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Synthesis and structural characterization of $6^I,6^{II}$-diamino-$6^I,6^{II}$-dideoxy-cyclomaltoheptaose, a difunctionalized β-cyclodextrin [1]

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Abstract

$6^I,6^{II}$-Diamino-$6^I,6^{II}$-dideoxy-cyclomaltoheptaose was prepared using the regioselective procedure described by Tabushi. The difunctionalized β-cyclodextrin crystallizes as hexadecahydrate in the orthorhombic space group $P2_12_12_1$, with $a = 11.395(3)$, $b = 32.989(9)$, $c = 17.560(5)$ Å, $V = 6601$ Å^3, $Z = 4$. The structure was solved by molecular replacement techniques using the program PATSEE and was refined to a conventional final $R = 0.058$ for the 5031 observed reflections with $I \geq 3\sigma(I)$. The β-CD macrocycle presents only slight differences with respect to uncomplexed hydrated or methylated β-CD. The macrocycle structure maintains an approximate

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[1] Crystallographic data deposited with the Cambridge Crystallographic Data Centre. These data may be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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seven-fold symmetry. The round shape of the cyclodextrin ring is stabilized by intramolecular O–H · · · O H-bonds between the secondary hydroxyl groups of neighbouring glucose residues. Along the ***a*** axis, the β-CD molecules are arranged in columns; the macrocycles form a herring-bone pattern, so that the cavity of each β-CD molecule is closed at each end by neighbouring molecules. The macrocycles are directly linked to each other by H-bonds involving either primary and secondary hydroxyl or amino groups of symmetry-related molecules. The resulting layers are connected to each other by a dense intermolecular hydrogen-bond network, in which solvent molecules participate.

Keywords: Cyclodextrins; Cyclomaltoheptaose; Difunctionalized β-cyclodextrin; Crystal structure

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1. Introduction

Cyclomaltooligosaccharides (cyclodextrins, CDs) are chiral hosts which have been widely studied as receptors for a large variety of molecules [1–5]. Cyclodextrins carry only hydroxyl groups and, thus, the introduction of other functional groups on their skeleton can modify and improve some features of these molecules such as solubility, stability and selectivity when forming inclusion complexes [1,6]. By replacing one or more OH groups at a desired position, multisite recognition systems involving a hydrophobic cavity and two polar groups (NH_2, COO^-, etc.) as recognition elements can be obtained and selectivity and enantioselectivity can be greatly increased [7].

The amino derivatives of cyclodextrins have been widely investigated. Perfunctionalized cyclodextrins with amino groups have shown significant antimicrobical activities against gram-negative bacteria, and furthermore they have a hypocholesterolemic effect in vivo [8].

It has been recently reported that selective functionalization with amino groups makes CDs effective receptors for anionic guests such as carboxylic acids [9], nucleotides [10] and catecholates [11] because the interaction with the ammonium centres can contribute to the binding constant and to the enantioselectivity of the recognition process.

Furthermore, it is known that CDs are able to complex metal ions through the deprotonated hydroxyl groups [12–14], only in aqueous alkaline solution. Functionalization is a useful way to improve CD ability to yield stable metal complexes in milder conditions. In fact, different functionalizing moieties have been attached to the CD cavity, and the resulting complexes have been used as metal enzyme models [1,15,16] and as multisite recognition systems [17,18]. The copper(II) complex of cyclomaltoheptaose (β-CD) functionalized with two amino groups in positions A and B has recently been investigated, and the chiral recognition ability towards aromatic amino acids has been evaluated [19]. A growing interest is emerging in the study of metal complexes of functionalized CDs as receptors [20–23]. The amino derivatives may have the advantage of having the functional group on the rim of the cyclodextrin cavity, and a stronger interaction with guest molecules or a metal ion can be supposed.

We now report the structural characterization by X-ray diffraction analysis of $6^{I},6^{II}$-diamino,$6^{I},6^{II}$-dideoxy-cyclomaltoheptaose [24], a β-cyclodextrin selectively difunctionalized with two amino groups, together with a reinvestigation of its preparation.

2. Experimental

General methods.—β-Cyclodextrin was purchased from Fluka, anhydrous *N,N*-dimethylformamide was purchased from Aldrich. They were used without further purification. TLC was carried out on silica gel plates (E. Merck 60-F254). CDs derivatives were detected with UV light and with anisaldehyde reagent, while amino derivatives were detected by the ninhydrin test. A Merck Lichroprep RP-8 column (40–63 μm) was used for reverse-phase column chromatography.

NMR spectra were recorded with a Bruker AC-200 spectrometer without a reference compound.

$6^{I},6^{II}$-Diazido-$6^{I},6^{II}$-dideoxy-cyclomaltoheptaose (**2**).—To a solution of $6^{I},6^{II}$-*O*-(benzene-1,3-disulfonyl)-cyclomaltoheptaose (**1**) (1 g) [25,26] in water (3 mL), NaN_3 (0.4 g) was added. The mixture was kept at 100 °C, stirred for 4 h and then the solvent was evaporated. The resulting solid was purified by chromatography using a Rp-8 column and a linear gradient H_2O–EtOH (0–30%) as eluent, yielding $6^{I},6^{II}$-diazido-$6^{I},6^{II}$-dideoxy-cyclomaltoheptaose (0.53 mg, 60%). R_f 0.38 (5:3:3:1 PrOH–H_2O–EtOAc–NH_3); mp 210 °C (dec); $[\alpha]_D^{25}$ +136° (*c* 0.8, water). ^1H NMR (200 MHz, D_2O): δ 5.09 (m, 1 H) 4.01–3.84 (m, H-3,6,5) 3.70–3.53 (m, H-2,4). ^{13}C NMR (50.3 MHz, Me_2SO): δ 102.0 (C-1), 83.1 (C-4^{I},4^{II}), 81.6 (C-4), 73.1–72.1 (C-5,2,3), 70.4–70.0 (C-5^{I},5^{II}), 59.9 (C-6), 51.4–51.0 (C-6^{I},6^{II}). Anal. Calcd for $C_{42}H_{68}N_6O_{33} \cdot 6H_2O$: C, 32; H, 5.3, N, 6.5. Found: C, 32.3; H, 5.5; N, 6.3.

$6^{I},6^{II}$-Diamino-$6^{I},6^{II}$-dideoxy-cyclomaltoheptaose (**3**).—To a solution of $6^{I},6^{II}$-diazido-$6^{I},6^{II}$-dideoxy-cyclomaltoheptaose (0.5 g) in DMF (5 mL), triphenylphosphine (0.74 g) was added and the solution was heated at 40 °C for 1 h under stirring. Ammonium hydroxide (30%, 5 mL) was added at room temperature [27] and after 12 h the solvent was concentrated under vacuum and the residue washed with acetone. The solid was purified using a CM-Sephadex C-25 column (NH_4^+ form). A linear gradient 0–0.2 M of NH_4HCO_3 solution was used as eluent. The appropriate fractions were combined (R_f 0.25; 5:3:1:1 PrOH–H_2O–EtOAc–NH_3) and concentrated to give the final product $6^{I},6^{II}$-diamino-$6^{I},6^{II}$-dideoxy-cyclomaltoheptaose (0.43 g, 90%). R_f 0.25 (5:3:1:1 PrOH–H_2O–NH_3–EtOAc); mp 195 °C (dec); $[\alpha]_D^{25}$ +131° (*c* 1, water). FABMS *m/z* 1136 $[M+H]^+$; ^1H NMR (200 MHz, D_2O): δ 5.04 (m, 7 H, 1-H), 4.0–3.7 (m, 24 H, 3,6,5-H), 3.67–3.37 (m, 12 H, 2,4-H), 3.08 (d, 2 H, H-$6a^{I}$ and $6a^{II}$, $J_{6a^{I},6b^{I}} = J_{6a^{II},6b^{II}} = 13.8$ Hz), 2.85 (dd, 2 H, $6b^{I}$ and $6b^{II}$, $J_{6^{I},5^{I}} = J_{6^{II},5^{II}} = 7$ Hz). ^{13}C NMR (50.3 MHz): δ 104.5 (C-1), 85.4 (C-4^{I},4^{II}), 83.8 (C-4), 75.7–73.4 (C-5,2,3), 62.9 (C-6), 43.8 (C-6^{I},6^{II}). Anal. Calcd for $C_{42}H_{72}N_2O_{33} \cdot 8H_2O$: C, 39.5; H, 6.9; N, 2.1. Found: C, 40.2; H 7.0; N, 2.2.

X-Ray diffraction analysis.—Colorless, prismatic crystals of the difunctionalized β-CD were obtained from a saturated aq soln. A crystal of dimensions 0.3 × 0.5 × 0.5 mm^3 was sealed in a Lindemann glass capillary with a drop of mother liquor to avoid water loss, which quickly yields opaque crystals. Diffraction intensities were measured on a CAD4-Turbo Enraf-Nonius diffractometer with graphite-monochromated Cu*Kα* radiation ($\lambda = 1.5418$ Å). The unit cell dimensions and estimated standard deviations, in Å, were determined at room temperature by least-squares methods using 25 reflections in the 20–25° θ range. The crystals are orthorhombic with space group $P2_12_12_1$;

Table 1
Fractional atomic coordinates and equivalent isotropic thermal parameters for non-hydrogen atoms of $6^{I},6^{II}$-diamino-$6^{I},6^{II}$-dideoxy-cyclomaltoheptaose. $B_{eq} = (8/3)p_{ij}^2 U_{ij} a_i^* a_j^* \boldsymbol{a}_i \boldsymbol{a}_j$

Atom	x	y	z	B_{eq} (Å^2)
C-1$_1$	0.3838(6)	0.2056(2)	0.0562(4)	4.0(1)
C-2$_1$	0.3105(7)	0.1680(2)	0.0791(4)	4.1(2)
O-2$_1$	0.2668(5)	0.1492(2)	0.0125(3)	5.0(1)
C-3$_1$	0.2216(6)	0.1789(2)	0.1377(4)	3.6(1)
O-3$_1$	0.1617(4)	0.1436(1)	0.1627(3)	4.4(1)
C-4$_1$	0.2773(6)	0.2005(2)	0.2045(4)	3.7(1)
O-4$_1$	0.1847(4)	0.2130(1)	0.2534(2)	3.75(9)
C-5$_1$	0.3477(6)	0.2378(2)	0.1766(4)	3.9(1)
O-5$_1$	0.4323(4)	0.2244(1)	0.1213(3)	4.0(1)
C-6$_1$	0.4115(7)	0.2585(2)	0.2395(4)	4.7(2)
N-6$_1$	0.4802(5)	0.2938(2)	0.2148(3)	4.6(1)
C-1$_2$	0.1904(6)	0.2032(2)	0.3315(4)	4.2(1)
C-2$_2$	0.0701(7)	0.1851(2)	0.3530(4)	4.2(2)
O-2$_2$	0.0451(5)	0.1511(1)	0.3082(3)	5.6(1)
C-3$_2$	−0.0211(6)	0.2175(2)	0.3457(4)	3.9(1)
O-3$_2$	−0.1300(4)	0.2026(2)	0.3717(3)	5.1(1)
C-4$_2$	0.0120(6)	0.2561(2)	0.3852(4)	3.8(1)
O-4$_2$	−0.0721(4)	0.2864(1)	0.3602(2)	3.9(1)
C-5$_2$	0.1358(6)	0.2696(2)	0.3685(4)	4.0(1)
O-5$_2$	0.2160(4)	0.2365(1)	0.3770(3)	4.4(1)
C-6$_2$	0.1804(7)	0.3027(3)	0.4204(5)	5.6(2)
O-6$_2$	0.2941(5)	0.3170(2)	0.3976(4)	7.5(2)
C-1$_3$	−0.1339(7)	0.3084(2)	0.4155(4)	4.0(2)
C-2$_3$	−0.2652(6)	0.3080(2)	0.3984(4)	3.7(1)
O-2$_3$	−0.3003(4)	0.2670(1)	0.3848(3)	4.6(1)
C-3$_3$	−0.2977(6)	0.3346(2)	0.3314(4)	3.6(1)
O-3$_3$	−0.4224(4)	0.3390(1)	0.3271(3)	4.3(1)
C-4$_3$	−0.2429(6)	0.3765(2)	0.3393(4)	3.7(1)
O-4$_3$	−0.2679(4)	0.3979(1)	0.2715(3)	3.9(1)
C-5$_3$	−0.1120(6)	0.3723(2)	0.3516(4)	4.1(2)
O-5$_3$	−0.0927(4)	0.3489(1)	0.4201(3)	4.4(1)
C-6$_3$	−0.0483(9)	0.4123(2)	0.3638(5)	6.5(2)
O-6$_3$ [a]	0.0727(6)	0.4102(2)	0.3708(6)	5.9(2)
O-6$_{3b}$ [b]	−0.092(1)	0.4313(4)	0.429(1)	7.5(4)
C-1$_4$	−0.3246(7)	0.4360(2)	0.2770(4)	4.0(1)
C-2$_4$	−0.4238(7)	0.4359(2)	0.2193(4)	4.6(2)
O-2$_4$	−0.5043(5)	0.4040(2)	0.2363(3)	5.5(1)
C-3$_4$	−0.3813(6)	0.4348(2)	0.1393(4)	4.1(2)
O-3$_4$	−0.4745(5)	0.4384(2)	0.0868(3)	6.2(1)
C-4$_4$	−0.2911(6)	0.4684(2)	0.1261(4)	3.8(1)
O-4$_4$	−0.2419(4)	0.4631(1)	0.0533(2)	3.82(9)
C-5$_4$	−0.1948(7)	0.4661(2)	0.1858(4)	4.1(2)
O-5$_4$	−0.2448(5)	0.4681(1)	0.2613(3)	4.3(1)
C-6$_4$	−0.1070(8)	0.5009(3)	0.1819(5)	5.6(2)
O-6$_4$	−0.1606(6)	0.5392(2)	0.1857(3)	6.9(2)
C-1$_5$	−0.2507(7)	0.4947(2)	−0.0012(4)	3.8(1)
C-2$_5$	−0.2968(6)	0.4767(2)	−0.0743(4)	3.9(1)

Table 1 (continued)

Atom	x	y	z	B_{eq} (Å^2)
O-2$_5$	−0.4093(4)	0.4579(2)	−0.0602(3)	5.4(1)
C-3$_5$	−0.2114(6)	0.4466(2)	−0.1044(3)	3.4(1)
O-3$_5$	−0.2476(5)	0.4308(1)	−0.1778(3)	4.4(1)
C-4$_5$	−0.0913(6)	0.4654(2)	−0.1133(4)	3.5(1)
O-4$_5$	−0.0115(4)	0.4339(1)	−0.1350(3)	4.3(1)
C-5$_5$	−0.0524(6)	0.4852(2)	−0.0397(4)	3.8(1)
O-5$_5$	−0.1408(4)	0.5131(1)	−0.0138(3)	4.2(1)
C-6$_5$	0.0593(7)	0.5083(2)	−0.0455(4)	4.7(2)
O-6$_5$	0.0617(5)	0.5369(2)	−0.1052(3)	6.0(1)
C-1$_6$	0.0702(7)	0.4414(2)	−0.1938(4)	4.5(2)
C-2$_6$	0.0553(7)	0.4088(2)	−0.2525(4)	4.6(2)
O-2$_6$	−0.0636(5)	0.4083(2)	−0.2799(3)	6.0(1)
C-3$_6$	0.0905(6)	0.3683(2)	−0.2205(4)	4.1(2)
O-3$_6$	0.0855(5)	0.3383(2)	−0.2779(3)	5.8(1)
C-4$_6$	0.2116(6)	0.3705(2)	−0.1859(4)	3.9(1)
O-4$_6$	0.2333(4)	0.3330(1)	−0.1475(2)	3.62(9)
C-5$_6$	0.2195(7)	0.4052(2)	−0.1306(4)	4.6(2)
O-5$_6$	0.1841(5)	0.4424(1)	−0.1654(3)	5.1(1)
C-6$_6$	0.3430(8)	0.4132(3)	−0.0983(6)	6.5(2)
O-6$_6$	0.4214(7)	0.4250(3)	−0.1541(5)	13.5(3)
C-1$_7$	0.3287(6)	0.3087(2)	−0.1712(4)	3.7(1)
C-2$_7$	0.2862(6)	0.2654(2)	−0.1851(4)	3.8(1)
O-2$_7$	0.1889(4)	0.2653(1)	−0.2370(3)	4.3(1)
C-3$_7$	0.2506(6)	0.2455(2)	−0.1106(4)	3.5(1)
O-3$_7$	0.2218(5)	0.2039(1)	−0.1263(3)	5.2(1)
C-4$_7$	0.3510(6)	0.2491(2)	−0.0537(4)	3.9(1)
O-4$_7$	0.3089(4)	0.2322(1)	0.0168(2)	4.0(1)
C-5$_7$	0.3855(6)	0.2933(2)	−0.0451(4)	3.8(1)
O-5$_7$	0.4189(4)	0.3090(1)	−0.1179(3)	4.0(1)
C-6$_7$	0.4925(7)	0.2998(3)	0.0044(5)	5.4(2)
N-6$_7$	0.5322(6)	0.3422(2)	0.0067(4)	6.5(2)
Ow1	0.4767(5)	0.2571(2)	0.4253(3)	6.5(1)
Ow2	0.4909(7)	0.3867(2)	0.4503(4)	8.4(2)
Ow3	0.3222(7)	0.3745(2)	0.5684(5)	10.2(2)
Ow4	−0.0367(7)	0.3280(2)	0.5911(4)	9.9(2)
Ow5	−0.1415(9)	0.5990(2)	0.0734(5)	11.9(3)
Ow6	0.1142(8)	0.4046(3)	0.5216(6)	14.0(3)
Ow7	0.3426(8)	0.3701(3)	0.1180(6)	13.6(3)
Ow8	0.1071(9)	0.5687(3)	0.1770(6)	13.8(3)
Ow9	−0.128(1)	0.4056(4)	0.5701(6)	18.6(5)
Ow10	0.210(1)	0.4917(3)	0.1653(6)	15.7(4)
Ow11	−0.058(1)	0.3738(3)	0.0882(6)	15.5(4)
Ow12	0.150(1)	0.4224(3)	0.0780(6)	16.4(4)
Ow13 [a]	0.227(1)	0.4665(4)	0.3146(7)	24.5(5)
Ow14	0.232(1)	0.3631(4)	0.2716(7)	18.0(4)
Ow15	0.400(1)	0.5121(4)	0.0932(9)	21.0(5)
Ow16	0.044(2)	0.3171(5)	0.174(1)	20.5(9)
Ow17 [a]	0.105(3)	0.4891(8)	0.414(2)	22.3(10)

[a] Occupancy factor 0.6.

[b] Occupancy factor 0.4.

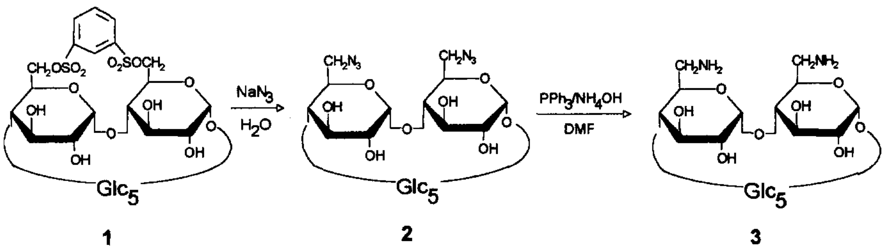
$a = 11.395(3)$, $b = 32.989(9)$, $c = 17.560(5)$ Å, $V = 6601(5)$ Å^3; $Z = 4$, and $D_{calc} = 1.430$ g/cm^3, for $C_{42}H_{72}N_2O_{33} \cdot 16H_2O$.

Up to the 2θ limiting value of 140°, 6908 independent reflections were collected in ω–2θ scan mode with two reference reflections; they were stable during data collection. Of these, 5031 with intensities greater than 3σ were used for structure determination and refinement. Orientation matrix checks were made with respect to the scattering vectors of two well-centered reflections every 400 measured reflections. Lorentz and polarization corrections were applied to the intensity data.

Straightforward application of the phase determination procedures, using various programs (SHELX76 [28], SHELX84 [29], MULTAN [30] and SIR92 [31]), failed to give sensible interpretations of the E-map. The phase problem was solved applying the molecular replacement technique by using the known β-CD structure of a previously determined β-CD derivative [32] and the search program PATSEE [33]. The initial model, containing only 3 glucosyl rings, was correctly orientated and positioned with respect to the origin of the unit cell. The "best" solution was used in the SIR92 program by applying the PARTIAL procedure. The direct phase expansion led to a molecular fragment containing all non-hydrogen atoms. Subsequent difference Fourier analysis revealed 16 water molecules in the unit cell and a statistical disorder of the O-6_3 primary hydroxyl group. The hydrogen atoms were introduced in their stereochemically expected positions with an isotropic temperature factor equal to the equivalent B factor of the atom to which they were bonded. Their parameters were kept fixed. The occupancy factors for the statistical O-6_3 atoms and for two water molecules (Ow13 and Ow17) were refined (see Table 1). A final full-matrix least-squares refinement, using anisotropic temperature factors for non-hydrogen atoms, was carried out with the SDP package [34] of crystallographic programs. For the refinements, the standard least-squares procedure minimizing the quantity $w[F_o^2 - F_c^2]^2$, with w equal to $1/\sigma(F_o)^2$, was used. The final conventional and weighted R factors converged at 0.058 and 0.057, respectively. Atomic scattering factors for all atomic species were calculated from Cromer and Waber [35]. Table 1 reports the final atomic parameters.

3. Results and discussion

Synthesis of 6^I,6^{II}-diamino-6^I,6^{II}-dideoxy-cyclomaltoheptaose.—The diamino derivative **3** of β-CD was synthesized by the route shown in Scheme 1, following the



Scheme 1.

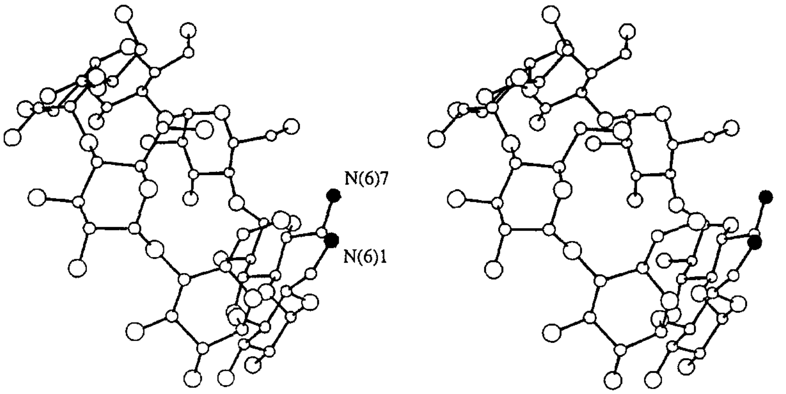


Fig. 1. Stereoview of molecular model of $6^I,6^{II}$-diamino-$6^I,6^{II}$-dideoxy-cyclomaltoheptaose. Only the *N*-6 nitrogen atoms are labelled.

preliminary results of Tabushi et al. [24]. The derivative **1** was used as starting product to obtain the I, II regioisomer of CD. The reaction of cyclic sulfonate with NaN_3 in aq soln gave the azido derivative **2**, which was isolated by chromatography. The reduction of **2** with triphenylphosphine in DMF followed by the hydrolysis of the iminophosporane intermediate with NH_4OH gave the diamino derivative **3**. This derivative was purified by ion-exchange chromatography. Even if the synthesis of other diamino 6-derivative regioisomers of β-CD have been reported [10,24], the synthesis and purification of $6^I,6^{II}$-diamino-$6^I,6^{II}$-dideoxy-cyclomaltoheptaose have not been properly described and the product **3** has not been fully characterized until now.

Conformation of $6^I,6^{II}$-diamino-$6^I,6^{II}$-dideoxy-cyclomaltoheptaose.—A stereoview of the molecular structure of $6^I,6^{II}$-diamino-$6^I,6^{II}$-dideoxy-cyclomaltoheptaose is represented in Fig. 1. Bond distances and bond angles of primary hydroxyl and amino groups of the β-CD molecule are listed in Table 2. The identification of the two *N*-6 atoms on the macrocycle was obtained from the observed values of the distance C-6–X-6 (where X-6 is an oxygen atom for five glucose units or a nitrogen atom for the other two glucose units) and from the corresponding thermal factor after refinement. The only two longer distances (both 1.47 Å) corresponded to those of units 1 and 7. The refined thermal factors of these atoms as nitrogen atoms confirmed the assignment. The *N*-6 amino groups are found at a distance of 4.03 Å. A selection of torsion angles which define the bonds between the glucose units and the orientation of the primary hydroxyl groups and the Cremer and Pople puckering parameters of glucose units [36] are given

Table 2
Bonding geometry of primary hydroxyl and amino groups of β-CD

Group [a]	G1	G2	G3	G4	G5	G6	G7
C-6–X-6	1.47	1.43	1.39	1.41	1.41	1.38	1.47
C-5–C-6–X-6	114.0	111.9	109.5	112.9	114.2	112.2	113.6

[a] X-6 is a nitrogen atom for G1 and G7 and an oxygen atom for the other residues.

Table 3
Selected torsion angles (deg) describing the linkage bonds between the glucose residues and the orientations of the primary hydroxyl and puckering parameters of the glucose units

Orientation	G1	G2	G3	G4	G5	G6	G7
C-3$_n$–C-4$_n$–O-4$_n$–C-1$_{n+1}$	129.0	126.4	125.2	128.5	135.8	119.4	134.7
C-5$_n$–C-4$_n$–O-4$_n$–C-1$_{n+1}$	−112.2	−110.1	−115.1	−118.3	−102.8	−119.9	−105.5
O-5$_n$–C-1$_n$–O-4$_{n-1}$–C-4$_{n-1}$	106.0	106.6	107.0	106.6	109.1	112.0	108.7
C-2$_n$–C-1$_n$–O-4$_{n-1}$–C-4$_{n-1}$	−132.9	−131.6	−130.3	−133.0	−129.9	−125.6	−128.8
O-5$_n$–C-5$_n$–C-6$_n$–O-6$_n$	–	63.4	64.4 [a] −58.4 [b]	−66.2	−69.7	−58.6	–
C-4$_n$–C-5$_n$–C-6$_n$–O-6$_n$	–	−174.5	−176.3 [a] 61.0 [b]	54.9	52.3	64.4	–
O-5$_n$–C-5$_n$–C-6$_n$–N-6$_n$	59.5	–	–	–	–	–	55.7
C-4$_n$–C-5$_n$–C-6$_n$–N-6$_n$	179.4	–	–	–	–	–	174.5
Parameters							
Q (Å)	0.55	0.53	0.56	0.55	0.56	0.54	0.57
θ (deg)	2.96	8.56	7.77	3.14	2.72	1.13	2.71

[a] Values for O-6$_3$ atom.
[b] Values for O-6$_{3b}$ atom.

in Table 3. Glucose units are found with a small degree of flexibility in the usual ${}^4C_1$ chair conformation. The average total puckering amplitude Q for all residues (0.55 Å) is slightly lower than the corresponding value for an ideal cyclohexane chair (0.63 Å), whereas the θ parameter which measures the magnitude of ring distortion is in the range 1.2–8.6°. Three consecutive primary hydroxyl groups (of the G4, G5, and G6 glucose) units assume the *gauche*$^-$–*gauche*$^+$ orientation (mean torsion angles O-5–C-5–C-6–O-6 and C-4–C-5–C-6–O-6, −64.8° and 57.2°, respectively). The other four consecutive glucose units, G2 and G3 having two primary hydroxyl groups and G7 and G1 having two amine groups, show the *trans*–*gauche*$^+$ orientation (mean torsion angles O-5–C-5–C-6–O-6 or O-5–C-5–C-6–N-6, and C-4–C-5–C-6–O-6 or C-4–C-5–C-6–N-6, −179.1° and 60.9°, respectively). It is worth noting that glucose unit 3 presents two statistically disordered orientations of the primary hydroxyl group, one *gauche*$^-$–*gauche*$^+$, the other *trans*–*gauche*$^+$. The β-CD macrocycle presents only conformationally slight differences with respect to uncomplexed hydrated or methylated β-CD molecules. The macrocycle structure maintains an approximate seven-fold symmetry. The glucosidic O-4 atoms form a heptagon with radii (the distances between the centre of gravity of the seven O-4 atoms and each O-4 atom) and side lengths (the distance between two consecutive O-4 atoms), given in Table 4, in the range 4.81–5.30 and 4.24–4.57 Å, respectively. The angle between three O-4 atoms of consecutive glucose units (O-4$_{n-1}$–O-4$_n$–O-4$_{n+1}$) is on the average 128.5°. The O-4 atoms are nearly coplanar: a maximum deviation from the least-squares plane of 0.13 Å is observed for the O-4 atom of unit 7, all other O-4 are 0.05 Å away from the mean plane. The tilt angles (the dihedral angles between the O-4s plane and the least-squares plane through O-4$_{n+1}$, C-1$_n$, C-4$_n$, O-4$_n$) lie in the range 6.7–18.1°. The round shape of the cyclodextrin ring is stabilized by intramolecular O–H ··· O bonds between the sec-

Table 4
Geometrical data

Residue	Radius (Å) [a]	Distance (Å) [b]	Angle (deg) [c]	Tilt angle (deg) [d]	Planarity (Å) [e]
G1	5.21	4.24	123.6	15.8	−0.06
G2	4.89	4.57	130.3	16.3	−0.05
G3	4.81	4.40	131.0	13.9	0.04
G4	5.18	4.33	126.6	12.3	0.04
G5	5.30	4.35	126.7	6.7	−0.05
G6	5.08	4.49	131.2	18.1	−0.06
G7	5.05	4.43	130.3	9.0	0.13

[a] The radius is measured from the centre of gravity of the seven O-4 atoms to each O-4 atom.

[b] The distance is defined as the O-4_n–O-4_{n+1} distance.

[c] The angle is defined as the O-4_{n-1}–O-4_n–O-4_{n+1} angle.

[d] The tilt angle is defined as the angle made by O-4 atoms plane and the plane formed by O-4_{n+1}, C-1_n, C-4_n, O-4_n of each glucose residue.

[e] Planarity is the defined as the O-4_n distance from the O-4 atoms plane.

ondary hydroxyl groups of neighboring glucose residues: O-2_n–O-3_{n-1} hydrogen bonds lie in the usual range (2.76–2.89 Å) of hydrogen-bond distances found in β-CDs, with exception of the O-2_1–O-3_7 distance of 3.07 Å which is indicative of a weaker hydrogen bond.

Molecular packing: the interaction of the β-CD with water molecules.—In Fig. 2, the crystal structure of the difunctionalized β-CD molecules, as viewed along the ***a***

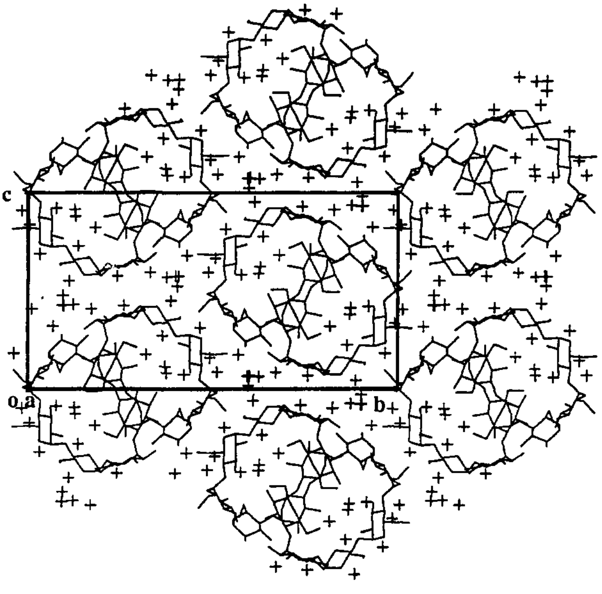


Fig. 2. Crystal packing of $6^{\mathrm{I}},6^{\mathrm{II}}$-diamino-$6^{\mathrm{I}},6^{\mathrm{II}}$-dideoxy-cyclomaltoheptaose as viewed down the crystallographic ***a*** axis. Water molecules are indicated as crosses.

direction is shown. The relative orientation of the O-4_n's plane of the β-CD rims with respect to the two-fold screw axis along the ***a*** axis gives rise to the formation of infinite columns of β-CD molecules. In each column, the macrocycles are arranged in a herring-bone fashion, so that the cavity of each β-CD molecule is closed at each end by neighboring molecules. The macrocycles are directly linked to each other by H-bonds involving either primary and secondary hydroxyl or amino groups of symmetry-related molecules. The NH_2 groups form H-bonds with secondary hydroxyl groups of G1, G3 and G7 symmetry-related glucosidic units and with the hydroxyl group of unit G3 translated along the ***a*** direction. In the ***bc*** plane, the β-CD molecules pack in layers with a hexagonal arrangement. Similar solid-state arrangements have been observed for several functionalized β-CD or host-guest CDs. The layers are connected to each other by a dense intramolecular hydrogen-bond network, in which solvent molecules participate.

In the crystal, water molecules are located in two well-defined regions. Out of 16 water molecules per β-CD unit, 9 (Ow11, Ow16, Ow12, Ow7, Ow14, Ow13, Ow17, Ow10, Ow8) are located on the narrower side of the macrocycle cavity, distributed over 10 positions, and are hydrogen-bonded to each other or with hydroxyl groups of the β-CD. In particular, Ow11 is hydrogen-bonded to a secondary hydroxyl (O-2_1) of a symmetry-related β-CD and to two water molecules (Ow12 and Ow16). Ow11 and Ow16 are included in the cavity of the β-CD almost in the O-4 plane and are involved in hydrogen bonds to other water molecules, giving rise to a five-membered ring of intermolecularly linked atoms. Furthermore, a six-membered circular arrangement of hydrogen bonds is formed by other water molecules (Ow7, Ow12, Ow10, Ow13 or Ow17, Ow10) and a primary oxygen atom (O-6_3). These two rings are fused together through three water molecules (Ow7, Ow12 and Ow14). Seven water molecules are located in the interstices generated by columns of packed β-CD molecules. Some of these (Ow2, Ow3, Ow5, Ow6 and Ow9) form, in the crystal, a second five-membered ring of H-bonded molecules which also interact with hydroxyl atoms of adjacent columns of β-CD molecules. This network of intra- and inter-molecular H-bond interactions stabilizes the packing, giving rise to the formation of water channels along the ***a*** direction.

4. Conclusion

A crystal-structure analysis by X-ray diffraction has been reported for methylated cyclodextrins and for inclusion compounds of cyclodextrins, in order to correlate the characteristics of the cyclodextrin derivatives with some of their physical and chemical properties.

While methylation of hydroxyl groups is one of the simplest modifications, the chemical modification with other organic functions for the preparation of mono- or di-functionalized CDs involves a number of reaction and purification steps.

Recently, structural studies of some monofunctionalized β-CDs have been reported providing a structural basis for host design [37].

The crystal stucture of 6^I,6^{II}-diamino-6^I,6^{II}-dideoxy-cyclomaltoheptaose is the first example of a difunctionalized cyclodextrin. In general, small chemical changes are of relevant significance, bringing noteworthy consequences in the reactivity and chemical behaviour of the modified molecule. Kirby and co-workers [38,39] have shown for instance that a variation of 0.03 Å for a C–O bond undergoing spontaneous hydrolysis in alkyl-aryl acetals corresponds to a 10^6 fold or more change in reactivity in the hydrolysis-rate constant. The functionalization of the β-CD molecule and packing effect influence the *gauche*$^-$–*gauche*$^+$ orientation generally observed in the β-CD crystal structure: the two functionalized glucose rings and the two adjacent glucose rings show a *trans*–*gauche*$^+$ orientation. Consequently, some of the 6-OH groups point outside the β-CD cavity, while the two amino groups and one hydroxyl group are parallel to the edge of the cavity. Other crystallographic features are similar to the uncomplexed cyclodextrins and to methylated derivatives. Furthermore, it is worth pointing out that some metal complexes of this class of molecules can act as chiral selectors [20,23,19]; in addition, some copper(II) [40] and platinum complexes [41] have been shown to be biologically active.

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