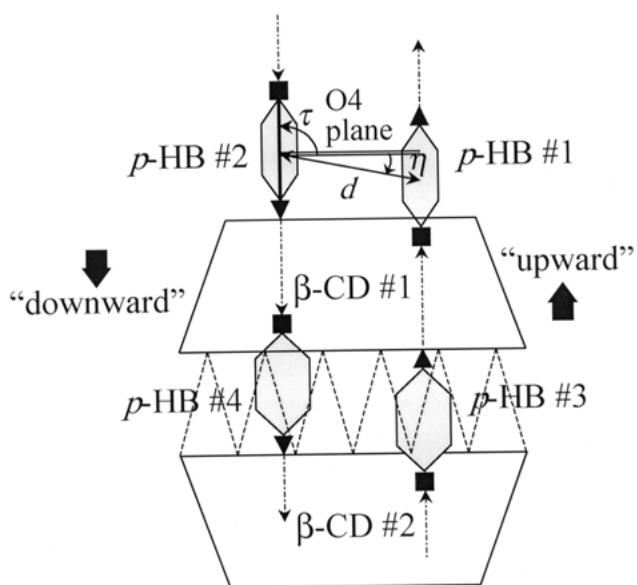


Figure 7. Schematic presentation of the inclusion geometry of the $p\text{-HB}$ molecules in the $\beta\text{-CD}$ cavities. The four $p\text{-HB}$ molecules are represented with hexagons with their OH groups (triangles) direct 'upward' for $p\text{-HB}$ #1, 3 and 'downward' for $p\text{-HB}$ #2, 4 (see arrow directions); the squares are the CHO groups. d are the center-to-center distances of the two aromatic rings of $p\text{-HB}$ #1, 2; #3, 4. Angles η and τ showing inclination of the $p\text{-HB}$ molecular axis (thicker line) and the line d to the glycosidic O4 plane (double line), respectively. Dashed-dotted lines with ended-arrows indicate intermolecular $\text{O-H}\cdots\text{O}$ hydrogen bonds between $p\text{-HB}$ molecules and dashed lines show $\text{O}2(m)_1/\text{O}3(m)_1\cdots\text{O}2(n)_2/\text{O}3(n)_2$ hydrogen bonds in the $\beta\text{-CD}$ dimer.

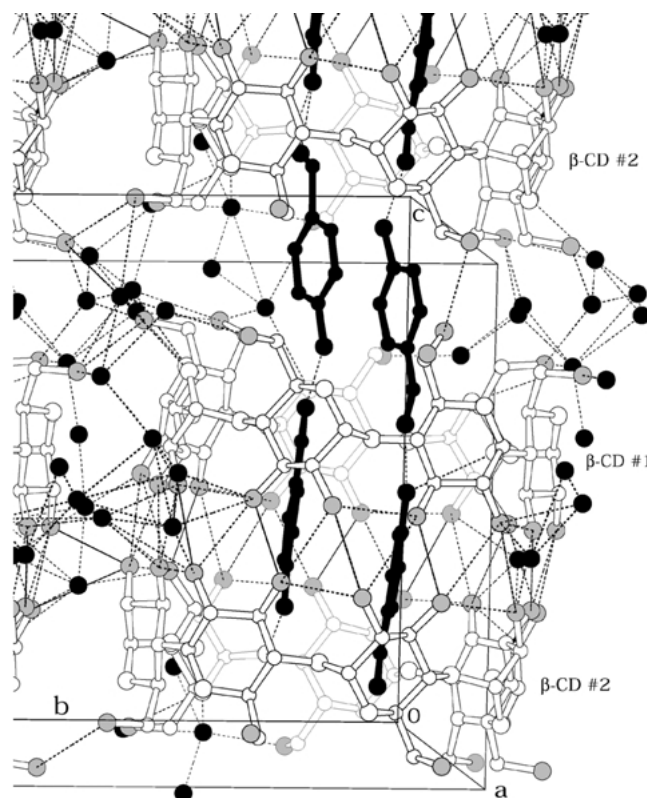


Figure 8. Crystal packing of the $2\beta\text{-CD-}4p\text{-HB-}9.45\text{H}_2\text{O}$ inclusion complex in channel mode that is stabilized by $\text{O}2(m)_1/\text{O}3(m)_1\cdots\text{O}2(n)_2/\text{O}3(n)_2$ (tail-to-tail), $\text{O}6(m)_1\cdots\text{O}_{\text{w}}\cdots(n)_1$ (head-to-head) hydrogen bonds (dashed lines) between $\beta\text{-CD}$ #1 and 2. $\text{O}2_{\text{CD}}$, $\text{O}3_{\text{CD}}$, $\text{O}6_{\text{CD}}$ and O_{w} are represented with gray and black spheres, respectively. The $p\text{-HB}$ molecules are black and H-atoms not shown. Drawn with program MOLSCRIPT [36].

cupancy of 0.38 and are hydrogen bonded to each other and to CD hydroxyl groups (Figures 6, 8, Table 5). The O...O distances of W9–W10, W21–W22, W21–W23, W22–W23 are too short (0.64, 0.37, 0.88, 1.02 Å) – these water sites cannot be occupied simultaneously.

• Crystal packing

The β -CD molecules are stacked along the crystallographic c -axis, in the alternative head-to-head and tail-to-tail channel mode [27] as frequently observed in β -CD crystal structures [28], see Figure 8. The glycosidic O4 planes of β -CD #1, 2 are almost coplanar. They are slightly inclined at about 2.6° and 2.8° to the ab -plane, and make an angle of 0.8° with respect to each other. This molecular arrangement is stabilized at one end of the β -CD (in the same column) by intermolecular O2(m)_1/O3(m)_1...O2(n)_2/O3(n)_2 hydrogen bonds (O...O distances 2.75–3.37 Å), Figures 6, 7, 8, Table 2. At the other end, the O6–H groups are not directly hydrogen bonded to the O6–H groups of the adjacent β -CD but linked by one or two bridging water molecules, e.g., O61_1...W1...W2...O61_2, O61B_1...W11...W24...O61_2, O64_1...W3...O63_2, O64_1...W12...O62_2. Except for the O61A_1...O66_2 ($x, y, z + 1$) hydrogen bond (O...O distance 3.26 Å), see Figure 8, Table 5. In addition, a number of O_{CD}...O_{CD}, O_{CD}...O_w...O_{CD}, O_{CD}...O_w...O_w...O_{CD} hydrogen bonds found between neighbouring β -CD columns contribute to the stability of the entire crystal structure (Figure 8, Table 5).

In comparison to the complexes of β -CD with p -disubstituted benzenes, although the crystal packings of the host are similar, the host:guest stoichiometries are different, i.e., 2:2 for p -ethylaniline [29], 4- t -butylbenzoic acid [30], 4- t -butylbenzyl alcohol [31], 4- t -butyltoluene [32] and, p -bromoacetanilide [33] and 2:3 for p -iodophenol [34] (2:4 for the present structure).

Conclusions

The β -CD- p -HB inclusion complex has been characterized with various methods both in solution and in the crystalline state. ¹H-NMR spectroscopy has shown that in solution p -HB forms a stable complex with β -CD with the apparent inclusion constant of $3\text{--}4 \times 10^2 \text{ M}^{-1}$, and a 1:1 stoichiometry. This finding contrasts with the solid state X-ray structure, where the β -CD: p -HB stoichiometric ratio is 2:4. Moreover, the β -CD molecules form dimers and these dimers are stacked like coins in a roll constructing infinite channels where the p -HB molecules are embedded. The p -HB molecules direct their polar CHO and OH groups into the nonpolar β -CD cavities. These polar groups are hydrogen bonded to each other, yielding infinite, antiparallel chains. In aqueous solution both β -CD and p -HB molecules are separately hydrated and far away from one another, therefore the host:guest ratio of 1:1 is feasible. By contrast, in the crystalline state, β -CD molecules tend to form dimers [28] and p -HB molecules form antiparallel, infinite chains [26], hence the proportion of 2:4 is preferable.

References

- W. Saenger: *Angew. Chem. Int. Ed. Engl.* **19**, 344 (1980).
- J. Szejtli: *Chem. Rev.* **98**, 1743 (1998).
- For a recent review on applications of cyclodextrins, see J. Szejtli: *Proceedings of the 10th International Symposium on Cyclodextrins*, Kluwer Academic Publishers, Dordrecht (2000).
- M.V. Rekharsky and Y. Inoue: *Chem. Rev.* **98**, 1875 (1998).
- K.-H. Frömring and J. Szejtli: *Cyclodextrins in Pharmacy*, Kluwer Academic Publishers, Dordrecht (1994), pp. 66.
- For examples of inclusion complexes of β -CD and organometallic guests, see (a) S.S. Braga, I.S. Gonçalves, A.D. Lopes, M. Pillinger, J. Rocha, C.C. Romão, and J.J.C. Teixeira-Dias: *J. Chem. Soc. Dalton Trans.*, 2964–2968 (2000); (b) I. Turel, A. Demšar, and J. Košmrlj: *J. Incl. Phenom. Macrocycl. Chem.* **35**, 595 (1999).
- L. Sente, *Comprehensive Supramolecular Chemistry*, J.L. Atwood, J.E.D. Davies, D.D. MacNicol and F. Vögtle Exec. Ed., Vol 3, J. Szejtli and T. Osa (ed.), chap. 7.
- K. Harata: *Chem. Rev.* **98**, 1883 (1998).
- A. Moreira da Silva, A. Amado, P. Ribeiro-Claro, J. Empis, and J.J.C. Teixeira-Dias: *J. Carbohydr. Chem.* **14**, 677 (1995).
- P. Job: *Ann. Chim.* **9**, 113 (1928).
- G.M. Sheldrick: SHELXS97, Program for Crystal Structure Solution, University of Göttingen, Germany (1997).
- G.M. Sheldrick: SHELXL97, Program for Crystal Structure Refinement, University of Göttingen, Germany (1997).
- D.E. McRee: *Practical Protein Crystallography*, Academic Press, San Diego (1993).
- Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-167931. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2, IEZ, UK, (fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk).
- J. Redondo, J. Frigola, A. Torrens, and P. Lupón: *Mag. Reson. Chem.* **33**, 104 (1995).
- A.S. Moreira, J. Empis, and J.J.C. Teixeira-Dias: *J. Incl. Phenom. Macrocycl. Chem.* **33**, 81 (1999).
- P. V. Demarco and A.L. Thakkar: *J. Chem. Soc. Chem. Commun.* **2** (1970).
- Y. Bahaddi, H. Galons, and N. Rysanek: *Bull. Soc. Chim. Fr.* **132**, 330 (1995).
- F. Djedaini, S.Z. Lin, B. Perly, and D. Wouessidjeswe: *J. Pharm. Sci.* **79**, 643 (1987).
- A. Ganza-Gonzalez, J.L. Vila-Jato, S. Anguiano-Igea, F.J. Otero-Espinar, and J. Blanco-Méndez: *Int. J. Pharm.* **106**, 179 (1994).
- H.-S. Choi, C. Chang, and A.M. Knevel: *Pharm. Res.* **9**, 582 (1992).
- M.J. Gidley and S.M. Bociek: *J. Am. Chem. Soc.* **110**, 3820 (1988).
- X.-T. Li, J.-H. Li, G.-E. Zhang, G.-X. Xi, and X.-D. Lou: *Thermochim. Acta* **262**, 165 (1995).
- D. Cremer and J.A. Pople: *J. Am. Chem. Soc.* **97**, 1354 (1975).
- IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN) Symbols for specifying the conformation of polysaccharide chains, Recommendations 1981, *Eur. J. Biochem.* **131**, 5 (1983).
- F. Iwasaki: *Acta Crystallogr.* **B33**, 1646 (1977).
- W. Saenger: *Isr. J. Chem.* **25**, 43 (1985).
- K. Harata: *Crystallographic Studies* (Comprehensive Supramolecular Chemistry, Vol. 3, J. Szejtli and T. Osa (eds.)), Pergamon, Oxford (1996), pp. 279.
- R. Tokuko, T. Fujiwara, and K.-I. Tomita: *Acta Crystallogr.* **B37**, 1158 (1981).
- A. Rontoyianni, I.M. Mavridis, E. Hadjoudis, and A.J.M. Duisenberg: *Carbohydr. Res.* **252**, 19 (1994).
- D. Mentzafos, I.M. Mavridis, G. le Bas, and G. Tsoucaris: *Acta Crystallogr.* **B47**, 746 (1991).
- (a) F.H. Herbststein and R.E. Marsh: *Acta Crystallogr.* **B54**, 677 (1998); (b) I.M. Mavridis and E. Hadjoudis: *Carbohydr. Res.* **229**, 1 (1992).
- M.R. Caira and D.R. Dodds: *J. Incl. Phenom. Macrocycl. Chem.* **34**, 19 (1999).
- J.J. Stezowski, K.H. Jogun, E. Eckle, and K. Bartels: *Nature* **274**, 617 (1978).

35. M.N. Burnett and C.K. Johnson: ORTEPIII, Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations, Oak Ridge Natl. Lab., USA (1996).
36. P.J. Kraulis: *J. Appl. Crystallogr.* **24**, 946 (1991).

