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Molecular and Crystal Structure of the 1 : 1 Complex of Adamantanone with *β*-Cyclodextrin

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A 1 : 1 inclusion complex of adamantanone with *β*-cyclodextrin (*β*-CyD) has been crystallized and its structure determined by single crystal X-ray methods. This complex crystallizes in space group $P2_1$, $Z=4$, $Dc=1.25\,\mathrm{g/cm^3}$, $a=15.428\,(5)$, $b=32.545\,(5)$, $c=15.437\,(5)\,\text{Å}$, $\beta=103.56\,(2)°$. The structure was solved by a Patterson search and was refined on F^2 for all reflections to a final value of $R(F)=0.116$ for 6306 reflections with $I>2\sigma(I)$. The *β*-CyD molecules follows the screw channel mode of packing. Guests are disordered in three well-defined regions inside the CyD cavities, while water molecules surround the CyD.

Keywords: Cyclodextrin, X-ray, host-guest, adamantanone

INTRODUCTION

Cyclodextrins (CyDs) are molecules widely used as hosts in supramolecular chemistry [1]. Many organic molecules are known to form inclusion complexes with CyDs in solution as well as in the solid state. Among them, experimental details on the geometrical features of inclusion complexes with adamantane and some of its derivatives have already been reported [2,3]. The interest in these complexes is based both in their pharmacological properties (*i.e.*, the amine derivative of adamantane, adamantine, has shown interesting antiviral properties [4]) and in their purely structural characteristics. Most of the experimentally available data on CyDs have been obtained from samples in aqueous solution. In these cases, researchers usually assume the formation of inclusion complexes and assign values to the association constants, geometries, *etc.*, based on this assumption. However, no clear proof of the inclusion complexes formation is provided, opening thoughts on the possibility of sharing the internal (inclusion) with the external association. In this study, we present the preparation and the structural elucidation for the complex between adamantanone and *β*-CyD which will demonstrate that even in solid

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phase, this guest is not fully inside the cavity, but in what may be considered as the "interphase", leaving an empty CyD cavity.

RESULTS AND DISCUSSION

All glucose residues (see Fig. 1 for numbering scheme) present the $^4C_1$ conformation. Two primary hydroxyl groups are disordered over two positions. Occupancies for these positions are (0.55/0.45 for O146-O147 and 0.49/0.51 for O256/O257). Only the two disordered sites present a (−) gauche conformation for the C6-O6 pointing toward the cavity (O146, O256). The rest, including the components for the disorder pointing outwards from the macrocyclic cavity, are in the (+) gauche conformation.

The equatorial belt formed by the 7 glycosidic oxygens is plane. Averages for the seven absolute values of the O—O—O—O torsion angles are, 0.4 for CyD1 and 1.2 for CyD2 Table I. These values are in the range of planarity considered by Lipkowitz for *β*-CyDs in the solid state [5]. Distances from the glycosidic oxygens to their mean plane are always smaller than 0.03 Å. Moreover, the seven glycosidic oxygens can be considered as forming a regular heptagon. The maximum deviation from the 128° value (regular heptagon) is 2 for CyD1 and CyD2 Table II. The mean planes defined by C2, C3, C5 and O5 and the glycosidic oxygen mean plane are close to ortogonality. Previous work had already shown this disposition, and molecular mechanics calculations also revealed its stability [5].

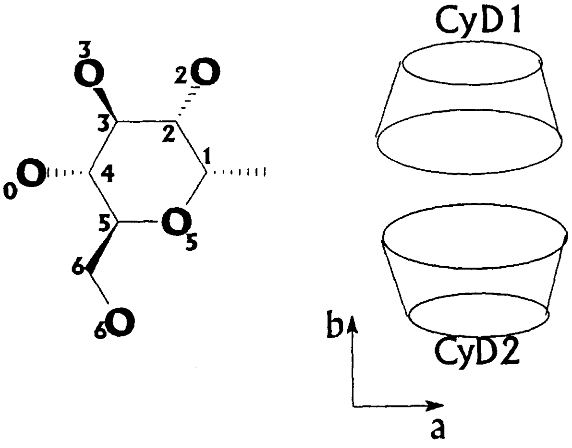

FIGURE 1 Numbering scheme for the CyD atoms. It is composed of the atom symbol followed by three numbers (CXYZ or OXYZ) where X corresponds to the CyD molecule of the unit cell, Y the glucose residue (from 1 to 7) and Z the atom number according to the figure.

TABLE I O—O—O—O high order torsion angles (degrees) in the glycosidic belt for the two cyclodextrins

	$X=1$	$X=2$
OX10-OX20-OX30-OX40	0.8 (7)	−0.5 (7)
OX20-OX30-OX40-OX50	−0.6 (6)	1.9 (6)
OX30-OX40-OX50-OX60	−0.1 (6)	−2.7 (6)
OX40-OX50-OX60-OX70	−0.6 (6)	2.1 (6)
OX50-OX60-OX70-OX10	−0.4 (6)	−0.8 (6)
OX60-OX70-OX10-OX20	0.1 (7)	0.2 (6)
OX70-OX10-OX20-OX30	−0.4 (7)	−0.1 (6)

The complex can be described as a head to head dimer (as many of *β*-CyD complexes) while the crystal can be described as a screw channel mode packing of dimers along *b*-axis (Fig. 2). The dimer stabilization arises from the hydrogen bonds formed exclusively between the secondary hydroxyl groups (see Fig. 3).

A total of 14.5 water molecules were located; 8.5 were disordered over 15 sites surrounding the dimer, none within the macrocyclic cavity (Fig. 4). Water molecules form hydrogen bonds between them and also with the hydroxyl groups of the host molecule.

Adamantanones were placed from a plot of the 100 more intense residual peaks after

TABLE II O—O—O angles (degrees) in the glycosidic oxygen belt for the two CyDs

	$X=1$	$X=2$
OX10-OX20-OX30	129 (1)	129 (1)
OX20-OX30-OX40	128 (1)	129 (1)
OX30-OX40-OX50	129 (1)	128 (1)
OX40-OX50-OX60	128 (1)	129 (1)
OX50-OX60-OX70	130 (1)	128 (1)
OX60-OX70-OX10	127 (1)	130 (1)
OX70-OX10-OX20	129 (1)	127 (1)

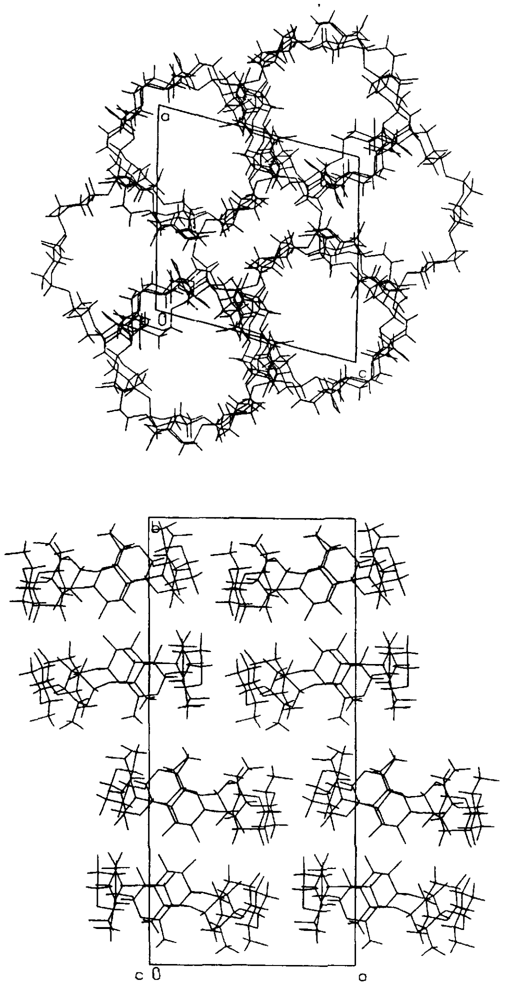

FIGURE 2 Crystal packing; Top: view along *b* axis; Bottom: view along *c* axis.

location of cyclodextrin and water molecules. In this map, three populated zones (U1, U2 and U3) were found and they were associated to disordered adamantanones. The three centroids were considered as the adamantanone centroids. U1 and U2 are inside CyD1 and CyD2, respectively, and U3 is inside the dimeric cavity (Fig. 5). The distances between U1 and U3 to cyclodextrin oxygens are compatible with the presence of hydrogen bonds. The refinement of these adamantanones has been carried out assigning carbons to the different residual

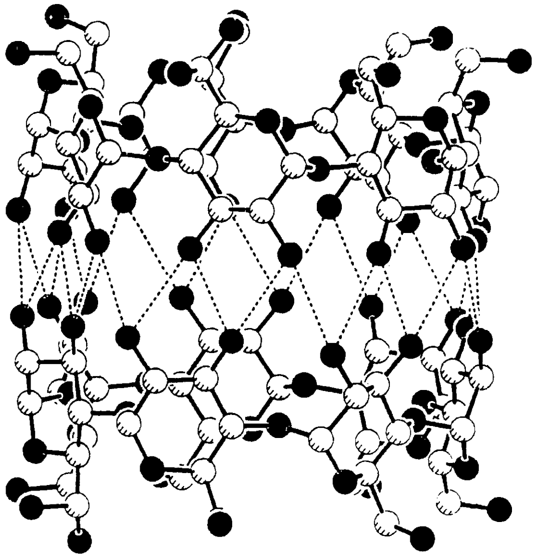

FIGURE 3 Hydrogen bonds between the CyD dimeric molecules accounting for the dimer stabilization.

density positions. The sum of their occupation factors was softly restrained in such a way that 2 adamantanones are present in the asymmetric unit, accordingly to the stoichiometry experimentally established by ^{1}H-NMR. Only in one of the zones could one adamantanone be fit and refined as a rigid body. In this case, the formation of a hydrogen bond between the adamantanone carbonylic oxygen and the CyD hydroxyl group can be considered (the distance between these two oxygen atoms was found to be 2.55 Å). This adamantanone is inside the macrocyclic cavity (CyD2) and can be related to the inner component of the disorder for O256/O257. The conformation of this hydroxyl group is likely to depend on the presence of the adamantanone by hydrogen bond formation. Accordingly to this, the hydroxyl group must be oriented inwards (corresponding to a (−) gauche conformation of the C6—O6 bond) otherwise, the hydroxyl adopts an outwards conformation (corresponding to a (+) gauche conformation) stabilized by hydrogen bonding with water molecules. A similar behaviour has also been described for hydrates with β-CyD [6, 7].

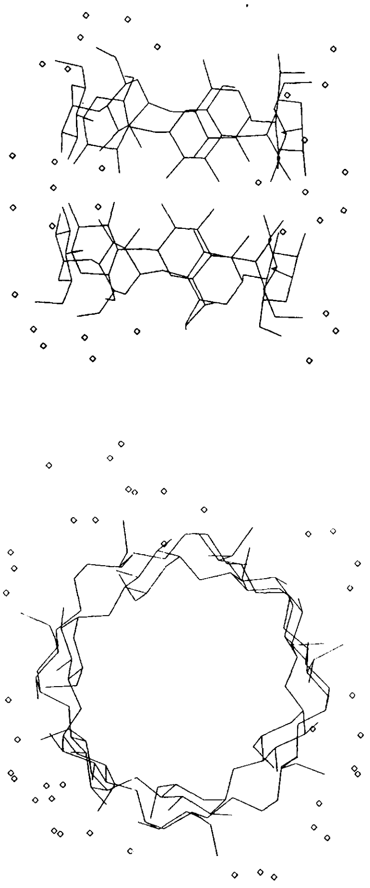

FIGURE 4 Water molecules surrounding the CyD dimer; Top: side view; Bottom: upper view.

It is interesting to point out that a similar inclusion complex has been described: the 1 : 1 menthol/β-CyD inclusion complex [8], which has the same β-CyD packing ($a = 15.342(3)$, $b = 32.54(2)$, $c = 15.324(3)$, β 102.44(2)°, space group $= P2_1$ and $Z = 4$). The menthol occupies the CyD cavity and hydrophobic forces have been invoked for explaining the host-guest relationship. Our guest has been found not only in the CyD cavity but also in the dimeric cavity. Molecular volumes could be invoked to be the reason for this similarity because computed molecular volumes for adamantanone and menthol are similar: 146.5 and 157.4 Å^3, respectively [9].

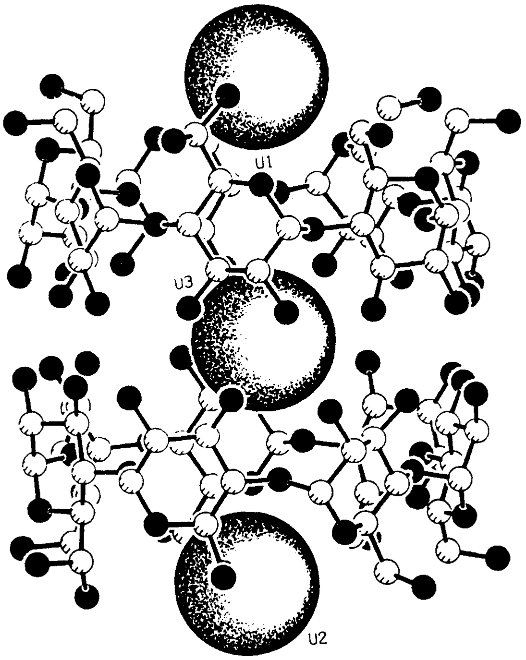

FIGURE 5 Adamantanone regions U1–U3 found in the crystal.

However, in the 1 : 1 β-CyD inclusion complex [10] with 1,3,5,7-tetraazaadamantane [11], a totally different packing mode (cage type) is present being the guest molecular volume very similar (134.4 Å^3) to that of adamantanone.

EXPERIMENTAL SECTION

Materials

β-Cyclodextrin (Janssen chimica), and adamantanone (Aldrich Chemicals) were used with no further purification.

Preparation of Complexes

Crystals of the adamantanone-β-cyclodextrin complex, which are colourless and prismatic, were grown by stirring a $1.62\,10^{-2}$ M β-CD aqueous solution with adamantanone, giving a 1 : 1 molar ratio. Complete dissolution was obtained by the help of sonication. The solution was left at room temperature to allow crystal formation.

X-ray Experimental Details

A single crystal of dimensions 0.5 × 0.2 × 0.2 mm was mounted in a Lindemann capillary which had been filled with quick-setting cyanoacrylate glue. Intensity data were collected at room temperature (298 K) on an Enraf-Nonius CAD-4 diffractometer using grafite monochromated MoKα radiation ($\lambda = 0.71069$ Å). Accurate cell dimensions were obtained by least-squares analysis of the setting angles of 25 reflections in the range $10 \leq \theta \leq 15$. Data were collected by the $\omega - 2\theta$ scan technique to $(\sin\ \theta/\lambda)_{\max} = 0.595\ \text{Å}^{-1}$. 13458 unique reflections were measured ($-18 \leq h \leq 17, 0 \leq k \leq 38,\ 0 \leq l \leq 18$) and monitored every hour showing no decrease in intensity during data collection. Orientation control was performed every 200 reflections and data were corrected for Lp effects. The structure was solved using Patterson search (SHELXS-86 [12] and PATSEE [13]). All the non hydrogen atoms of the two cyclodextrins molecules were located in a difference Fourier map. Refinement was carried out by least squares method on F^2 for all reflections (SHELXL97) [14]. During refinement, water molecules were located and one adamantanone was refined as a rigid body. 51 additional peaks grouped in three regions (one corresponding to the fit adamantanone) were considered as disordered adamantanone atoms and were refined with a common fixed arbitrary isotropic temperature factor $U = 0.15\ \text{Å}^2$. Adamantanones site occupation factors were refined restrained in such a way that four adamantanone molecules per unit cell are present. Non-disordered water atoms were refined anisotropically; the rest of the water atoms were refined isotropically. H atoms bonded to CyD; C atoms were placed in calculated positions with isotropic temperature factors fixed at 1.2 times U_{eq} for the corresponding C atoms. The weighthing scheme was $w = 1/[\sigma^2(F_o^2) + (0.2\,P)^2]$ where $P = [\text{Max}(F_o^2, 0)$ $+2F_c^2]$. Final $R(F)$ and $Rw(F^2)$ values were 0.116 and 0.287 for 6306 reflections with $I > 2\sigma(I)$.

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[11] IUPAC name for the guest is 1,3,5,7-tetraazacyclo [3.3.1.1^{3,7}]decane.

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