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Crystal structure of the supramolecular linear polymer formed by the self-assembly of mono-6-deoxy-6-adamantylamide-β-cyclodextrin

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Mono-6-deoxy-6-adamantylamide-β-cyclodextrin–dimethylformamide–15H_2O, $C_{53}H_{85}NO_{35}\cdot C_3H_7NO\cdot 15H_2O$, crystallizes in the orthorhombic space group $P2_12_12_1$. The adamantyl group is inserted into the cyclodextrin cavity of the adjacent molecule, entering by the side of the secondary hydroxy rim, thus forming a supramolecular linear polymer by self-assembly. Adjacent macrocycles are linked into columns by hydrogen bonds involving the nearest glucose residues, and the structure is further stabilized by their involvement in hydrogen bonding with water molecules which reside in channels surrounding the polymer columns, thus acting as bridges between the cyclodextrin units. The centroid of the adamantyl group lies below the plane formed by the seven glycosidic O atoms of the host cyclodextrin, excluding water molecules from the secondary side of β-cyclodextrin (β-CD). Between the adamantyl group and the primary hydroxy rim of the cyclodextrin cavity lies a dimethylformamide molecule, which shields the hydrophobic adamantyl group from the primary hydroxy rim of its carrying β-CD and excludes water molecules from the primary side of the β-CD cavity.

1. Introduction

It is well known that cyclodextrins form inclusion complexes with a variety of organic molecules, a property used to increase the bioavailability of poorly soluble drugs (Szejtli, 1988, 1996). Although most of the inclusion complexes formed have simple stoichiometries (1:1, 1:2 *etc.*; Rekharsky & Inoue, 1998), cyclodextrins also form high-order superstructures, such as polyrotaxanes (Wenz & Keller, 1994; Harada *et al.*, 1999; Raymo & Stoddart, 1999), catenanes (Nepogodiev & Stoddart, 1998), nanotubes (Harada & Kamachi, 1994; Harada *et al.*, 1995) and linear polymer-like (Ramos Cabrer *et al.*, 1999; Alvarez Parrilla *et al.*, 2002) or Cayley-tree type conglomerates (Alvarez Parrilla *et al.*, 2000). However, although thousands of papers have been published on these cyclic oligosaccharides, the formation by cyclodextrins of interlocked chains (Raymo & Stoddart, 1999) has received much less attention (Hirotsu *et al.*, 1982; Kamitori *et al.*, 1987; Harata *et al.*, 1993; Mentzafos *et al.*, 1996; Liu *et al.*, 2003).

The generation of chains from interlocked monomers requires that the monomer simultaneously incorporates host and guest sites in its structure and a bridge between them. In order to interact favourably with each other, the two sites have to be mutually complementary units. Furthermore, the self-inclusion of the guest inside its own host must be prevented by designing a rigid or short bridge. Examples of this self-inclu-

sion in cyclodextrins are also known (Hamada *et al.*, 1993; Corradini *et al.*, 1996; Park *et al.*, 2001; Michels *et al.*, 2002).

If the host is a cyclodextrin unit, the required complimentarity suggests that the substituting group (the guest) must be hydrophobic in order to enter the hydrophobic cavity. It is well established that adamantyl derivatives form inclusion complexes with cyclodextrins (Cromwell *et al.*, 1985; Gelb & Schwartz, 1989; Palepu & Reinsborough, 1990; Zhang & Breslow, 1993; McAlpine & Garcia-Garibay, 1996; Ruediger *et al.*, 1996; Narita *et al.*, 1998; Ueno *et al.*, 1999; May *et al.*, 2000; van Bommel *et al.*, 2001; Vashi *et al.*, 2001; Michels *et al.*, 2002). From a thermodynamic point of view, this interaction is highly favourable, with equilibrium constants in excess of $10^5\ M^{-1}$ being reported (Cromwell *et al.*, 1985). This preference is a consequence of the fact that the adamantyl group fits perfectly inside the β-cyclodextrin cavity and suggests that an adamantyl-β-cyclodextrin derivative can be a suitable synthon for obtaining large acyclic linear polymer compounds. However, May *et al.* (2000) observed self-inclusion in 6A-{6-[*N*-(1-adamantylcarbonyl)amino]hexylamino}-6A-deoxy-β-cyclodextrin, where the separating bridge is a long alkyl chain. As an adamantyl-β-cyclodextrin derivative with a short bridge (to prevent the self-inclusion of the guest moiety into the host moiety of the same monomer) seems to be the most obvious solution, we synthesized mono-6-deoxy-6-adamantylamide-β-cyclodextrin (AdA-β-CD). We report here the formation of a polymer-like structure in the solid state.

2. Experimental

2.1. Synthesis of mono-6-deoxy-6-adamantylamide-β-cyclodextrin

6-Aminocyclodextrin (2 g, 1.8 mmol) and triethylamine (0.5 ml, 0.363 g, 3.6 mmol) were dissolved in dry dimethylformamide (DMF, 60 ml). The solution was cooled under argon with an ice-water bath for 20 min, and then adamantoyl chloride (0.19 g, 9.97 mmol) in dry DMF (3 ml) was added. The ice-water bath was removed after 30 min and the reaction mixture was stirred at room temperature for 24 h. The DMF was partially removed and the solution was poured into $CHCl_3$ (50 ml) with stirring. The solid was filtered off and washed with $CHCl_3$. The product was purified in a Sephadex CM 25 column using water as eluent and yielded the following NMR spectra: ^{1}H NMR (D_2O, δ): 4.76 (*m*, H_1), 3.97 (*m*, H_3, H_5, H_6), 3.56 (*m*, H_4, H_2), 2.98 (*m*, H_4'), 2.81 and 2.90 (*m*, H_6'), 2.29 (*m*, $H_{Ad\text{-}c}$), 2.02 (*m*, $H_{Ad\text{-}a}$), 1.90 (*m*, $H_{Ad\text{-}b}$); ^{13}C NMR (D_2O, δ): 102.0 (C_1), 84.2 (C_4'), 81.6 (C_4), 71.9–72.9 (C_3, C_2, C_5), 59.5 (C_6), 40.4, (C_6'), 39.1 ($C_{Ad\text{-}b}$), 36.10 ($C_{Ad\text{-}a}$), 27.6 ($C_{Ad\text{-}a}$) (Fig. 1).

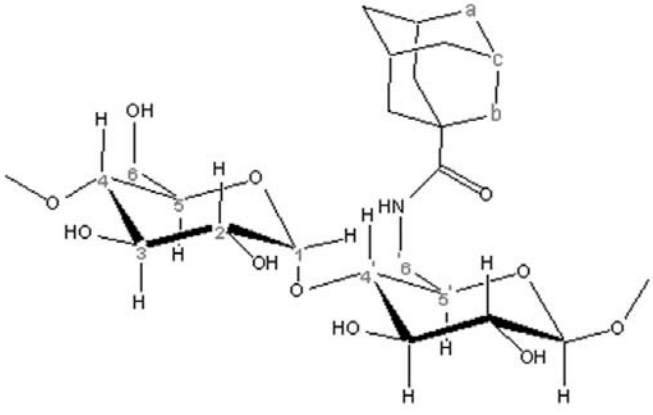

Figure 1
The numbering scheme for the glucose units of β-CD and for the adamantyl moiety.

Table 1
Experimental details.

Crystal data	
Chemical formula	$C_{53}H_{85}NO_{35}\cdot C_3H_7NO\cdot 15H_2O$
M_r	1639.56
Cell setting, space group	Orthorhombic, $P2_12_12_1$
a, b, c (Å)	15.0687 (1), 17.6502 (2), 29.4386 (3)
V (Å^3)	7829.65 (13)
Z	4
D_x (Mg m^{-3})	1.391
Radiation type	Cu $K\alpha$
No. of reflections for cell parameters	8125
θ range (°)	1.0–74.5
μ (mm^{-1})	1.07
Temperature (K)	100.0 (1)
Crystal form, colour	Plate, colourless
Crystal size (mm)	0.63 × 0.2 × 0.05
Data collection	
Diffractometer	Bruker–Nonius KappaCCD 2000
Data collection method	ω and φ scans
Absorption correction	Multi-scan (*SORTAV*; Blessing, 1995)
T_{min}	0.731
T_{max}	0.955
No. of measured, independent and observed reflections	83 976, 15 082, 13 779
Criterion for observed reflections	$I > 2\sigma(I)$
R_{int}	0.063
θ_{max} (°)	72.3
Completeness to θ_{max} (%)	98.5
Range of h, k, l	$-17 \Rightarrow h \Rightarrow 18$ $-21 \Rightarrow k \Rightarrow 20$ $-36 \Rightarrow l \Rightarrow 36$
Refinement	
Refinement on	F^2
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.085, 0.250, 1.05
No. of reflections	15 082
No. of parameters	914
H-atom treatment	Mixture of independent and constrained refinement
Weighting scheme	$w = 1/[\sigma^2(F_o^2) + (0.1598P)^2 + 4.5528P]$, where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max}$	−0.048
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	1.10, −0.54
Symmetry-equivalent position as x, y, z	x, y, z $-x+\frac{1}{2}$, $-y$, $z+\frac{1}{2}$ $x+\frac{1}{2}$, $-y+\frac{1}{2}$, $-z$ x, $y+\frac{1}{2}$, $-z+\frac{1}{2}$
Extinction method	*SHELXL*97
Extinction coefficient	0.0028 (2)
Absolute structure	Flack (1983)
Flack parameter	0.0 (2)

Computer programs: *COLLECT* (Nonius, 1997–2000), *HKL SCALEPACK* (Otwinowski & Minor 1997), *HKL DENZO* (Otwinowski & Minor 1997), *SIR*97 (Altomare *et al.*, 1999), *SHELXL*97 (Sheldrick, 1997), *ORTEP*-3 *for Windows* (Farrugia, 1997), *WinGX* (Farrugia, 1999).

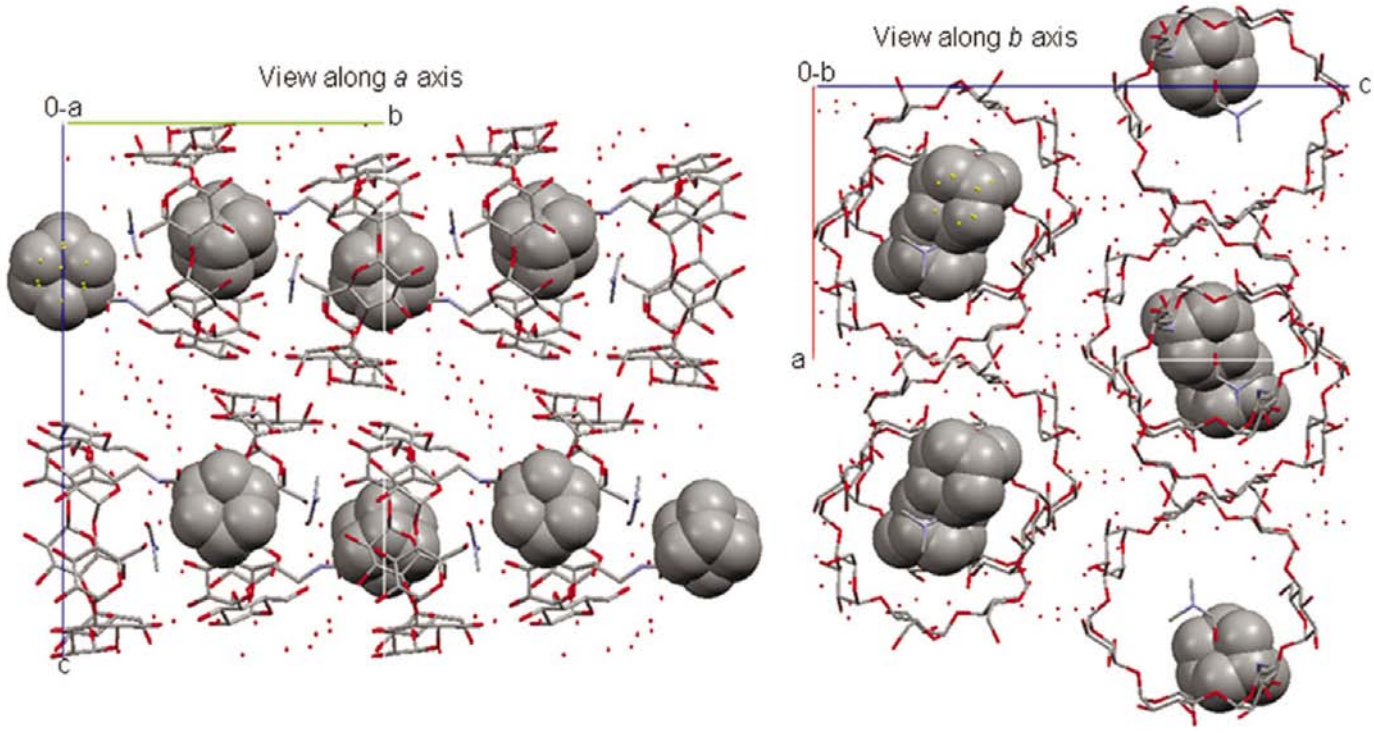

Figure 2
A view of the structure along the *a* and *b* axes. Red points represent water molecules in the channels between columns of macrocycles.

The product was dissolved in DMF. Single crystals were obtained by slow diffusion of water vapour into the AdA-β-CD/DMF solution. Starting from a 4.5 wt% AdA-β-CD solution in DMF, crystal formation was observed when adding water up to a mixture composition at 33 wt% H_2O. Final composition: AdA-β-CD 3%, DMF 64%, H_2O 33%.

2.2. X-ray data collection and reduction

Details of crystal data, data collection and structure refinement are reported in Table 1. The structures were refined on F^2 by full-matrix least-squares against all reflections, using anisotropic displacement parameters, except for the disordered part of the molecule (Sheldrick, 1997). The weighted R factor, wR value and goodness-of-fit are based on F^2. The absolute structure for the compound was known from the synthesis and was confirmed by the Flack (1983) parameter. A correction for secondary extinction was required.

Cell constants and orientation matrices were obtained after post-refinement (Otwinowski & Minor, 1997) of 307 frames collected with a Bruker–Nonius KappaCCD 2000 rotating-anode diffractometer. Data were collected using Cu $K\alpha$ radiation (λ = 1.5418 Å). Atomic scattering factors were taken from Cowley (1999). The program *MERCURY* (Bruno *et al.*, 2002) was used for visualizing the structure and drawing the figures.[1]

[1] Supplementary data for this paper are available from the IUCr electronic archives (Reference: BM5006). Services for accessing these data are described at the back of the journal.

3. Results and discussion

Mono-6-deoxy-6-adamantylamide-β-cyclodextrin–DMF–15H_2O (AdA-β-CD·DMF·15H_2O) crystallizes in the orthorhombic space group $P2_12_12_1$. Unit-cell parameters are given in Table 1 and a packing diagram is shown in Fig. 2. The adamantyl group is inserted into the cyclodextrin cavity of the adjacent molecule, entering by the side of the secondary hydroxy rim. As expected, a single species acts as both guest and host. The consequence is the formation of a supramolecular linear polymer formed by the self-assembly of the AdA-β-CD molecules. Supramolecular polymer columns are stacked parallel to the *b* axis and perpendicular to the *a* axis. The macrocycles are aligned along a twofold screw axis. All D-glucose residues are in a $^4C_1$ chair conformation.

The seven O4 atoms are nearly coplanar (least-squares mean plane *Og*), the maximum deviation from this plane (−0.31 Å) being for the O44 atom.[2] With O44 omitted, the maximum deviation (−0.16 Å) is for O43, which suggests that glucosyl residue G4 is distorted compared with the other six residues. In fact, the pyranoid rings of G2, G3, G5 and G6 are almost perpendicular to *Og*, the angles being in the range 85–90°. However, the other residues G1, G4 and G7 are inclined towards the inside of the macrocycle (angles in the range 71–79°). It should be noted that on going from G2 to G6 the only glucosyl residue that is not perpendicular to *Og* is G4. In the

[2] The numbering scheme is as follows: O atoms are denoted O*mn*, where the first subscript denotes the *m*th atom within the *n*th glucopyranose residue (G*n*). The numbering of glucose residues (G) is counterclockwise starting from the substituted unit.

direction G3⇒G4⇒G5, tilt angles of −19 and +18°, respectively, are observed. Therefore, the macrocycle has the shape of a distorted truncated cone. The seven glycosidic O atoms form a distorted heptagon (Fig. 3), with angles ranging from 126.3 to 131.8° and an average value of 128 (2)°, which compares well with that of 128.6° for an ideal heptagon. The side lengths of the heptagon are in the range 4.302−4.415 Å, the average value being 4.36 (5) Å. These values are identical to those obtained by Hamilton (1985) for the β-CD-1-adamantylmethanol complex [4.36 (6) Å and 128 (3)°] and very close to those for uncomplexed β-CD (4.27 Å and 125.2°; Saenger *et al.*, 1998). The heptagon is also well defined when distances and angles between atoms C6 or O3 are used to define it. These lengths are close to those obtained by Kamitori *et al.* (1987) for phenylthio and phenylsulphinyl derivatives of β-CD, and by Harata *et al.* (1993) for the 6-*O*-(*R*)- and -(*S*)-hydroxypropyl derivatives.

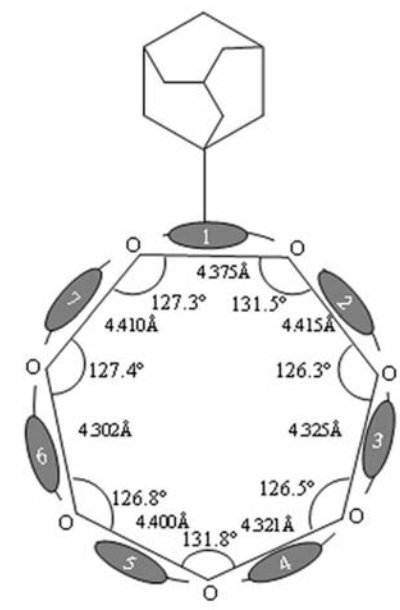

Figure 3
Side lengths (Å) and angles (°) for the heptagon consisting of O4 (glucosidic) atoms. The numbering of glucose residues (G) is counter-clockwise starting from the substituted unit viewed from the secondary hydroxy rim side.

The adamantyl group is located above the glucose residue G1, but is slightly inclined towards the residue G2 (angle ∼80°) and to the centre of the cyclodextrin ring. The amide N atom, and atoms C5 and C3 of G1, are on a straight line that forms an angle of 81° with the *Og* plane. It should also be noted that the angle formed by G1 and the *Og* plane is far from perpendicular, being inclined towards the inside of the macrocycle.

Fig. 4 shows that the centroid of the adamantyl group is below the *Og* plane of the host cyclodextrin. As Hamilton & Sabesan (1982) have pointed out, the interior of the cavity is not a smooth cone or cylinder but has a constriction in the neighbourhood of the O4 atoms, *i.e.* O4 atoms protrude furthest into the β-CD cavity, blocking the entrance of the guest molecules. These authors observed the protuberances while studying the β-CD-1-adamantylcarboxylic acid complex; they noticed that two 1-adamantylcarboxylic acid guests (belonging to two β-CD hosts forming a dimer in a head-to-head orientation produced by strong hydrogen bonding involving the secondary hydroxy groups) have different orientations and different depths of penetration into the β-CD cavities. The *Og* plane can be considered as a *frontier* for the two guests since, in the case of guest 1, the centroid of the adamantyl moiety lies just above the circle formed by the 14 C2 and C3 atoms or the β-CD residue, *i.e.* the adamantyl moiety is located in the wider part of the cavity where the van der Waals contacts are weaker. However, in the case of guest 2, the centroid of the adamantyl moiety lies just outside the circle formed by atoms C5 and O5 of the seven glucosyl groups of the β-CD residue, in a region where the fit of the guest in the cavity is tight and the van der Waals contacts are strong. Therefore, it is obvious that in the present case the adamantyl moiety lies in a position similar to that of guest 1 of the β-CD-1-adamantylcarboxylic complex. As a result of having this location, the adamantyl moiety excludes any water molecule

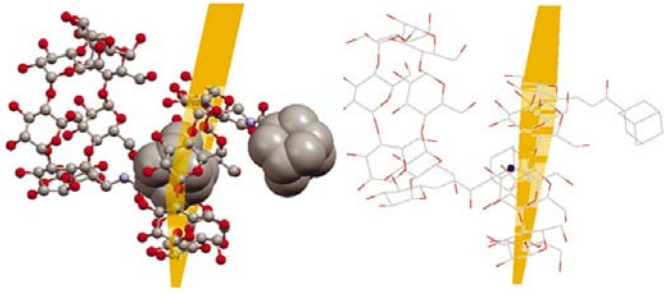

Figure 4
The degree of inclusion of the adamantyl moiety into the β-CD cavity. The central sphere of the right-hand figure represents the centroid of the C atoms of the adamantyl moiety. The guest does not penetrate beyond the plane defined by the seven glucosidic atoms. The adamantyl residue enters by the side of the secondary hydroxy rim of the β-CD group. The DMF molecule has been omitted for clarity.

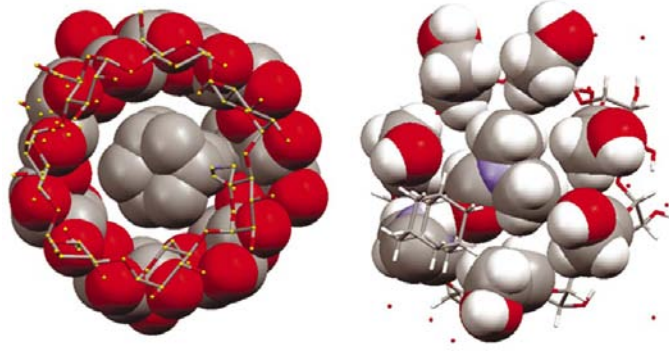

Figure 5
Left: A space-filling model of the adamantyl moiety inside the β-CD cavity, viewed from the secondary hydroxy rim of the β-CD group. For clarity, the DMF molecule and H atoms have been omitted. Right: A space-filling model of the DMF molecule intercalated between the β-CD cavity and the adamantyl moiety. Both figures illustrate the absence of water molecules within the cyclodextrin cavity.

Table 2
Intramolecular and intermolecular hydrogen bonds involving the O atoms of the cyclodextrin group.

The intermolecular bonds occur between neighbouring cyclodextrins in the same column. The numbering scheme is as follows: O atoms are denoted as O*mn*, where the suffix *mn* identifies the *m*th atom within the *n*th glucopyranose residue (G*n*).

Hydrogen bond	O···O (Å)	O···H—O (°)
Intramolecular		
O22—H···O33	2.781 (5)	165
O27—H···O31	2.860 (5)	163
O32—H...O21	2.733 (6)	136
O34—H···O23	2.866 (4)	170
O37—H···O26	2.831 (4)	174
Intermolecular cyclodextrin–cyclodextrin		
O62—H···O36	2.788 (5)	138
O63—H···O27	2.947 (5)	111
O63—H···O37	2.736 (4)	144

Table 3
Examples of water molecules acting as bridges between consecutive cyclodextrins in the same column or between adjacent columns.

Numbering scheme for O atoms as for Fig. 6; *W* indicates a water bridge.

Water bridges between cyclodextrin residues	O···O (Å)	O···*W* (Å)	*W*···O (Å)	Angle (°)
Same column				
O32···*W*···O67	4.813	2.721	2.710	124.8
O62···*W*···O25	3.585	2.942	2.710	78.6
O51···*W*···O25	5.357	2.759	2.710	156.7
O33···*W*···O67	4.337	2.737	2.698	105.9
$O_{carbonyl}$···*W*···O34	4.478	2.989	2.801	101.3
Adjacent columns				
O26···*W*···O65	4.446	2.756	2.723	108.5
O25···*W*···O66	4.618	2.710	2.807	113.6
O36···*W*···O21	4.542	2.791	2.702	111.5

from the secondary side of the β-CD cavity, since the adamantyl moiety completely fills this side of the cyclodextrin cavity (Fig. 5). As a result, all the water molecules are located in the cavities between the columns of the supramolecular polymer, forming hydrogen bonds with hydroxy groups of the cyclodextrin ring (see below). This situation differs from those found by Hamilton (1985) for the β-CD-1-adamantylmethanol adduct and by Harata (1984) while studying the β-CD-hexamethylenetetraamine complex. Like the β-CD-1-adamantylcarboxylic acid system, β-CD-1-adamantylmethanol forms a dimer in a head-to-head orientation. Hamilton (1985) found that the hydroxy group of 1-adamantylmethanol is oriented towards the primary hydroxy end of the host and hydrogen bonds directly to the primary hydroxy group on residues G5 of adjacent β-CD molecules. Furthermore, water is trapped in three disordered sites at the dimer interface, preventing the adamantyl from binding in this zone, as observed for one of the 1-adamantylcarboxylic acid molecules (guest 1, see above). The 1-adamantylmethanol binds as guest 2 but is further out of the cavity.

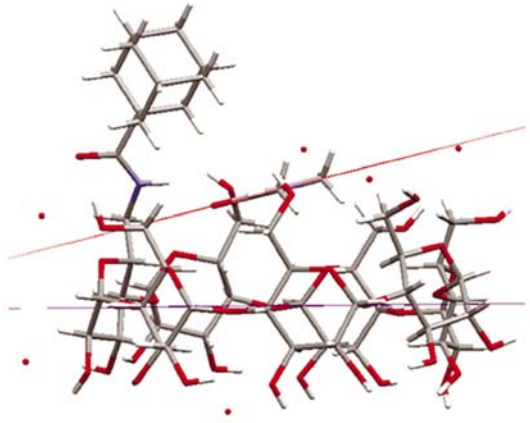

Figure 6
The dihedral angle formed between the *Og* and DMF planes.

On the other hand, in the β-CD-hexamethylenetetraamine complex (Harata, 1984), although both guests (adamantyl moiety and hexamethylenetetraamine) have a spherical geometry that fits well within the β-CD cavity, hexamethylenetetraamine forms O—H···N hydrogen bonds with the water molecule located at the primary hydroxy side and with the O2—H hydroxy group of the G3 residue in an adjacent β-CD molecule at the secondary hydroxy side. Therefore, the hexamethylenetetraamine group is fixed within the β-CD cavity by hydrogen bonding and van der Waals forces. This situation is reminiscent of that in the β-CD-1-adamantylcarboxylic complex, since there is no direct hydrogen bonding of the carboxylic acid groups to the primary hydroxy groups (they are linked by two water molecules). For AdA-β-CD, only van der Waals host–guest interactions can be considered. The average of the shortest distances between each C atom of the adamantyl group and each glycosidic O atom of the cyclodextrin ring is 3.9 (4) Å (range 3.5—4.2 Å).

Between the adamantyl group and the primary hydroxy rim of the cyclodextrin cavity lies a dimethylformamide molecule, which occupies a plane that forms a dihedral angle of 14° with the *Og* plane (Fig. 6), while the angle between the least-squares *Og* planes of two consecutive AdA-β-CD molecules in the same column is 16°. This value is much lower than that (43.3°) found by Mentzafos *et al.* (1996) in the crystal structure of 6^1-(6-aminohexyl)amino-6^1-deoxycyclomaltoheptaose. The DMF N atom is almost equidistant from all glycosidic O atoms [mean N···O = 6.3 (5) Å; range 5.8–7.0 Å]. The distance between the N atoms of two consecutive equivalent DMF molecules in the same column is 17.650 Å (equal to any other distance considered between identical atoms located in two equivalent molecules), over twice the expected height for the truncated cone of a cyclodextrin (7.9 Å; Saenger *et al.*, 1998).

The DMF molecule is anchored by a hydrogen bond between the nitrogen-amide bridge linking the cyclodextrin and adamantyl moieties and the carbonyl O atom of the DMF molecule (N_{amide}—H···O_{DMF}: 2.825 Å and 145.3°). Thus, the DMF molecule shields the hydrophobic adamantyl group from the primary hydroxy rim of its β-CD carrier and excludes

water molecules from the primary side of the β-CD cavity (see Fig. 5).

In the crystal of unsubstituted β-CD, the macrocyclic cavity is filled with water molecules, considered to be in a high energy state because they cannot form their full complement of hydrogen bonds within that hydrophobic environment (Lindner & Saenger, 1982). The inclusion of a guest means that the water molecules lie outside the β-CD cavity, mainly surrounding the columns of the supramolecular polymer, where they can form hydrogen bonds with the hydroxy groups of the cyclodextrin ring (Fig. 2).

The secondary hydroxy groups between neighbouring glucose residues form intramolecular hydrogen bonds involving atoms O2 and O3. Hydrogen-bond distances are in the range 2.73–2.86 Å (Table 2). In the crystal structure of the β-CD-1-adamantylmethanol complex, Hamilton (1985) observed O2$\cdots$O3 hydrogen-bonding distances in the range 2.72–2.79 Å. The absence of an O24$\cdots$O35 hydrogen bond is probably due to the distorted orientation of the residue G4 (see above).

Water molecules reside in channels (Fig. 2) and form a network of hydrogen bonds among themselves and with the cyclodextrin moieties. Adjacent macrocycles within the columns are bound together by hydrogen bonds involving the nearest glucose residues; these interactions are formed between primary (G2 and G3 residues) and secondary (G6 and G7 residues) hydroxy groups. The structure is further stabilized by the formation of hydrogen bonds with water molecules, which act as bridges for the formation of hydrogen bonds between different polymer columns. Table 3 gives details of bridges in which one water molecule is hydrogen bonded to two cyclodextrin residues belonging either to the same column or to adjacent columns. Again, most of these bonds involve one secondary and one primary hydroxy O atom. The glucose-oxygen–water distances are in the range 2.70–2.99 Å and the glucose-oxygen–glucose-oxygen distances are in the range 3.59–5.36 Å. The glucose-oxygen–water-oxygen–glucose-oxygen angles are in the range 79–157°.

The primary hydroxy groups (torsion angles in parentheses) of the G2 (−66.40°), G4 (−56.35°), G5 (−66.85°) and G6 (–64.27°) residues have a (−)*gauche* orientation pointing out of the cyclodextrin cavity. The remaining groups, *i.e.* G1 (considering the amide N atom, which replaces the G1 hydroxy group; 68.71°), G3 (62.39°) and G7 (66.36°) have a (+)*gauche* orientation and thus point into the cavity.

Fig. 7 shows the average molecular geometry over the seven glucopyranose units. The mean glucosidic C4—O4—C1 angle [118.1 (7)°] is similar to those found by Hamilton (1985) for the β-CD-1-adamantylmethanol complex [119 (1)°], by Hamilton & Sabesan (1982) for the β-CD-1-adamantylcarboxylic acid complex [117 (1)°] and by Harata (1984) for the β-CD-hexamethylenetetraamine complex [118 (1)°], and is also comparable to the value found for β-CD dodecahydrate [118 (1)°; Lindner & Saenger, 1982].

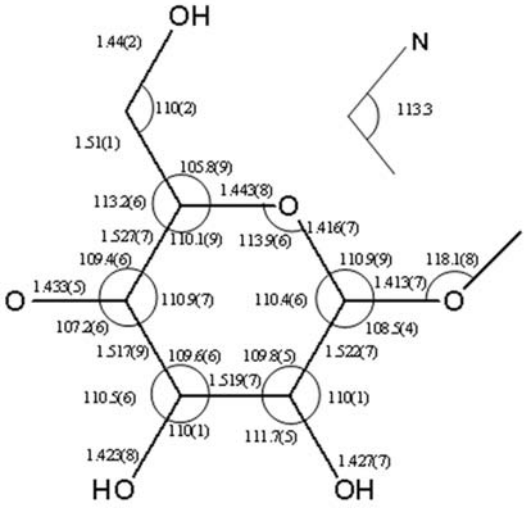

Figure 7
Average geometry (Å, °) for the glucose unit in the AdA-β-CD complex. Standard deviations are given in parentheses.

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