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Inclusion of Nonopiate Analgesic Drugs in Cyclodextrins. I. X-Ray Structure of a 1 : 1 β-Cyclodextrin-*p*-bromoacetanilide Complex

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Abstract. The preparation and X-ray crystal structure of a 1 : 1 complex between β-cyclodextrin (β-CD) and the analgesic *p*-bromoacetanilide are reported. Thermogravimetric and UV spectrophotometric analyses of single crystals grown from an aqueous solution containing host and guest in 1 : 1 molar ratio yielded the composition β-CD · *p*-bromoacetanilide · 13.5H_2O. Crystals of the complex are triclinic, space group P1, with a = 15.197(3), b = 15.613(2), c = 15.743(4) Å, α = 87.16(2), β = 98.29(2), γ = 103.39(1)° and Z = 2 crystallographically independent complex units per unit cell. The β-CD molecules form head-to-head dimers which pack in the channel-mode. Each dimer contains two guest molecules whose acetylamino substituents are located at the dimer interface while the bromine atoms protrude from the β-CD primary faces. The acetyl residues of both guest molecules were found to be disordered but the X-ray data permitted successful resolution and modelling of this feature.

Key words: analgesic, *p*-bromoacetanilide, cyclodextrin, inclusion complex, X-ray diffraction.

Supplementary Data relating to this article are deposited with the British Library as Supplementary Publication No. SUP 82252 (76 pages)

1. Introduction

In previous reports we described the preparation, thermal analysis and X-ray crystal structures of cyclodextrin (CD) complexes of several important non-steroidal anti-inflammatory drugs including diclofenac sodium [1], naproxen [2] and ibuprofen [3]. These studies have focused on the use of physicochemical methods of characterization to demonstrate the integrity of such species as inclusion complexes, with a view to their potential clinical use. In addition, it has been possible to obtain useful information relating to complex stability and dehydration behaviour by thermal methods of analysis and to correlate some of these results with the structural information obtained crystallographically [4]. We have recently extended these studies to investigate CD inclusion of nonopiate analgesic drugs, several of which have poor aqueous solubility or display other adverse features (e.g. low stability,

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poor compaction properties, acrid taste) which may be eliminated by inclusion in a suitable host. The title complex contains the guest *N*-(4-bromophenyl)acetamide (common name *p*-bromoacetanilide), an analgesic and antipyretic agent which is poorly soluble in water [5]. The structure and crystallographic numbering used are shown in Figure 1. This drug is a structural analogue of phenacetin and acetaminophen (paracetamol) whose inclusion in CDs is also under investigation in this laboratory. Here we report the preparation, preliminary characterization and the X-ray structure of the title complex. The latter reveals that the complex is a dimeric species in which the acetyl residues of both independent guest molecules are disordered in two orientations in the region of the dimer interface. Careful analysis led to the location of all four orientations of the acetyl groups and their inclusion in the structural model. The results are of interest in the context of the possible orientations adopted by guest molecules in the β-CD cavity. Also, this is only the second example of structural elucidation of a β-CD complex containing a guest with an acetylamino substituent and the first in which disorder of the acetyl group has been detected and successfully modelled. Paracetamol and phenacetin, which are important analgesic agents, also contain the acetylamino substituent and form analogous dimeric complexes with β-CD. The X-ray structures of these complexes will be published separately but it is noted here that while the orientation of the guest paracetamol in the β-CD cavity is analogous to that in the title *p*-bromoacetanilide complex, with the acetylamino substituent also at the dimer interface and the *p*-OH group at the β-CD primary face, the phenacetin molecule is included in the opposite sense, with the acetylamino group protruding from the β-CD primary face and the *p*-ethoxy group located at the dimer interface.

2. Experimental

2.1. COMPLEX PREPARATION AND CHARACTERIZATION

Single crystals of the title complex were grown by slow cooling of an aqueous solution containing β-CD (Cyclolab, Hungary) and *p*-bromoacetanilide (Fluka, Switzerland) in 1 : 1 molar ratio. The crystals were colourless prisms. A 1 : 1 host-guest stoichiometry was deduced from UV spectrophotometric analysis of an aqueous solution of the complex at 247.5 nm. Thermogravimetry on a Perkin-Elmer PC-7 series thermal analysis system using a 15.342 mg sample and a heating rate of 10 °C min^{-1} yielded a 15.2% mass loss in the temperature range 30–350 °C, corresponding to 13.5 water molecules of crystallization per β-CD molecule.

2.2. CRYSTAL STRUCTURE ANALYSIS

Preliminary X-ray photography indicated the triclinic system and yielded unit cell dimensions very similar to those reported for the β-CD-*p*-nitroacetanilide complex [6]. Intensity data were collected in the $\omega - 2\theta$ mode (max. scan time 80s per reflection) on an Enraf-Nonius CAD4 diffractometer with graphite-monochromated

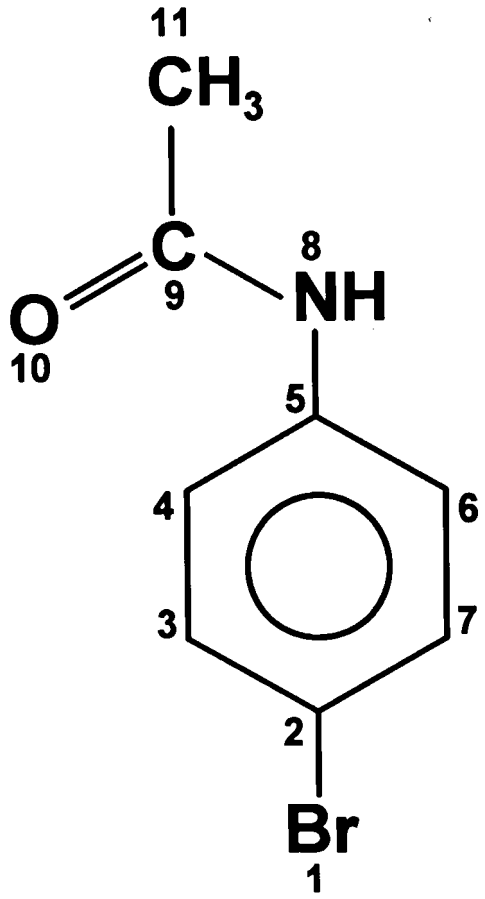

Figure 1. Structure and atomic numbering of the guest molecule *p*-bromoacetanilide.

MoKα radiation (λ = 0.71069 Å). Accurate unit cell parameters were obtained by least-squares analysis of the setting angles of 24 reflections in the θ-range 16–17°. For all measurements, the specimen was immersed in mother liquor in a Lindemann capillary and cooled to 278K by means of a Cryostream cooler (Oxford Cryosystems). Despite the above measures taken to optimise data quality, crystal decay during data-collection was severe, amounting to an overall decrease of 25% in the intensities of three reference reflections which were monitored every hour. A catastrophic decrease in intensity at the end of data-collection signalled complete decay, preventing recording of further intensity measurements which could have been used to correct for absorption effects (estimated at $\pm$5%). All data were, however, corrected for the major problem of crystal decay (which varied linearly with time) as well as for Lorentz-polarization effects. Crystal data-collection and refinement details are listed in Table I.

Table I. Crystal data, experimental and refinement parameters for the title compound

Molecular formula	$C_{42}H_{70}O_{35} \cdot C_8H_8NOBr \cdot 13.5H_2O$
M_r/g mol^{-1}	1592.3
Crystal system	Triclinic
Space group	P1
Z	2
a (Å)	15.197(3)
b (Å)	15.613(2)
c (Å)	15.743(4)
α (°)	87.16(2)
β (°)	98.29(2)
γ(°)	103.39(1)
V (Å^3)	3595(1)
D_c (g cm^{-3})	1.471
F(000)	1686
μ(MoKα)/cm^{-1}	6.83
Crystal dimensions (mm)	$0.3 \times 0.3 \times 0.4$
Range scanned θ (°)	$1 \leq \theta \leq 25$
Index range	h-18,18; k-18,18; 10,18
Scan width (°)	0.8 + 0.35 tan θ
Aperture width (mm)	1.12 + 1.05 tan θ
No. of reflections collected	13561
No. of unique reflections	11475
R_{int}	0.0506
No. of reflections with $I > 3\sigma(I)$	7351
No. of L.S. parameters	975
R	0.0948
wR	0.1011
w	$[\sigma^2(F_0) + 1.077 \times 10^{-3} F_0^2]^{-1}$
S	4.92
Shift/e.s.d. max., average	0.318 , 0.006
($\Delta\rho$)max final (eÅ^{-3})	0.36
($\Delta\rho$)min final (eÅ^{-3})	−0.30

The structure was solved using coordinates of the non-hydrogen atoms (excluding the primary hydroxyl O atoms) of the two independent host molecules of the isomorphous β-CD-p-nitroacetanilide (PNA) complex [6]. The guest atoms, water molecules and remaining atoms of the host were located in successive difference electron density maps following least-squares refinements. At an advanced stage of

refinement, it became apparent from difference electron density maps that in each of the two independent guest molecules, the acetyl residue was disordered over two sites with the torsion angle C(4)-C(5)-N(8)-C(9) (Figure 1) approximately 0° for one site and 180° for the other. Each of the four independent acetyl residues was included in the model with variable site occupation factor (s.o.f.) initially set at 0.5 each, based on electron density peak heights and a sufficient number of distance constraints was applied to ensure reasonable geometries. Further reduction of the number of least-squares variables was effected by treating the phenyl groups as regular hexagons and assigning two separate common variable U_{iso} values to the C atoms of the two phenyl rings. Host and guest H atoms were included in geometrically calculated positions at 1.00 Å from their parent atoms and were treated isotropically. The final cycles involved the blocked full-matrix technique [7] with all atoms refining isotropically except the Br atoms which were assigned anisotropic thermal parameters. The function minimised was $\Sigma w(|F_0| - |kF_c|)^2$ with weights w which yielded a constant distribution of $\Sigma(w\Delta F)^2$ with sin θ/λ and $(F_0/F_{0,\max})^{1/2}$. Four reflections (100, 010, 200, 020) displayed secondary extinction and were excluded from the refinement. The final refined s.o.f. s for atoms of the acetyl residues were 0.58, 0.42 (guest molecule A) and 0.59, 0.41 (guest molecule B). One of the primary hydroxyl groups was found to be disordered over two sites with final refined s.o.f. s of 0.63 and 0.37. The final structural model included 21 water molecules with s.o.f. 1.00 each and 12 with s.o.f. s in the range 0.41–0.59, accounting for a total of 27 H_2O molecules, or an average of 13.5 H_2O molecules per β-CD molecule, in agreement with the estimate from thermogravimety.

3. Results and Discussion

3.1. OVERALL DESCRIPTION OF THE COMPLEX STRUCTURE

The two crystallographically independent β-CD molecules are in head-to-head orientation forming a dimeric cage which contains two independent guest molecules (A, B) as shown in Figure 2. The guest molecules adopt essentially planar conformations and are orientated with their hydrophobic Br atoms at the primary face of the host and with their hydrophilic acetylamino residues at the dimer interface.

3.2. CHARACTERISTICS OF THE β-CD DIMER

Geometrical properties of the β-CD dimeric motif, as it occurs in e.g. the isomorphous β-CD-PNA [6] and β-CD-4-*t*-butyltoluene [8] complexes, have been discussed in some detail [9]. In the title complex, the two halves of the dimer are related by an approximate twofold axis. Dimer formation is effected by seven hydrogen bonds of the type O(3) $\cdots$ O(3)′ which link the β-CD secondary faces and have an O $\cdots$ O distance range of 2.79(1)–2.99(1) Å. Contiguous D-glucopyranose rings are linked by hydrogen bonds of the type O(3n) $\cdots$ O[2(n + 1)] [9] with O $\cdots$

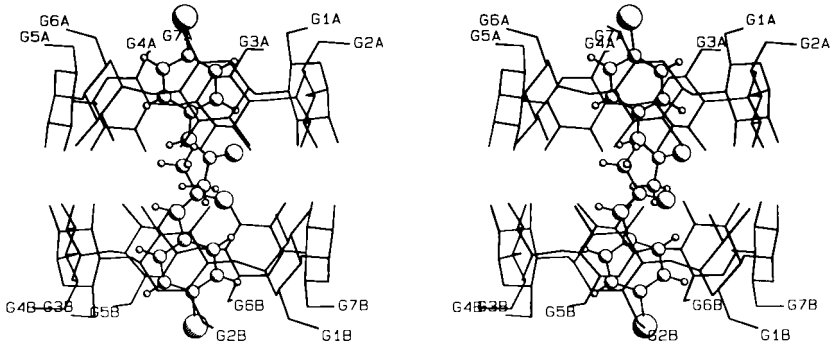

Figure 2. Stereodiagram of the structure of the *p*-bromoacetanilide/β-CD complex. For clarity, only the major disordered position of each acetyl group is shown.

O distance ranges of 2.70(1)–2.83(1) Å for molecule A and 2.74(2)–2.82(2) Å for molecule B. Each host molecule contains D-glucopyranose units in the $^4C_1$ conformation with the primary hydroxyl groups in the (−)-gauche conformation [10], i.e. pointing away from the host cavity and therefore not interacting with the included guests. Table II lists geometrical data for the two independent β-CD units. From these data it is evident that the host molecules maintain their 'round' shape but that there are small differences in the distribution of the tilt angles for molecules A and B, which may be the result of guest disorder and the unsymmetrical distribution of water molecules in the cavity (see below).

3.3. GUEST LOCATION, CONFORMATION AND DISORDER

Atomic coordinates for the acetylaminobenzene portions of the *p*-bromoacetanilide guests are very similar to those for the same residue in the isomorphous β-CD complex containing PNA [6], showing that these different guests adopt the same degree of tilt with respect to the host molecules. This tilt permits the guests to occupy most of the available space in the cavity and is necessary in order to avoid abnormally close approach of the acetyl residues [6, 9]. The major structural difference between the title complex and that containing PNA is the substitution of the hydrophilic —NO_2 substituent in PNA by a hydrophobic bromine atom. Despite the difference in the electronic properties of these substituents, they are both located at the β-CD primary rim in their respective complexes. This can be attributed to roughly comparable steric bulk for these substituents as well as analogous stabilisation of the acetylamino residues by N—H $\cdots$ O(water) hydrogen bonds to H_2O molecules inside the cavity in the region of the dimer interface. Such interactions, together with the absence of hydrogen bonding between the guest polar group and the host secondary hydroxyl groups, have been cited as evidence for the hydrophobic nature of the region between the two β-CD molecules forming the dimer [9].

Table II. Geometrical data for β-cyclodextrin

$O(4)\cdots O(4')\cdots O(4'')$ angle (°) and radii (Å) of the O(4) heptagon (measured from the centre of gravity of seven O(4) atoms to each O(4) atom).			
O(4A7) · · · O(4A1) · · · O(4A2)	127.0	A1	5.11
O(4A1) · · · O(4A2) · · · O(4A3)	125.7	A2	5.17
O(4A2) · · · O(4A3) · · · O(4A4)	131.3	A3	4.90
O(4A3) · · · O(4A4) · · · O(4A5)	130.4	A4	4.96
O(4A4) · · · O(4A5) · · · O(4A6)	124.6	A5	5.22
O(4A5) · · · O(4A6) · · · O(4A7)	129.0	A6	5.03
O(4A6) · · · O(4A7) · · · O(4A1)	132.1	A7	4.86
Average	128.6	Average	5.04
O(4B7) · · · O(4B1) · · · O(4B2)	127.2	B1	5.09
O(4B1) · · · O(4B2) · · · O(4B3)	132.1	B2	4.86
O(4B2) · · · O(4B3) · · · O(4B4)	128.0	B3	5.04
O(4B3) · · · O(4B4) · · · O(4B5)	126.1	B4	5.16
O(4B4) · · · O(4B5) · · · O(4B6)	129.0	B5	4.98
O(4B5) · · · O(4B6) · · · O(4B7)	131.8	B6	4.89
O(4B6) · · · O(4B7) · · · O(4B1)	125.6	B7	5.16
Average	128.5	Average	5.03
$O(4)\cdots O(4')$ distances (Å)			
O(4A1) · · · O(4A2)	4.29	O(4B1) · · · O(4B2)	4.41
O(4A2) · · · O(4A3)	4.40	O(4B2) · · · O(4B3)	4.39
O(4A3) · · · O(4A4)	4.42	O(4B3) · · · O(4B4)	4.32
O(4A4) · · · O(4A5)	4.38	O(4B4) · · · O(4B5)	4.33
O(4A5) · · · O(4A6)	4.26	O(4B5) · · · O(4B6)	4.47
O(4A6) · · · O(4A7)	4.47	O(4B6) · · · O(4B7)	4.34
O(4A7) · · · O(4A1)	4.37	O(4B7) · · · O(4B1)	4.29
Average	4.37	Average	4.36

Tilt angles (°) and torsion angle indices (°)

Residue	Tilt angle[a]	Torsion-angle index[b]
A1	8.0	123.3
A2	4.2	119.1
A3	6.3	114.7
A4	7.1	122.5
A5	8.3	124.1
A6	13.8	111.9
A7	7.0	114.5
Average	7.8	118.6
B1	16.2	117.8
B2	5.6	119.0
B3	6.6	128.2
B4	7.9	121.6
B5	11.9	116.2
B6	6.0	124.2
B7	4.5	125.2
Average	8.4	121.7

[a] The tilt angle is defined as the angle between the O(4) plane and the plane through C(1), C(4), O(4) and O(4′) of each glusose residue.

[b] The torsion-angle index is defined as: $|\tau(\text{C(1)—C(2)})| + |\tau(\text{C(2)—C(3)})| - |\tau(\text{C(3)—C(4)})| - |\tau(\text{C(4)—C(5)})| + |\tau(\text{C(5)—O(5)})| + |\tau(\text{O(5)—C(1)})|$, where τ(C(1)—C(2)) is the torsion angle O(5)—C(1)—C(2)—C(3).

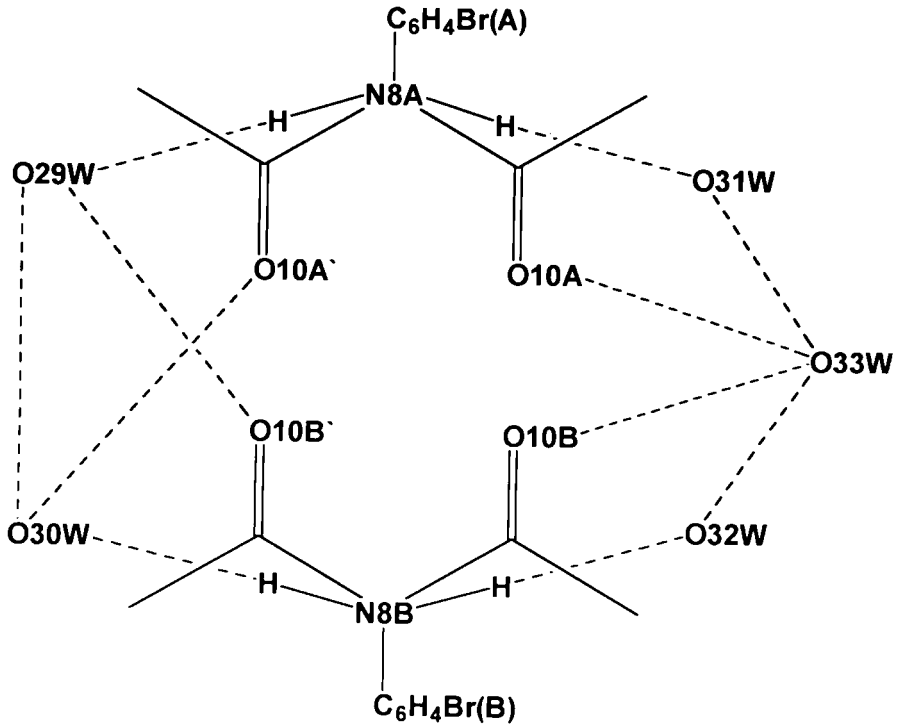

Figure 3. Schematic diagram showing details of the disordered acetyl residues and relevant hydrogen bonds (dashed lines).

Table III. Hydrogen bond data for Figure 3

				Distance (Å)		Angle (°)
D	H	A	D—H	H · · · A	D · · · A	D—H · · · A
N(8A)	H(8A)	O(29W)	1.00	2.26	3.19(4)	155
N(8B)	H(8B)	O(30W)	1.00	2.11	3.02(4)	150
N(8A)	H(8A′)	O(31W)	1.00	1.93	2.95(7)	169
N(8B)	H(8B′)	O(32W)	1.01	2.01	3.03(6)	169
O(10A)		O(33W)			2.61(4)	
O(10B)		O(33W)			2.35(5)	
O(10A′)		O(30W)			2.66(6)	
O(10B′)		O(29W)			2.81(5)	
O(29W)		O(30W)			2.68(4)	
O(31W)		O(33W)			2.88(7)	
O(32W)		O(33W)			2.75(8)	

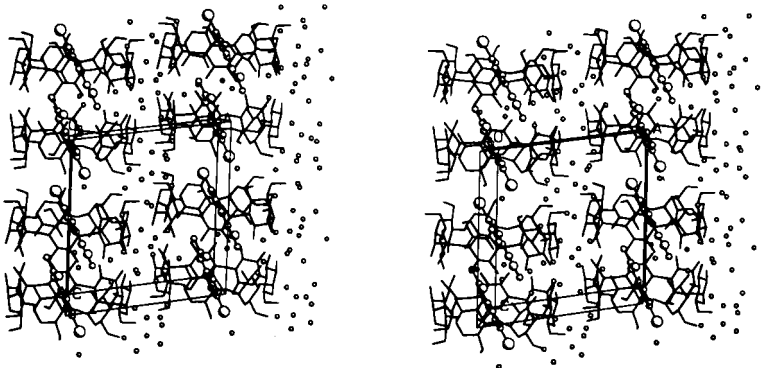

Figure 4. Stereodiagram of the crystal structure of the *p*-bromoacetanilide/β-CD complex showing head-to-tail packing of the dimeric complexes along the *c*-axis. Oxygen atoms of water molecules are drawn as open circles.

Table IV. Additional O—H · · · O hydrogen bond data[a]

O · · · O type	Number	O · · · O range/Å	O · · · O average/Å
O2 · · · O2	2	2.77–2.78	2.78
O6 · · · O6	7	2.63–3.07	2.85
O2 · · · OW	13	2.63–3.18	2.86
O3 · · · OW	15	2.78–3.17	2.99
O5 · · · OW	4	3.10–3.19	3.17
O6 · · · OW	23	2.62–3.19	2.80
OW · · · OW	39	2.52–3.19	2.86

[a] E.s.d. s are in the range 0.01–0.05 Å.

The *p*-bromoacetanilide molecules adopt an approximately planar conformation, with the carbonyl group *endo* with respect to the phenyl ring. A similar conformation is observed in the uncomplexed molecule [11] where the torsion angle C(4)-C(5)-N(8)-C(9) (Figure 1) is 14.3°. An important feature of the present analysis is the finding that the acetyl residues of both guest molecules A and B are disordered in two orientations. The relevant torsion angles of the type C(4)-C(5)-N(8)-C(9) have values of −13(4), −176(3)° for the two disordered sites in molecule A and −7(4), 157(4)° for molecule B. Details of the disorder are shown schematically in Figure 3 where the labels O(10A), O(10A′) denote the two disordered positions of the carbonyl O atom for molecule A and labels O(10B), O(10B′) denote those for molecule B. It is significant that for each of the four disordered orientations found, a N—H · · · O(water) hydrogen bond occurs. Table III lists geometrical data for these hydrogen bonds, relevant O(water) · · · O(water) distances, as well as O(10) · · · O(water) distances, the latter indicating that all disordered guest carbonyl O atoms also engage in hydrogen bonding to water molecules. It

is possible that analogous guest disorder occurs in the β-CD-PNA complex [6]; the reported structural analysis was incomplete (R = 17%) and the PNA molecules were assigned a s.o.f. of 0.75 on the basis of peak heights in the electron density maps. As regards the important general question of the orientation of guests in the β-CD cavity [9], we have evidence that if the guest contains the acetylamino residue, the latter may be located at either the host primary face or at the secondary face (as reported here), depending on the nature of the substituent in the position *para-* to it.

3.4. CRYSTAL PACKING

Figure 4 shows the stacking of the dimers in columns parallel to the crystal *c*-axis. This stacking mode has been classified as type CH (for 'channel') [9], which is common for β-CD complexes crystallizing in the space group C2 and for those crystallizing in P1 with cell dimensions similar to those reported here (viz. with a, b, c each approximately 15 Å). The guest bromine atoms are seen to be sandwiched between the primary faces of two host molecules while the acetylaminobenzene moieties are fully enclosed within the β-CD dimer.

Dimeric layers are formed by extensive intermolecular hydrogen bonds involving the primary hydroxyl groups as well as water molecules. Figure 4 shows the location of water molecules including those within the β-CD cavity. Detailed examination of contact distances shows that in addition to the hydrogen bonds already mentioned, there are many others which stabilise the crystal structure. The relevant types of hydrogen bond contact distances, their frequencies of occurrence, average O $\cdots$ O distance ranges and averages are listed in Table IV.

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