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Crystal structure of α-cyclodextrin-acetonitrile-hexahydrate[1]

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Abstract

Crystals of the ternary α-cyclodextrin-acetonitrile hexahydrate inclusion complex belong to the orthorhombic space group $P2_12_12_1$ with unit cell dimensions $a=9.479(2)$, $b=14.323(4)$, $c=37.397(9)$ Å. Refinement against 4202 X-ray diffraction data converged at $R=0.059$. The α-cyclodextrin macrocycle forms a regular torus which is stabilized by intramolecular O-3–O-2 hydrogen bonds between neighboring glucose units. Within the cavity, one acetonitrile and one water molecule are located with occupancy factors of 0.8 and 0.7, respectively. They are hydrogen bonded to disordered O65B, and acetonitrile is stabilized in position by C-5–H···N interactions. The remaining five water molecules link symmetry related cyclodextrin molecules.

Keywords: Crystal structure; α-Cyclodextrin; Acetonitrile; Hydrogen bonding

1. Introduction

α-Cyclodextrin is a cyclic carbohydrate comprised of 6 D-(+)-glucopyranoside units linked by α-(1→4)-glycosidic bonds. It forms a torus-like macro ring with a cavity of 4.5 Å diameter and 6.7 Å in depth [1] which is large enough to accommodate small hydrophobic as well as hydrophilic guest molecules. The ring is conformationally stabilized by intramolecular hydrogen bonds formed between secondary hydroxy groups O-2–H and O-3–H of neighboring glucose units. In the α-cyclodextrin-water complex one of the six glucopyranose units is rotated relative to the other five residues in the macrocycle, and a hydrogen bond from its O-6–H hydroxyl is formed to one of the two water molecules inside the cavity [2,3]. In the case of other inclusion complexes where the water molecules are replaced by larger compounds, the ring system, however, forms a regular macrocycle. Depending on their size, the guest molecules may not fill the whole cavity and are statistically disordered or exhibit high thermal motions. So far, in the group of small non-aromatic solvents, inclusion complexes with molecules like *N*,*N*-dimethylformamide [4], methanol [5], dimethylsulfoxide [6], acetone [7] and propanol [8] have been characterized crystallographically.

Since acetonitrile/water mixtures are frequently used in the HPLC purification of cyclodextrins, it

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[1] Data have been deposited with the Cambridge Crystallographic Data Center. These data may be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, UK, CB2 IEZ. Tel: +44 223 336408; Fax: +44 223 336033.

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was of interest to determine whether an inclusion complex can be formed. Here we report the structure of an α-cyclodextrin–acetonitrile hexahydrate complex and analyze the network of hydrogen bonds formed in the crystal lattice.

2. Experimental

Materials and methods.—α-Cyclodextrin and acetonitrile were purchased from Merck (Darmstadt, Germany) and used without further purification.

Crystallization.—Large colorless single crystals, up to 5 mm in size, were obtained by dissolving α-cyclodextrin in an aqueous solution of 50% acetonitrile (v/v) at 80 °C followed by slow cooling to 18 °C, making use of the positive solubility coefficient of α-cyclodextrin.

X-ray diffraction experiments.—For diffraction experiments, a prismatic crystal $0.8\times0.3\times0.3\,mm^3$ in size was mounted in a thin-walled glass capillary. X-ray diffraction data were collected at room temperature on a Turbo-CAD4 automated diffractometer (Enraf-Nonius) using Ni-filtered CuK_α radiation ($\lambda = 1.5418$ Å) from a rotating anode generator (Enraf–Nonius FR571) operating at 40 kV and 90 mA, focal size $0.3\times3\,mm^2$.

Systematic extinctions indicated the space group to be orthorhombic $P2_12_12_1$. Unit cell dimensions $a = 9.479(2)$, $b = 14.323(4)$, $c = 37.397(9)$ Å, $V = 5077.3(2.3)$ Å^3 were determined by least-squares refinement with 25 automatically centered reflections. 4202 unique reflections were collected to a resolution of $2\Theta_{max} = 60°$ operating in an ω-scan mode. Data were corrected for variations in intensity of three reference reflections monitored periodically and for Lorentz and polarization effects, but not for absorption ($\mu = 1.135\,mm^{-1}$); $D_x = 1.435\,Mg\,m^{-3}$, $F(000) = 2317$.

Structure solution and refinement.—The initial model for the crystal structure was determined by direct methods [9], developed by difference Fourier techniques [10a,b] and refined by full-matrix least-squares techniques [10a,b]. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located by difference Fourier techniques and refined isotropically except for two hydrogen atoms of the acetonitrile which could not be located in the difference electron density map. These atoms were placed in the calculated positions with the 1.2-fold isotropic thermal displacement factor of the carbon atom to which they are bonded and were restrained to the ideal geometry during refinement. With one exception, the hydrogens of the water molecules were not found in the difference Fourier maps. During the course of refinement, hydrogen atoms were restrained to their ideal geometry according to the "riding model" [10a,b]. Finally, a total of 4202 reflections contributed to the refinement of 743 parameters to give $R(F) = 0.059$ and $wR(F^2) = 0.153$ [$R(F)_{obs} = 0.054$ and $wR(F^2)_{obs} = 0.146$ for 3844 reflections with $R(F)_{obs} > 2\sigma(F)$]. The weighting scheme applied was $w = 1/[s^2(F_o^2) + (0.1129\,P)^2 + 1.5548\,P]$ where $P = (F_o^2 + 2F_c2)/3$. S was 1.097, $(\Delta/\sigma)_{max}$ was 0.088, $(\Delta\varphi)_{max}$ and $(\Delta\varphi)_{min}$ were 0.679 and $-0.355\,e\,Å^{-3}$, respectively.

The final fractional coordinates and equivalent isotropic thermal displacement factors are listed in Table 1.

The structure was examined with Insight [11], and the diagram of the thermal ellipsoids was produced by Zortep [12].

3. Results and discussion

The α-cyclodextrin–acetonitrile–hexahydrate complex crystallizes in the orthorhombic space group $P2_12_12_1$. A stereoscopic plot of the inclusion complex, both as top and side views with selected atoms labelled, is shown in Fig. 1. The atomic labelling follows the convention for glucose; the second index indicates the glucose unit in the macrocycle, e.g., C21 means atom C-2 in glucose 1. Disordered O-6 atoms in glucose 5 are labelled A and B (for details see Fig. 1). The six glucose units form an almost regular macrocycle which is stabilized by intramolecular hydrogen bonds at the secondary side between O-3 and O-2 of adjacent glucose units. This is shown in Fig. 2a by the similarity of the conformational parameters and in Table 2 by selected torsion angles and torsion angle indices. The O-4 oxygen atoms which are linking these rings form a marginally distorted hexagon in a twisted conformation. The average angle at the glycosidic oxygens (119.9°) and the O-4–O-4′ distances (4.22 Å) between adjacent glucose residues are in good agreement with those of other α-cyclodextrins (119.9° and 4.24 Å, respectively) [8]. The deviation of the O-4 atoms from the least-squares plane are listed in Table 2; the average value is 0.122 Å.

Table 1
Fractional atomic coordinates and equivalent isotropic thermal displacement factors

Atom	x/a	y/b	z/c	U_{eq} (Å^2)
C11	0.5658(5)	0.5348(3)	0.06611(13)	0.0416(11)
C21	0.5675(6)	0.5211(3)	0.02566(13)	0.0459(11)
O21	0.4571(5)	0.5724(3)	0.01062(10)	0.0647(11)
C31	0.5602(5)	0.4185(3)	0.01707(11)	0.0362(10)
O31	0.5819(4)	0.4054(2)	−0.02068(8)	0.0442(8)
C41	0.6641(5)	0.3614(3)	0.03820(11)	0.0320(9)
O41	0.6248(3)	0.26559(1)	0.03417(8)	0.0343(7)
C51	0.6609(5)	0.3847(3)	0.07783(12)	0.0365(10)
O51	0.6725(3)	0.4838(2)	0.08282(8)	0.0416(8)
C61	0.7797(5)	0.3417(3)	0.09882(11)	0.0402(10)
O61	0.9147(3)	0.3747(2)	0.08768(8)	0.0437(8)
C12	0.7171(5)	0.2069(3)	0.01585(10)	0.0318(9)
C22	0.6296(5)	0.1435(3)	−0.00818(11)	0.0341(9)
O22	0.5511(4)	0.2026(2)	−0.03144(8)	0.0446(8)
C32	0.5366(5)	0.0820(3)	0.01432(11)	0.0333(9)
O32	0.4685(4)	0.0157(2)	−0.00873(8)	0.0405(7)
C42	0.6175(5)	0.0316(3)	0.04331(11)	0.0344(10)
O42	0.5121(4)	−0.0033(2)	0.06733(8)	0.0395(7)
C52	0.7155(5)	0.0964(3)	0.06415(11)	0.0373(10)
O52	0.7980(3)	0.1521(2)	0.03989(8)	0.0373(7)
C62	0.8231(6)	0.0453(4)	0.08700(13)	0.0503(13)
O62	0.9121(4)	−0.0130(3)	0.06694(11)	0.0605(10)
C13	0.5155(6)	−0.0973(3)	0.07780(13)	0.0407(11)
C23	0.3657(6)	−0.1338(3)	0.07342(12)	0.0459(12)
O23	0.3254(5)	−0.1230(3)	0.03689(9)	0.0606(10)
C33	0.2655(6)	−0.0848(4)	0.09779(13)	0.0475(12)
O33	0.1287(5)	−0.1274(3)	0.09764(11)	0.0692(12)
C43	0.3191(5)	−0.0847(3)	0.13646(12)	0.0403(11)
O43	0.2320(4)	−0.0221(2)	0.15565(9)	0.0492(9)
C53	0.4724(6)	−0.0529(3)	0.13858(12)	0.0429(11)
O53	0.5572(4)	−0.1053(2)	0.11374(8)	0.0455(8)
C63	0.5389(7)	−0.0654(5)	0.17471(15)	0.0652(16)
O63	0.5288(5)	−0.1591(4)	0.18714(10)	0.0796(14)
C14	0.1746(6)	−0.0497(4)	0.18886(14)	0.0522(13)
C24	0.0167(6)	−0.0303(4)	0.18719(15)	0.0553(14)
O24	−0.0480(5)	−0.0802(3)	0.15890(11)	0.0680(11)
C34	−0.0101(6)	0.0725(4)	0.18449(14)	0.0507(13)
O34	−0.1567(5)	0.0900(4)	0.18683(12)	0.0727(12)
C44	0.0694(6)	0.1254(4)	0.21353(13)	0.0485(12)
O44	0.0576(5)	0.2223(2)	0.20521(8)	0.0532(9)
C54	0.2241(6)	0.0984(4)	0.21505(14)	0.0520(13)
O54	0.2355(4)	−0.0021(3)	0.21759(9)	0.0552(9)
C64	0.3006(8)	0.1369(5)	0.24719(16)	0.0707(17)
O64	0.2242(7)	0.1240(3)	0.27990(11)	0.0859(15)
C15	0.0152(7)	0.2846(4)	0.23190(13)	0.0557(14)
C25	−0.1060(6)	0.3420(4)	0.21799(15)	0.0560(14)
O25	−0.2211(5)	0.2828(3)	0.20777(13)	0.0726(12)
C35	−0.0596(6)	0.3991(4)	0.18608(13)	0.0489(12)
O35	−0.1694(4)	0.4620(3)	0.17640(11)	0.0608(10)
C45	0.0734(6)	0.4536(4)	0.19461(12)	0.0466(12)
O45	0.1282(4)	0.4836(2)	0.16053(8)	0.0487(8)
C55	0.1869(6)	0.3958(4)	0.21340(13)	0.0554(14)
O55	0.1248(4)	0.3441(3)	0.24224(9)	0.0589(10)
C65	0.3022(8)	0.4552(5)	0.22903(16)	0.0702(18)
O65A[a]	0.2624(10)	0.5405(6)	0.24433(19)	0.095(3)
O65B[a]	0.4094(12)	0.3946(11)	0.2415(3)	0.070(4)
C16	0.1368(5)	0.5792(4)	0.15332(14)	0.0471(12)
C26	0.0952(5)	0.5942(3)	0.11461(13)	0.0425(11)
O26	−0.0432(4)	0.5584(3)	0.10891(10)	0.0546(9)
C36	0.1957(5)	0.5460(3)	0.08977(12)	0.0381(10)
O36	0.1719(4)	0.5715(2)	0.05310(9)	0.0491(8)
C46	0.3474(5)	0.5703(3)	0.09806(12)	0.0372(10)

(continued)

Table 1—*contd*

Atom	*x*/*a*	*y*/*b*	*z*/*c*	U_{eq} (Å^2)
O46	0.4313(3)	0.5065(2)	0.07830(9)	0.0414(8)
C56	0.3795(5)	0.5624(3)	0.13793(13)	0.0455(12)
O56	0.2758(4)	0.6129(3)	0.15857(9)	0.0518(9)
C66	0.5212(6)	0.6018(4)	0.14864(15)	0.0564(14)
O66	0.5344(6)	0.6955(4)	0.13484(18)	0.1012(18)
N1[b]	0.431(2)	0.2205(13)	0.1342(5)	0.194(7)
C2[b]	0.3292(19)	0.2195(10)	0.1190(4)	0.111(4)
C3[b]	0.203(3)	0.2140(16)	0.1045(5)	0.201(10)
O1W1[c]	0.5427(9)	0.3694(7)	0.1771(3)	0.115(3)
O1W2	−0.2070(6)	0.7041(3)	0.10183(16)	0.0862(15)
O1W3	0.3485(8)	0.7041(4)	−0.04056(17)	0.113(2)
O1W4	−0.3222(9)	0.2374(4)	0.27569(18)	0.124(2)
O1W5	0.1433(6)	−0.2587(3)	0.01436(14)	0.0921(16)
O1W6	0.8249(17)	−0.2438(5)	0.17122(18)	0.228(8)

[a]Occupancies of sites O65A and O65B are 0.65 and 0.35, respectively.
[b]Population parameter PP = 0.8.
[c]Population parameter PP = 0.7.

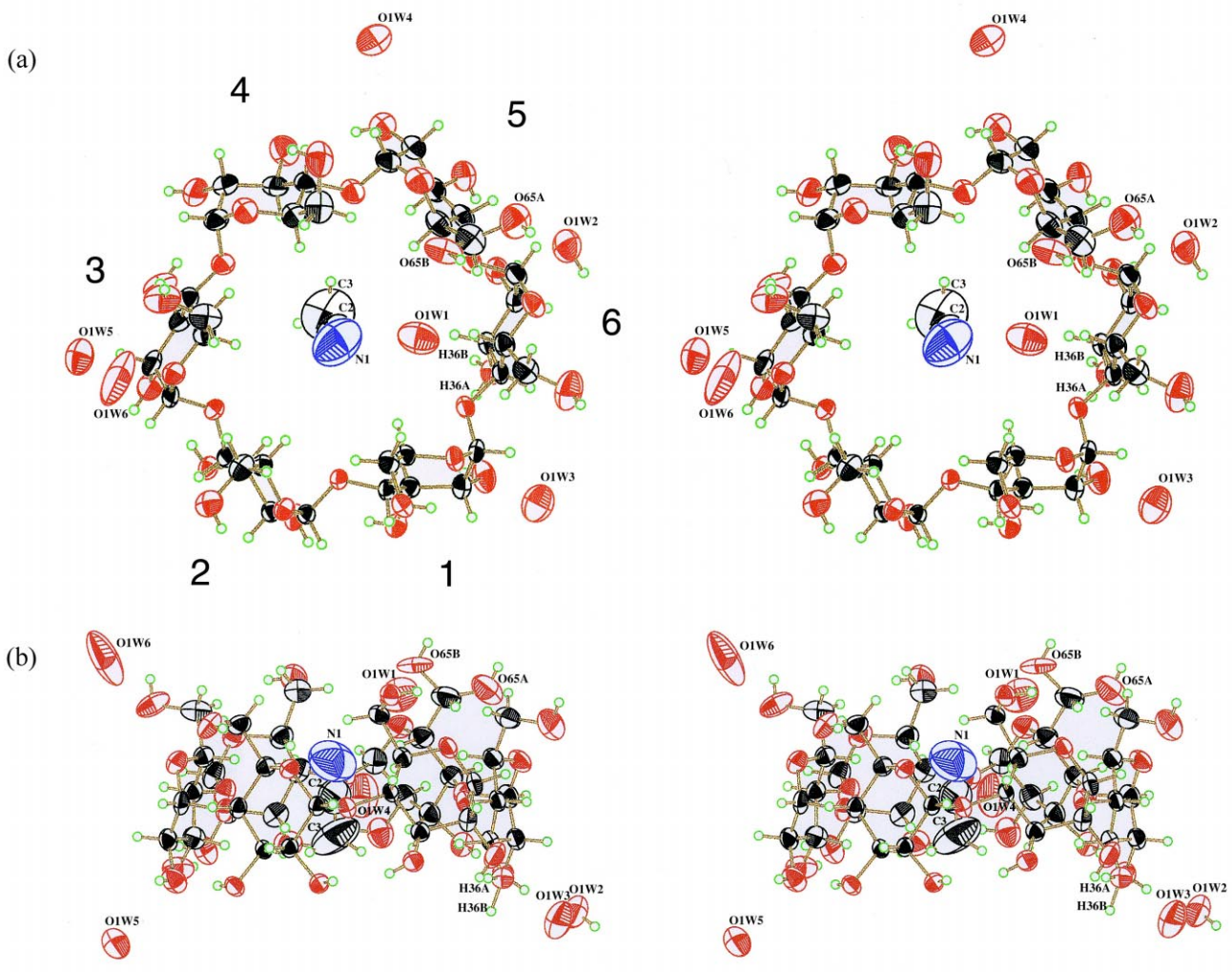

Fig. 1. Stereo plot of α-cyclodextrin–acetonitrile–hexahydrate inclusion complex drawn with thermal ellipsoid (50%) representation: (a) top view and (b) side view.

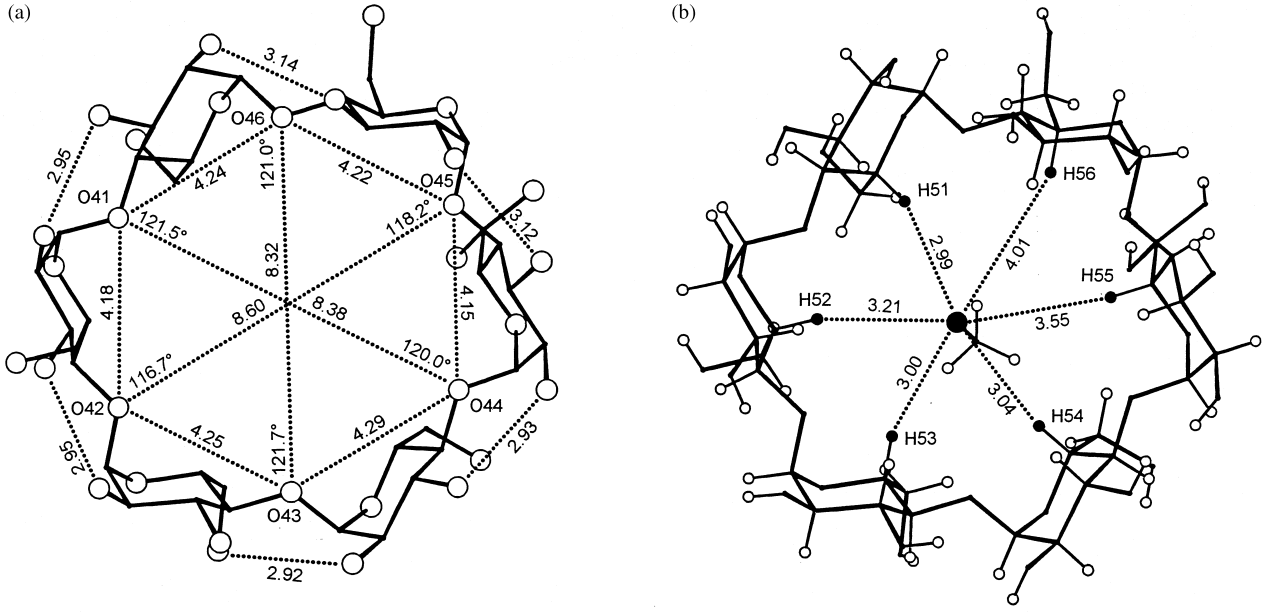

Fig. 2. (a) Hexagonal geometry of α-cyclodextrin represented by selected O-4–O-4′ distances and hydrogen bonds between neighboring glucoses (distances in Å, angles in degrees). (b) Location of acetonitrile in the cavity of α-cyclodextrin stabilized by interactions of type C-5–H···N (distances in Å).

Table 2
Geometrical data of the macrocyclic conformation (given in degrees for angles and Å for distances)

Residue	1	2	3	4	5	6
Torsion angles						
C1–C2–C3–C4	−48.5(6)	−51.2(5)	−51.0(5)	−51.2(6)	−51.3(6)	−51.1(5)
C2–C3–C4–C5	48.1(5)	47.6(5)	49.1(5)	50.4(6)	46.0(6)	47.5(5)
C3–C4–C5–O5	−50.8(5)	−48.5(5)	−51.1(5)	−52.3(6)	−47.3(5)	−50.6(5)
C4–C5–O5–C1	58.8(5)	57.6(5)	59.2(5)	59.6(6)	57.7(6)	60.1(5)
C2–C1–O5–C5	−61.7(5)	−62.7(4)	−61.1(5)	−62.3(6)	−64.9(5)	−63.5(5)
O5–C1–C2–C3	54.7(5)	57.5(4)	56.0(5)	56.9(6)	60.1(5)	58.2(5)
O2–C2–C3–O3	66.3(5)	68.0(4)	67.2(5)	61.6(6)	66.2(5)	68.7(5)
O3–C3–C4–O4	−70.7(4)	−73.5(4)	−68.0(5)	−67.8(6)	−74.68(5)	−69.3(4)
O4–C4–C5–C6	72.1(5)	78.0(5)	71.2(6)	71.3(6)	76.3(5)	72.2(5)
C4–C5–C6–O6	62.9(5)	59.7(6)	55.0(7)	46.5(7)	37.7(8)[a]	51.5(6)
					−172.5(6)[b]	
O5–C5–C6–O6	−58.3(5)	−60.8(5)	−66.8(6)	−73.4(7)	−83.1(7)[a]	−70.2(6)
					66.7(7)[b]	
C3–C4–O4–C1′	113.9(4)	130.1(4)	132.3(5)	130.6(5)	117.0(5)	149.5(4)
C5–C4–O4–C1′	−124.9(4)	−109.2(4)	−106.9(5)	−107.8(6)	−120.8(5)	−89.1(5)
C4–O4–C1′–C2′	−138.8(3)	−132.6(4)	−129.1(5)	−128.1(5)	−140.7(4)	−123.6(4)
C4–O4–C1′–O5′	100.8(4)	108.4(4)	109.7(5)	111.2(5)	99.8(5)	114.3(4)
Torsion angle index[c]	124.8	132.9	127.1	127.3	140.7	134.8
Tilt angle[d]	6.8(3)	7.2(1)	2.5(2)	6.9(3)	12.5(2)	3.5(2)
O4 deviation[e]	0.12	−0.13	−0.01	0.16	−0.17	0.03

[a,b]Torsion angles of disordered oxygen atoms with occupancy of 0.65 and 0.35, respectively.
[c]Torsion angle index, which is defined as $\phi = |\phi(C1–C2)| + |\phi\ (C2–C3)| + |\phi\ (C5–O5)| + |\phi\ (O5–C1)| - |\phi\ (C3–C4)| - |\phi(C4–C5)|$ and $|\phi\ (C2–C3)|$ is the torsion angle C1–C2–C3–C4.
[c]Tilt angle, which is defined as the angle of the O4 plane and the plane through C1, C4, O4 and O4′.
[d]Deviation of O4 atoms from the least-squares plane through six O4 atoms.
′Prime atoms belong to the adjacent glucose residue.

At the primary side the O6 hydroxy groups are directed away from the center of the molecule and adopt a *gauche–gauche* conformation as indicated by the torsion angles C4–C5–C6–O6 and O5–C5–C6–O6 which are in the range from 40 to 60° and from −60 to −80°, respectively, (Table 2). O65, however, is twofold disordered and found in *gauche–gauche* and *gauche–trans* orientations with

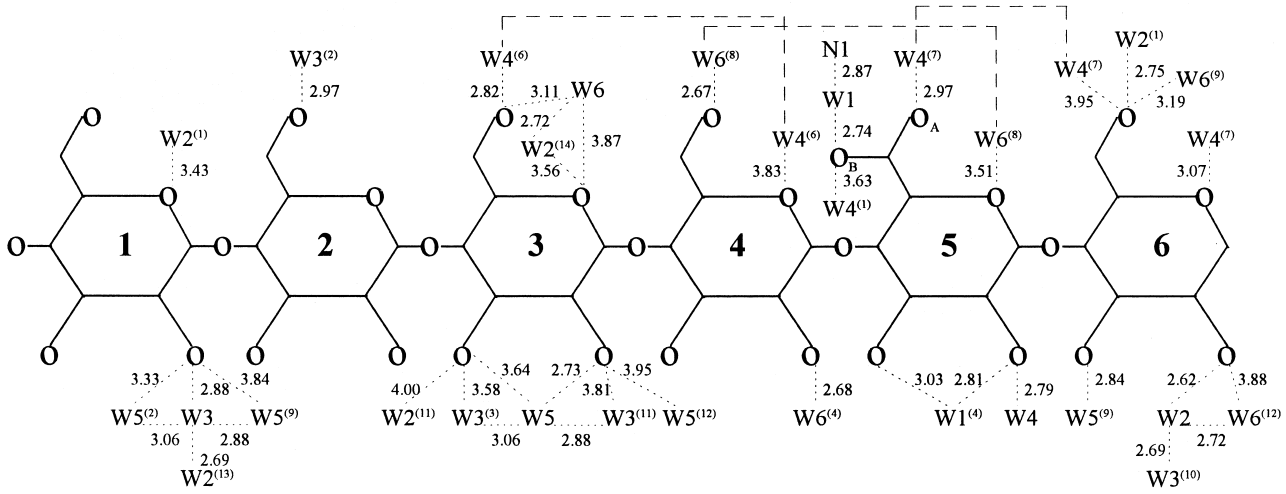

Fig. 3. Network of hydrogen bonds between water molecules and α-cyclodextrin (distances in Å). Superscripts in parentheses describe equivalent positions of water molecules:(0) x,y,z; (1) x+1, y,z; (2) x+1/2,−y+1/2,−z; (3) x−1/2,−y+1/2,−z; (4) x−1,y,z; (5) −x+1,y−1/2,−z+1/2; (6) −x,y−1/2,−z+1/2; (7) −x,y+1/2,−z+1/2; (8) −x+1/2,y+1/2,−z+1/2; (9) x,y+1,z; (10) x−1/2,−y+1/2,−z; (11) x,y+1,z; (12) x−1,y+1,z; (13) x+1/2,−y+1/2,−z; (14) x+1,y−1,z. α-Cyclodextrin and water molecules without superscript are in the 0 position; water molecules connected by dashed lines are in the same position.

population factors of 0.65 (for O65A) and 0.35 (for O65B), respectively. The corresponding torsion angles are 37.8(8)° and −83.0(7)° for O65A and −172.3(6)° and 66.8(8)° for O65B.

W1 (occupancy 0.7) forms two hydrogen bonds, one to O65B at 2.87 Å and one to N1 of the included acetonitrile (occupancy 0.8) at 2.74 Å. Acetonitrile is almost coaxial with the α-cyclodextrin ring, its methyl group at the level of C-2, C-3 atoms and its nitrogen atom at the level of the C-5, O-5 atoms. Weak interactions of type C-5–H···N, with π-electrons of the nitrile group might contribute to the stability of the complex; the H···N distances are in the range 2.99 to 4.01 Å (Fig. 2b); these interactions are comparable with the C-5–H···C≡C interaction (H···C distances of 2.78 and 2.82 Å) observed in β-cyclodextrin-but-2-yne-1,4-diol heptahydrate [13].

In general, small guest molecules do not fill the whole cavity of cyclodextrins and are often found disordered or reveal high thermal motions (for review see ref. 14). The latter phenomenon is observed in the acetonitrile-water complex. The anisotropic thermal displacement factors of CH_3CN are about 4 times above the average value of the other atoms, and the molecule teeters about the central carbon atom C-2 (Table 1, Fig. 1). In addition, only one of the three hydrogen atoms could be located in the difference Fourier maps. For W1 the B-values are about twice above the average.

The N-1–C-2–C-3 angle of acetonitrile refined to 173.19(1.80)°, a value significantly lower than the 180° expected for an sp-hybrid. However, a search in the Cambridge Structural Database [15] revealed several crystal structures with similar angles.

Another disorder could be located in the hydroxy group of O36–H where two hydrogen atoms were found with an occupancy factor of 0.35 (H3O6A) and 0.65 (H3O6B), respectively. In the first orientation the atom is involved in the belt of hydrogen bonds on the secondary side. In the second orientation, a hydrogen bond is formed to O32 of a symmetry related molecule.

In the crystal lattice, the molecules are packed in the typical "herring bone" arrangement often observed for α-cyclodextrins with small guest molecules [4–8,16]. The five additional water molecules outside the host compound serve as space filling mediators. The complex hydrogen bonding network of all water molecules in symmetry related positions with oxygen atoms of each glucose residue is depicted in Fig. 3. Water–water hydrogen bonds are formed with all water molecules except W1 and W4 because W1 is located inside the torus and W4 is only involved in bridging O-5 and O-6 atoms (Figs 1a,b and 3).

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