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# Inclusion of Nonopiate Analgesic Drugs in Cyclodextrins. II. X-ray Structure of a 1 : 1 $\beta$-Cyclodextrin – Acetaminophen Complex

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**Abstract.** Single crystals of a 1 : 1 complex between $\beta$-cyclodextrin ($\beta$-CD) and the analgesic acetaminophen (paracetamol) have been prepared and the mode of inclusion of the drug has been determined from X-ray data collected at 293 K. Complex characterization by UV and thermogravimetric analyses yielded the composition $\beta$-(CD)·acetaminophen·13.3$H_2O$. The complex crystallizes in the space group C2 with $a$ = 19.207(7), $b$ = 24.48(1), $c$ = 15.700(4)Å, $\beta$ = 109.52(2)° and $Z$ = 4 complex units in the crystal unit cell. The host molecules form dimeric motifs with $C_2$ crystallographic symmetry which pack in the channel mode. Guest molecules residing in the host dimer are disordered, each acetaminophen molecule being statistically distributed over two sites with equal occupancy. In each case, the guest hydroxyl group is located at the host primary face while the acetamide residue lies at the dimer interface. Two $C_2$-related water molecules are trapped inside the host cavity, being hydrogen bonded to the $C_2$-related carbonyl groups of one of the disordered guest conformers. Structural features of the complex are discussed with reference to recent spectroscopic and other studies aimed at elucidating the nature of the interaction between acetaminophen and $\beta$-CD.

**Keywords:** analgesic, acetaminophen, paracetamol, cyclodextrin, inclusion complex, X-ray diffraction.

**Supplementary Data** relating to this article are deposited with the British Library as Supplementary Publication No. SUP 82267 (32 pages)

## 1. Introduction

In the first paper of this series [1], we described the crystal structure of the $\beta$-CD complex containing the analgesic agent *p*-bromoacetanilide as guest. Substitution of the bromine atom of the former guest by a hydroxyl group yields the well-known analgesic and antipyretic drug acetaminophen [*N*-(4-hydroxyphenyl)acetamide, paracetamol, Figure 1]. Problems associated with the use of acetaminophen include poor compaction behaviour, low aqueous solubility and an acrid taste. Improvement in the tabletting behaviour has been achieved by a solvation/desolvation process [2], which yields pure acetaminophen with a fine, sintered-like texture

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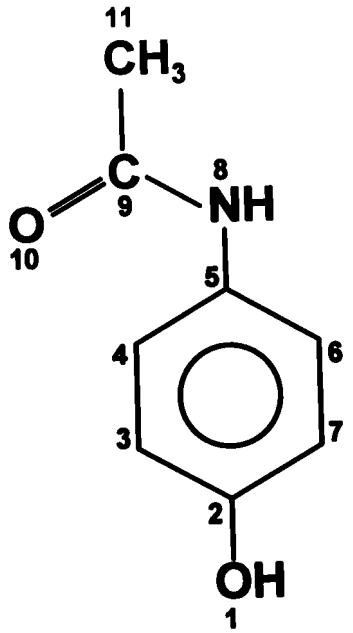


*Figure 1.* Structure and atomic numbering of the guest molecule.

having excellent compression characteristics. Elimination of the acrid taste of acetaminophen as well as increased solubility result when a cyclodextrin is employed, either as inclusion complexing agent [3] or as a component in a ground mixture with the drug [4]. Considerable attention has been given to the interaction between acetaminophen and $\beta$-CD, more recent studies including the determination of the stability constant of the inclusion complex from UV spectrophotometry [5] and assessment of the effect of mechanical grinding on the formation and crystallinity changes of the inclusion complex [6]. Models of the inclusion mode of the drug within the $\beta$-CD cavity have been proposed, based on UV data and space-filling considerations [5], and on analysis of infrared shifts accompanying complexation [6]. The present study was undertaken to determine unambiguously the orientation of the guest molecule in the $\beta$-CD cavity in the solid state for comparison with the above predictions and with analogous structures we are investigating.

Difficulties in guest location and/or resolution were expected for the title complex since it crystallizes in the channel mode [7] in space group C2 which is almost invariably associated with guest disorder. The latter may be so severe as to render the guest 'invisible' while the host molecule is nevertheless well-defined. In this instance, however, careful analysis using X-ray diffraction data captured at room temperature enabled location of the guest, thus settling the question of its orientation in the $\beta$-CD cavity unequivocally and allowing satisfactory modelling of its disorder.

## 2. Experimental

### 2.1. COMPLEX PREPARATION AND CHARACTERIZATION

Slow cooling of an aqueous solution containing $\beta$-CD (Cyclolab, Hungary) and acetaminophen (Sigma Chemical Co., USA) in 1 : 1 molar ratio yielded large colourless prismatic crystals. A host–guest stoichiometry of 1 : 1 was determined from UV spectrophotometric analysis of an aqueous solution of the complex at 244 nm. Thermogravimetry on a Perkin-Elmer PC-7 series thermal analysis system using sample masses in the range 2–5 mg and a heating rate of 10 °C $min^{-1}$ yielded a 15.7% mass loss in the temperature range 30–150 °C, corresponding to 13.3 water molecules of crystallization per $\beta$-CD molecule.

### 2.2. CRYSTAL STRUCTURE ANALYSIS

X-ray photography indicated Laue symmetry 2/m and systematic absences were consistent with the space group C2. Calculated unit cell dimensions were similar to those reported for the isomorphous complex with ibuprofen as guest [8]. Intensity data were collected in the $\omega - 2\theta$ mode (max. scan time 80 s per reflection) on an Enraf-Nonius CAD4 diffractometer with graphite-monochromated MoK$\alpha$ radiation ($\lambda$ = 0.71069Å). Accurate unit cell parameters were obtained by least-squares analysis of the setting angles of 24 reflections in the $\theta$-range 15–16.5°. Data were collected in successive shells with $\theta$ limits of 1–20°, 20–22°, 22–23° and 23–25°. Three reference reflections monitored every hour showed no significant crystal decay. Data were corrected for Lorentz-polarization effects. Crystal data-collection and refinement details are listed in Table I.

The structure was solved using coordinates of the non-hydrogen atoms (excluding the primary hydroxyl O atoms) of the isomorphous $\beta$-CD · ibuprofen complex [8]. After location of the primary hydroxyl O atoms from a difference electron density ($\Delta\rho$) map, extensive rounds of least-squares refinements and inspection of successive $\Delta\rho$ maps were necessary in order to locate the remaining atoms, namely those of water molecules and the guest acetaminophen molecule. The latter was found at an advanced stage of refinement to be disordered over two sites with comparable electron densities and with the phenyl rings of the individual components (A, B) roughly orthogonal. Site-occupancy factors (s.o.f.'s) for A and B were fixed at 0.50 each. Since the fraction of observed data was less than half the number of reflections collected, reduction in the number of least-squares variables was desirable. Thus, all atoms were refined isotropically and the disordered phenyl rings were treated as regular hexagons with separate variable common isotropic thermal parameters ($U_{iso}$) for the C atoms of each ring.

Oxygen atoms of the water molecules were located over 21 sites and were generally refined with variable s.o.f.'s and with a common, fixed $U_{iso}$ value. Hydrogen atoms were included in idealized positions (C—H 1.00 Å), those of the host being assigned a common variable $U_{iso}$ value and those of the guest a separate vari-

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

| | |
|---|---|
| Molecular formula | $C_{42}H_{70}O_{35}\cdot C_8H_9NO_2\cdot 13.3H_2O$ |
| $M_r$/g mol$^{-1}$ | 1525.8 |
| Crystal system | Monoclinic |
| Space group | C2 |
| $Z$ | 4 |
| $a$ (Å) | 19.207(7) |
| $b$ (Å) | 24.48(1) |
| $c$ (Å) | 15.700(4) |
| $\alpha$ (°) | 90 |
| $\beta$ (°) | 109.52(2) |
| $\gamma$ (°) | 90 |
| $V$ (Å$^3$) | 6959(5) |
| $D_c$ (g cm$^{-3}$) | 1.456 |
| F(000) | 3260 |
| $\mu$ (Mo K$\alpha$)/cm$^{-1}$ | 1.319 |
| Crystal dimensions (mm) | $0.4 \times 0.4 \times 0.4$ |
| Range scanned $\theta$ (°) | $1 \leq \theta \leq 25$ |
| Index range | $h$ − 18,18; $k$ 0,23; l 0,15 |
| Scan width (°) | $0.8 + 0.35 \tan\theta$ |
| Aperture width (mm) | $1.12 + 1.05 \tan\theta$ |
| No. of reflections collected | 6472 |
| No. of unique reflections | 5103 |
| $R_{\text{int}}$ | 0.0302 |
| No. of reflections with $I > 3\sigma(I)$ | 2176 |
| No. of L.S. parameters | 458 |
| $R$ | 0.1345 |
| $wR$ | 0.1390 |
| $w$ | $[\sigma^2(F_o) + 1.452 \times 10^{-3} F_o^2]^{-1}$ |
| $S$ | 7.60 |
| Shift/e.s.d., max., average | 0.548, 0.006 |
| $(\Delta\rho)$max. final (eÅ$^{-3}$) | 0.53 |
| $(\Delta\rho)$min. final (eÅ$^{-3}$) | −0.47 |

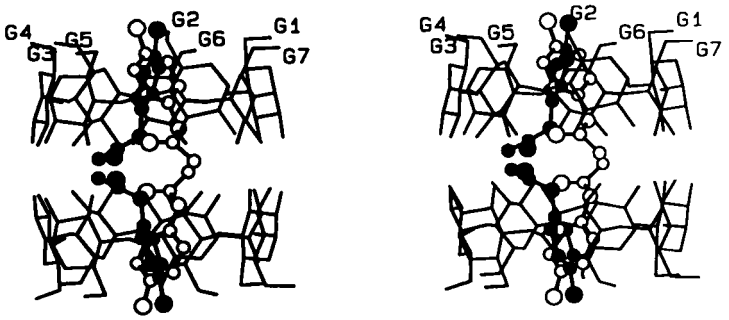


*Figure 2.* Stereoview of the dimer showing both disordered positions of the acetaminophen molecule (open circles, component A; filled circles, component B).

able $U_{\mathrm{iso}}$. Refinement of the disordered guest was a sensitive process and several distance constraints were imposed on the acetylamino residues of the individual components of disorder to maintain the reasonable geometries they displayed in the $\Delta\rho$ maps, but without compromising the observed conformations. Full-matrix least-squares refinement was carried out with program SHELX76 [9] minimising the function $\Sigma w(\mid F_o \mid - \mid kF_c \mid)^2$ with weights $(w)$ which yielded a constant distribution of $\Sigma(w\Delta F)^2$ with $\sin\theta/\lambda$ and $(F_o/F_{o,\max})^{1/2}$. The final structural model included three water O atoms with s.o.f. 1.00 each and 17 with s.o.f.'s in the range 0.34–0.72, accounting for a total of 12.3 $H_2O$ molecules per host molecule, or 92% of the water content estimated from thermogravimetry. Further inclusion of potential water oxygen atoms with s.o.f.'s less than about 0.20 was not considered meaningful.

## 3. Results and Discussion

### 3.1. OVERALL DESCRIPTION OF THE COMPLEX STRUCTURE

Two $\beta$-CD molecules related by a crystallographic twofold axis form a head-to-head dimer held together by O—H···O hydrogen bonds connecting their secondary faces. The dimer, shown in Figure 2, accommodates two acetaminophen molecules, each disordered over two sites, with their hydroxyl groups located at the host primary face and the acetamide moieties at the dimer interface.

### 3.2. STRUCTURAL FEATURES OF THE HOST AND ITS DIMER

Table II lists geometrical data for the $\beta$-CD molecule. All seven D-glucopyranose rings adopt the $^4C_1$ conformation. The primary hydroxyl O6 atoms of glucose residues G2, G3 and G7 were found to be ordered, whereas those of G1, G5 and G6 are disordered over two sites each, and that of G4 over three sites. In Figure 2, only the major components of disorder are shown for the O6 atoms and for these, all C6-O6 bonds are directed away from the macrocyclic cavity, adopting the (−)-*gauche*

conformation [10]. Hydrogen bonds involving O(3$n$)···O[2($n$ + 1)] contacts [10] in the narrow range 2.76(3)–2.94(3) Å link contiguous D-glucopyranose rings, contributing to the rigidity and 'roundness' of the host molecule. The relatively undistorted nature of the host molecule is also reflected in the small spread in the O(4)···O(4′)···O(4″) angles and the O(4)···O(4′) distances (Table II). The glucose residue tilt angles span the range 4.2–16.7° (Table II), compared with the ranges 4.2–13.8° and 4.5–16.2° for the two crystallographically independent $\beta$-CD molecules in the closely related $\beta$-CD ··· $p$-bromoacetanilide·13.5$H_2O$ [1], indicating that the host is distorted to a similar extent by inclusion of the guest acetaminophen. Seven hydrogen bonds of the type O(3)···O(3′) in the range 2.74(3)–2.87(3) Å link the $\beta$-CD secondary faces, effecting dimer formation.

### 3.3. GUEST LOCATION, CONFORMATION AND DISORDER

Figure 2 reveals that the two disordered guest components (referred to as A and B hereafter and represented by open and filled circles respectively) have the same substituent orientation when included in the $\beta$-CD cavity, namely with the hydroxyl group at the host primary face and the acetamide residue at the dimer interface. The phenyl rings of the disordered components intersect nearly orthogonally, with two C atoms of one ring (C(6A), C(2A)) almost coinciding with the corresponding chemically equivalent C atoms of the other (C(4B), C(2B)). The existence of two mutually orthogonal orientations of the phenyl groups is consistent with the 'roundness' of the macrocyle, as described above.

Figure 3 is a superposition of the guest conformers A and B in which the hydroxyphenyl groups have been overlayed. The conformation of the acetaminophen molecule is defined by the torsion angles around the bond C(5)—N(8), shown schematically in Figure 1. Specifically, these are C(4)—C(5)—N(8)—C(9), whose values are 165(5)° and 133(6)° for disordered components A and B respectively, and C(5)-N(8)-C(9)-O(10) which are 44(7)° and 91(7)° for A and B respectively. The observed conformations of the acetaminophen molecule included in the $\beta$-CD cavity differ from those reported for the drug in its polymorphs [11, 12], where the carbonyl group is in the *endo*-conformation with respect to the phenyl ring and the acetamide residue makes relatively small dihedral angles with the phenyl ring plane (21.2° and 17.7° in the monoclinic and orthorhombic forms respectively). Such small dihedral angles are conducive to close packing [11], whereas this requirement is relaxed for the acetaminophen molecule within the dimeric cavity in the present complex.

The acetamide substituents of disordered components A and B occupy different spatial positions and adopt significantly different conformations relative to their parent phenyl rings. They therefore engage in different sets of interactions with the host and/or water molecules. In contrast, guest hydroxyl atoms O(1A) and O(1B) of the disordered components nearly coincide and therefore should have common intermolecular interactions. This is confirmed by detailed inspection and

*Table II.* Geometrical data for $\beta$-cyclodextrin[a]

| O(4)...O(4‘)...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(4G7)···O(4G1)···O(4G2) | 129.7 | G1 | 4.98 |
| O(4G1)···O(4G2)···O(4G3) | 125.4 | G2 | 5.16 |
| O(4G2)···O(4G3)···O(4G4) | 129.4 | G3 | 5.00 |
| O(4G3)···O(4G4)···O(4G5) | 130.8 | G4 | 4.91 |
| O(4G4)···O(4G5)···O(4G6) | 127.4 | G5 | 5.08 |
| O(4G5)···O(4G6)···O(4G7) | 126.6 | G6 | 5.12 |
| O(4G6)···O(4G7)···O(4G1) | 130.4 | G7 | 4.94 |
| Average | 128.5 | Average | 5.03 |

| O(4)···O(4′) distances (Å) | |
|---|---|
| O(4G1)···O(4G2) | 4.35 |
| O(4G2)···O(4G3) | 4.30 |
| O(4G3)···O(4G4) | 4.42 |
| O(4G4)···O(4G5) | 4.35 |
| O(4G5)···O(4G6) | 4.36 |
| O(4G6)···O(4G7) | 4.33 |
| O(4G7)···O(4G1) | 4.46 |
| Average | 4.37 |

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

| Residue | Tilt angle[b] | Torsion-angle index[c] |
|---|---|---|
| G1 | 6.7 | 111.5 |
| G2 | 16.7 | 135.3 |
| G3 | 9.5 | 127.2 |
| G4 | 12.7 | 120.6 |
| G5 | 11.2 | 109.0 |
| G6 | 8.7 | 112.8 |
| G7 | 4.2 | 109.9 |
| Average | 10.0 | 118.0 |

[a] The e.s.d. ranges for distances and angles are 0.02–0.04Å and 1–2° respectively.

[b] 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 glucose residue.

[c] 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 $\tau$(C(1)—C(2)) is the torsion angle O(5)—C(1)—C(2)—C(3).

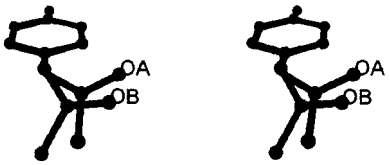


*Figure 3.* Stereoview of the superimposition of the disordered components of the guest molecule with the carbonyl oxygen atoms of A and B labeled for identification.

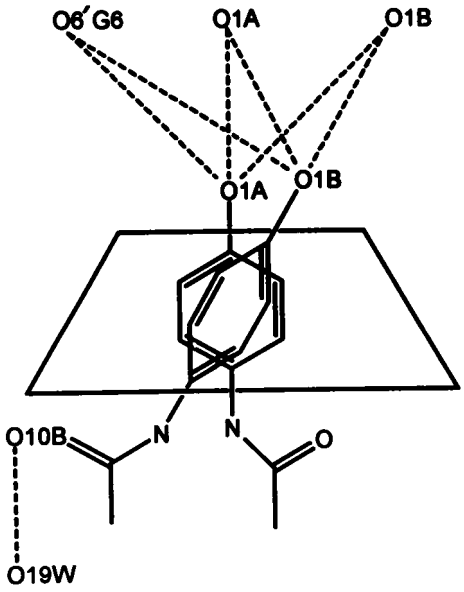


*Figure 4.* Schematic diagram showing principal hydrogen bonds (dotted lines) in which the disordered drug components A and B engage.

the principal interactions are shown schematically in Figure 4. Thus, carbonyl atom O(10B) is hydrogen bonded to a water molecule (O19W) while atom O(10A) has no hydrogen bonded counterpart. Water molecule O19W and its $C_2$-related equivalent are completely contained within the $\beta$-CD cavity as a result of their hydrogen bonding to the guest polar carbonyl group. A similar feature has been observed in the 3,3-dimethylbutylamine complex of $\beta$-CD [13] where the polar amino group at the dimer interface attracts a water molecule into the $\beta$-CD cavity. Both of the guest hydroxyl O atoms are hydrogen bonded to common partners, namely twofold related O(1A), O(1B) and O(6G6) atoms, the latter associated with the primary side of an adjacent dimeric complex unit. Distances for these hydrogen bonds are listed in Table III.

*Table III.* O···O contacts for Figure 4 and intermolecular contacts involving guest conformers A, A′, B, B′

| Atom 1 | Atom 2 | Distance (Å)[a] | Symmetry code for 2 |
|---|---|---|---|
| O(1A) | O(1A) | 3.0 | $-x+2,\ y,\ -z$ |
| O(1B) | O(1B) | 2.7 | $-x+2,\ y,\ -z$ |
| O(1A) | O(1B) | 3.0 | $-x+2,\ y,\ -z$ |
| O(1A) | O(6‘G6) | 2.9 | $-x+1$, y, $-z$ |
| O(1B) | O(6‘G6) | 2.6 | $-x+1,\ y,\ -z$ |
| O(10B) | O(19W) | 2.8 | $-x+2,\ y,\ -z+1$ |
| O(10B) | C(11B) | 1.4 | $-x,\ y,\ -z+1$ |
| O(10B) | C(9B) | 2.0 | $-x,\ y,\ -z+1$ |
| O(10B) | O(10B) | 2.7 | $-x,\ y,\ -z+1$ |
| C(9B) | C(11B) | 2.0 | $-x,\ y,\ -z+1$ |
| C(9B) | C(9B) | 2.0 | $-x,\ y,\ -z+1$ |
| C(11B) | C(11B) | 2.3 | $-x,\ y,\ -z+1$ |
| O(10A) | C(11A) | 5.2 | $-x,\ y,\ -z+1$ |
| O(10A) | C(9A) | 4.8 | $-x,\ y,\ -z+1$ |
| O(10A) | O(10A) | 4.9 | $-x,\ y,\ -z+1$ |
| C(9A) | C(11A) | 4.5 | $-x,\ y,\ -z+1$ |
| C(9A) | C(9A) | 4.3 | $-x,\ y,\ -z+1$ |
| C(11A) | C(11A) | 4.8 | $-x,\ y,\ -z+1$ |

[a] Mean e.s.d. 0.1 Å.

### 3.4. CRYSTAL PACKING

The dimer illustrated in Figure 2 is the repeating motif in an infinite column of dimers arranged in channel-packing mode parallel to the crystal c-axis. This is a well known stacking mode for dimeric $\beta$-CD complexes crystallizing in the space group C2 with cell dimensions similar to those reported here [7]. It is evident from the guest···guest contact distances, also listed in Table III, that the two acetamide residues of the disordered drug components B and B’ (filled circles, Figure 2) which are related by the $C_2$-axis of the dimer, are in prohibitively close contact at the dimer interface. In contrast, the corresponding contact distances between atoms of guests A and A′ all exceed 4 Å. Molecules B and B’ cannot therefore co-exist in one dimeric cavity and it must be concluded that successive dimers in a column contain, at random, allowed combinations of A, A′, B and B′ molecules (e.g. AB′, A′B), such that the statistically averaged structure through the macroscopic crystal is as represented in Figure 2.

## 4. Concluding Remarks

The most important feature of the present analysis is the finding that despite guest disorder, the included acetaminophen molecule invariably has its phenolic group at the primary rim and the acetamide residue at the secondary rim of the $\beta$-CD molecule. The entry of the phenolic group of the drug molecule from the secondary side of the host, leading to the same included guest orientation as observed here, was proposed from infrared spectroscopic data for the $\beta$-CD complex with acetaminophen prepared by freeze-drying [6]. These authors also suggested that intermolecular hydrogen bonding (N—H$\cdots$O) between the drug amido group and a hydroxyl group on the secondary rim of the $\beta$-CD molecule might be responsible for a lowering of the amido group frequency on complexation. The present analysis, however, reveals that the drug N—H group occupies a nearly central position in relation to the ring of host secondary O atoms and is therefore not within hydrogen bonding distance of these atoms. No significant hydrogen bond contacts were found for either of the disordered amido group N atoms.

We reported that the *p*-bromoacetanilide molecule included in $\beta$-CD has the Br atom at the primary face and the acetamide residue at the dimer interface [1]. This is analogous to the mode of inclusion in the present case, showing that substitution of Br by a hydroxyl group (with considerably different steric and electronic properties) does not change the guest orientation in the $\beta$-CD cavity.

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