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Crystal Structures and Molecular Conformations of Mono-6-Azido-6-Deoxy-α-Cyclodextrin and Mono-2-O-allyl-α-Cyclodextrin - The Formation of Polymeric Helical Inclusion Complexes

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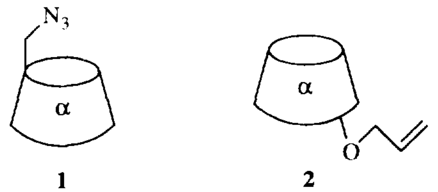
Abstract: The three dimensional X-ray structures of hydrated mono-6-azido-6-deoxy-α-cyclodextrin **1** and mono-2-O-allyl-α-cyclodextrin **2** were determined. The azido and allyl groups of each cyclodextrin (CD) unit are included in the cavity of adjacent units forming a helical polymer.

The versatility of the cyclodextrins in chemical and physico-chemical processes has been a long-standing area of interest in molecular recognition and catalysis.[1] Their unique torus shaped structures comprising a hydrophobic interior has led to the preparation of numerous inclusion complexes with a variety of organic molecules as guests.[2] Of the several physical, spectroscopic and analytical methods[3] that have been used to study the phenomenon of inclusion, none is more revealing than X-ray crystallography. Indeed, the three-dimensional structure of α-cyclodextrin (α-CD) hexahydrate was reported over 25 years ago, and subsequently refined.[4] X-ray crystal structures of many inclusion complexes have been reported over the years.[5] In comparison, relatively few structures of substituted CDs have been elucidated by X-ray crystallography.[6] In some instances, the tethered substituent on one CD unit is included in the cavity of another substituted CD, thus giving interesting three-dimensional arrays.[7] Particularly intriguing examples are provided by monosubstituted β-CD derivatives in which intermolecular inclusion of the substituent within the cavity of another unit results in a helical polymer.[8] Such structures provide an added functional element, particularly in the context of self-assembled supramolecular motifs[9] with potentially interesting properties in the design and engineering of solids.[10]

We report herein the results of our X-ray crystallographic studies of mono-6-azido-6-deoxy-α-CD hexahydrate, **1** [11,12], and of mono-2-O-allyl-α-CD, **2** containing 4.36 water molecules of hydration (Fig. 1).[11]



1 **2**

Figure 1. Structures of mono-6-azido-6-deoxy-α-CD, **1** and mono-2-O-allyl-α-CD **2**.

RESULTS AND DISCUSSION

The Molecular Conformation of 1

As shown in Figure 2, compound **1** crystallizes with six molecules of water, of which two are included inside the cavity of the macrocycle while the remaining four are situated outside the cavity. A hydrogen bonded network links water molecules to specific hydroxyl groups. Thus, W6 is hydrogen bonded to W4 and to O(6, G2) and O(6, G6). The O(6, G6) is also hydrogen bonded to W1. The O(6, G4) is hydrogen bonded to W4 and to W2. W5 is hydrogen bonded to O(2, G4), and W3 is hydrogen bonded to O(2, G3) and O(3, G3).

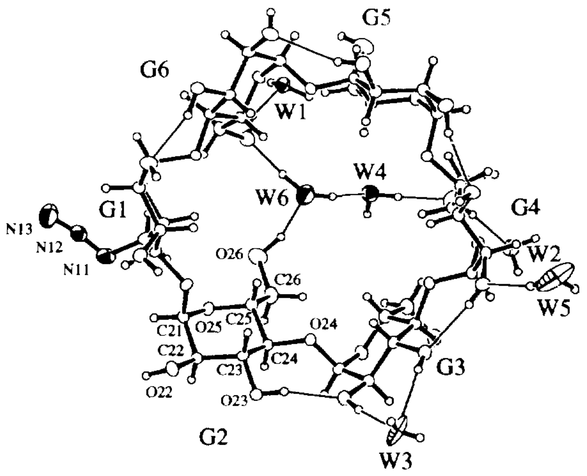


Figure 2. The structure of compound **1**. 6 H_2O viewed from the side of the secondary OH groups. Intramolecular H-bonds and those to water molecules are shown by thin lines.

Some parameters that describe the macrocyclic conformation in **1** are shown in Figure 3. All D-glucose residues are in the $^4C_1$ chair conformation. The six glucosidic atoms (O-4) deviate from their least-squares plane by 0.27 Å (Table 1) and form a distorted hexagon with a mean radius value of 4.23 Å (the distance from the center of gravity (CG) of the six O-4 atoms to each O-4 atom, max. variation 0.25 Å) and a mean O-4-O-4 length value of 4.24 Å (max. variation 0.16 Å). Furthermore, the torsion angles ϕ and ψ which better describe the relative orientation of α (1 $\rightarrow$ 4) linked glucose units in the α-CD macrocycle[13] have almost the same values as in α-CD hexahydrate[4]. The ϕ angle has a relatively constant average value of 165.0 Å (max. variation 10.7 Å compared to 10.8 Å in α-CD hexahydrate), while the ψ angle average value of -168.9 Å varies considerably (max. variation 34.1 Å compared to 34.4 Å in α-CD hexahydrate). The ψ angle value for the G2 unit (-134.8 Å) indicates considerable steric strain in the macrocycle as in α-CD hexahydrate.

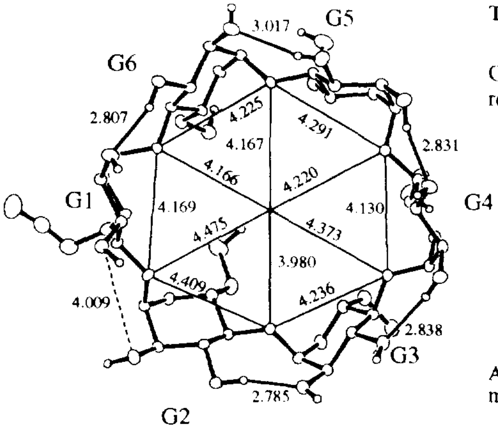


Figure 3. Geometrical data describing the macrocyclic conformation in **1**. Radius and O-4-O-4 length of the hexagons and the distance between O-2 and O-3 of the adjacent residue (Å). The dotted line represents the large O-2...O-3 distance where the hydrogen bonding ring is interrupted.

Table 1. Other Parameters Describing the Conformation of **1**

Glucose residue	ϕ(°)^a	ψ(°)^a	Tilt angle (°)^b	Deviation (Å)^c
G1	163.9(3)	-186.1(3)	04.46(7)	0.242(2)
G2	154.3(3)	-134.8(3)	35.27(11)	-0.261(2)
G3	163.0(3)	-187.0(3)	14.20(11)	0.083(2)
G4	167.0(3)	-177.4(3)	01.23(5)	0.161(2)
G5	172.0(3)	-167.7(3)	10.53(10)	0.181(2)
G6	169.7(3)	-160.6(3)	24.68(11)	-0.020(2)
Aver.	165.0	-168.9		
max.var.	(10.7)	(34.1)		

a : ϕ and ψ designate the torsion angles O(x4)...C(x1)-O((x-1)4)-C((x-1)4) and C(x1)-O((x-1)4)-C((x-1)4)...O((x-2)4). b : defined as the angle made by the plane through the six O-4 atoms and the plane through C(x1), C(x4), O(x4) and O((x-1)4) atoms. c : deviation of each O-4 atom from the least-squares plane through the six O-4 atoms.

On the secondary face, a set of hydrogen bonds connects O-2 and O-3 in the D-glucose units, except for the G1 unit which is hydrogen bonded to O(3, G6) only. As seen in Figure 2, the hydrogen bonding scheme is O(3, G6) $\rightarrow$ O(2, G1), O(3, G2) $\rightarrow$ O(2, G3), O(3, G3) $\leftarrow$ O(2, G4), O(3, G4) $\leftarrow$ O(2, G5), O(3, G5) $\rightarrow$ O(2, G6) indicating an heterodromic type of circular bonds.

The O(2, Gn)...O(3, Gn+1) distance is highly correlated with the tilt angles of the acceptor and donor residues and increased by the inclination of their O-6 side towards the inside of the macrocycle as a result of hydrogen bonding with water molecules in the cavity[7a]. The G1, G3 and G5 units are not hydrogen bonded to the included water molecules and their C-6-O-6 bonds are in a *gauche-gauche* orientation to the C-5-O-5 and C-4-C-5 bonds respectively. As a consequence, the tilt angles of the G1, G3 and G5 units are in the normal range

(1.2-14.2°, Table 1). The O-2 and O-3 of the G6 unit are hydrogen bonded to the O-3 and O-2 of the adjacent units G5 and G1 respectively. However, its C-6-O-6 bond is in a *(+) gauche* orientation to allow hydrogen bonding with W6. This increases relatively the tilt angle value (24.6°) of the G6 unit. The largest tilt angle (35.2°) corresponds to the G2 unit due to an important inclination of its C-6-O-6 bond which is in a *(+) gauche* orientation, and consequently to the largest O(3, G1)...O(2, G2) distance (4.009 Å). This facilitates hydrogen bonding with the enclosed water molecule W6 which is situated far from the wall of the cavity. The C-6-O-6 bond in the G4 unit is in a *(+) gauche* conformation, as in the G2 and G6 units, which allows hydrogen bonding with W4. Since W4 is situated nearer to O(6, G4), the tilt angle and O-2...O-3 distance are in the normal range.

The Molecular Conformation of 2

The X-ray structure of **2** shown in Figure 4 confirmed the position of the allyl group on O-2, of the secondary face and indicates that the allyl group is disordered over two sites, a major site occupied at 64 % (Fig. 4A) and a minor site filled to only 36 % (Fig. 4B). Compound **2** crystallizes with 4.36 water molecules. In both forms **2A** and **2B**, three water molecules are situated outside the cavity. W1 and W4 are hydrogen bonded to O(6, G2) and O(2, G2) respectively, while W2 is hydrogen bonded to O(6, G5). However, and depending on the disorder of the allyl group in the major form **2A**, there is only one water molecule W3 included in the cavity which is not hydrogen bonded in the asymmetric unit. In the minor form **2B**, two water molecules are enclosed inside the cavity where W5 is hydrogen bonded to W3 and to the G1, G3 and G6 units through their OH-6 which are in a *(+) gauche* orientation. However, these C-6-O-6 bonds in **2A** and **2B** are not in a fixed position which is related to the presence of W3 and W5 inside the cavity and consequently to the two-fold disorder of the allyl group. The hydrogen atoms attached to these O-6 atoms in **2B** could not be located. The OH-6 of the other units G2, G4 and G6 are in a *(-) gauche* orientation and are in a fixed position.

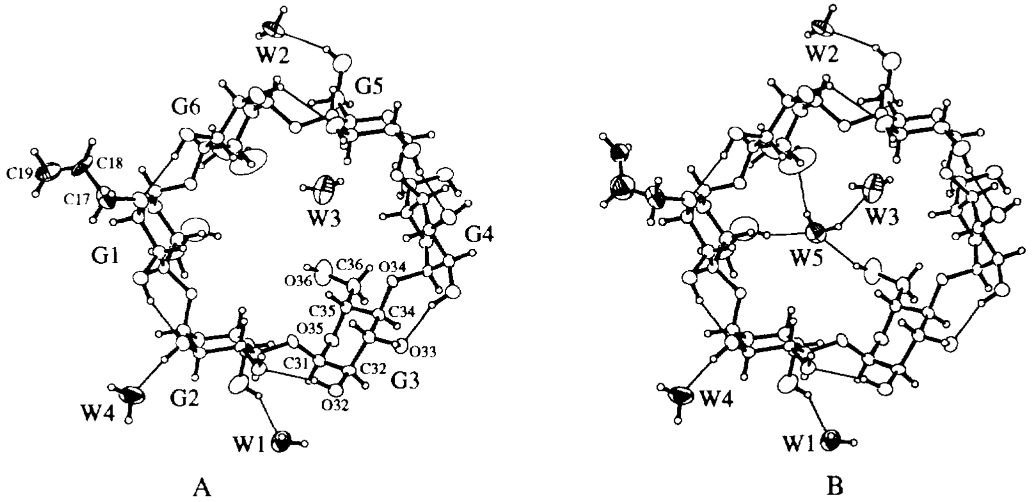


Fig. 4. The structure of compound 2. 4.36 H_2O viewed from the side of the secondary OH groups. Intramolecular H-bonds and those to water molecules are shown by thin lines. A. the major form **2A**, B. the minor form **2B**.

Some parameters that describe the similar macrocyclic conformation of **2A** and **2B** are shown in Figure 5. All D-glucose residues are in the $^4C_1$ chair conformation. The six glucosidic atoms (O-4) deviate from their least-squares plane by 0.18 Å (Table 2) and form a regular hexagon with a mean radius value of 4.230 Å (max. variation 0.19 Å) and a mean O-4-O-4 length of 4.235 Å (max. variation 0.16 Å). Compared to **1** and to α-CD hexahydrate, the average ϕ and ψ angle values (167.6°, max. variation 5.8° for ϕ and 170.1° max. variation 14.5° for ψ) are relatively constant.

On the secondary face, all the six possible O-2...O-3 intramolecular hydrogen bonds are present, and the six O(2, Gn)...O(3, Gn+1) distances are in the normal range 2.7-3.0 Å. The hydrogen bonding scheme is heterodromic as in **1**, with the following pattern : O(3, G1) → O(2, G2), O(3, G2) ← O(2, G3), O(3, G3) ← O(2, G4), O(3, G4) ← O(2, G5), O(3, G5) ← O(2, G6), O(3, G6) → O(2, G1).

As shown in Table 2, the tilt angles are in the normal range for the six glucose units in **2A** and **2B**. These results indicate that the α-CD macrocycle in these derivatives is in a relaxed state and is more symmetrical compared to **1** and α-CD hexahydrate.[14]

Table 2. Other Parameters Describing the Conformation of **2**

Glucose residue	ϕ(°)	ψ(°)	Tilt angle (°)	Deviation (Å)
G1	161.8(5)	-174.3(5)	14.6(3)	0.034(5)
G2	168.3(5)	-182.8(5)	02.0(2)	0.128(5)
G3	171.4(5)	-155.8(5)	19.7(3)	-0.187(5)
G4	168.0(5)	-174.6(5)	16.4(3)	0.110(6)
G5	163.4(5)	-177.3(5)	01.0(3)	0.078(6)
G6	172.6(5)	-155.6(5)	22.5(3)	-0.126(5)
Ave. (max. var.)	167.6 (5.8)	170.1 (14.5)		

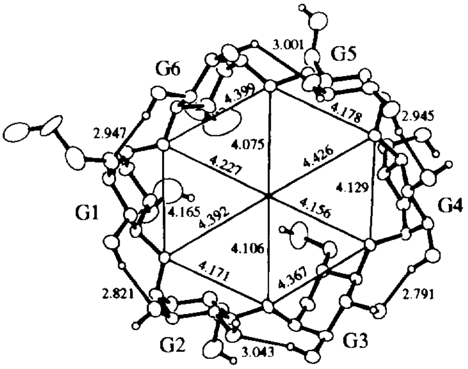


Fig. 5. Geometrical data related to the macrocyclic conformation of 2.

Helical Structure of 1 and 2

The interaction between two adjacent molecules of **1** is shown in Figure 6A. The azide group is inserted into the cavity of the adjacent molecule from the secondary hydroxyl side. A similar host-guest interaction has been observed in the literature in 6-O-(α-D-glucopyranosyl)-α-CD.$8H_2O$[7b] and in other derivatives of β-CD[7,8]. The N(13) atom is situated at 0.27 Å above the plane through the six O-4 atoms of the adjacent host molecule, while N(11) and N(12) are situated at 1.025 and 0.41 Å respectively below the same plane (Table 3, part I). This result indicates that the azide group is entirely included inside the cavity of the host macrocycle.

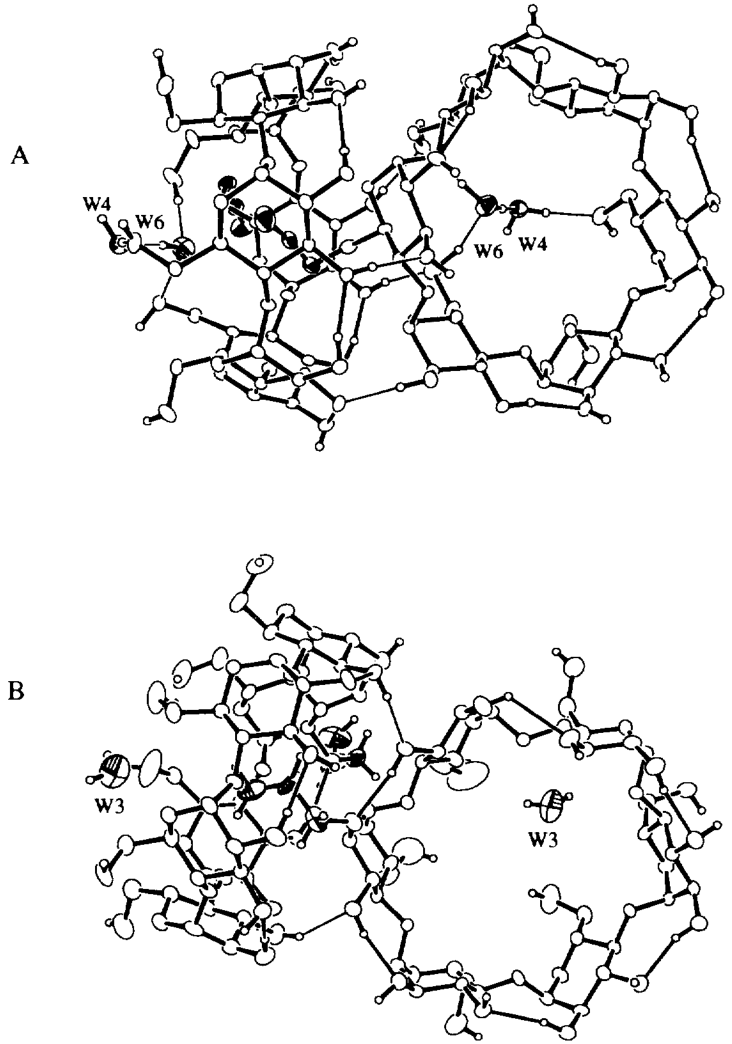


Fig. 6. Contact between two adjacent molecules, of **1** showing intermolecular inclusion of an azide group (A), and of the major form of **2** with intermolecular inclusion of an allyl group (B).

The important interaction contributing to the head to tail stacking is a strong hydrogen bonding between O(2, G1) and O(6, G2) (2.656 Å), between O(3, G1) and O(6, G6) (2.893 Å), between O(3, G5) and O(2, G2) (2.853 Å) and between O(3, G1) and O(3, G4) (2.844 Å). Van der Waals interactions between N(13) and W6 of the adjacent macrocycle and between the azide group and H-3, H-5 and O(4, G3) atoms of the adjacent α-CD macrocycle also contribute to this interaction (Table 3, part II).

Table 3. The Host-Guest Interactions in **1** and **2**

I. Distance from the plane through the six O-4 atoms to the guest molecule

Compound **1**		Compound **2**		
			2A	**2B**
N(11)	1.025(6)	C(17)	2.455(7)	2.455(7)
N(12)	0.410(3)	C(18)	1.206(9)	1.169(12)
N(13)	-0.270(4)	C(19)	0.094(14)	0.489(24)
W(4)	-4.449(3)	W(3)	-4.205(8)	-4.205(8)
W(6)	-2.860(3)	W(5)		-2.894(15)

II. The shortest contacts related to host-guest interactions

Compound **1**		Compound **2**			
		2A		**2B**	
N(13)-W(6)	2.96	H(17A)-H(3, G5)*	2.41	H(18)-H(3, G5)	2.12
N(13)-H(5, G3)	2.71	H(18)-H(3, G2)	2.46	H(19A)-H(5, G3)	2.70
N(13)-H(5, G4)	2.83	H(19B)-H(5, G5)	2.64	H(19B)-H(5, G1)	3.03
N(11)-H(3, G5)	2.96	H(19B)-H(5, G4)	2.72	H(18)-H(5, G5)	2.97
N(11)-H(3, G6)	3.03	H(19A)-H(5, G6)	2.88	H(19A)-W(5)	2.58
N(13)-O(4, G3)	3.21	H(19A)-H(5, G3)	3.01	H(19A)-HW(5B)	2.34
		H(19B)-O(4, G4)	3.02	C(19)-W(5)	3.44
		H(18)-O(4, G2)	3.08	C(19)-HW(5B)	3.26
				H(18)-O(4, G5)	2.87

* : The HA and HB designate the two protons on C(17) and C(19) of the allyl group and on W(5), sum of van der Waals radius are : C...O : 3.22, H...O : 2.77, H...H : 2.40, N...O : 3.07, N...H : 2.75 Å.

The molecule is stacked along the two-fold screw axis *a* in a helical arrangement with an inclination of 62.9° to this axis (Figure 7A). Such an arrangement, first observed in the literature in 6-deoxy-6-(tert-butylthio)-β-CD[8b], then in 6-deoxy-6-(phenylthio and phenylsulfinyl)-β-CD[8a] and 6-O-((R) and (S)-2-hydroxypropyl)-β-CD[7a], consists of a polymeric inclusion column structure formed from a single species acting both as a guest and as a host.

In compound **2**, the interactions between two adjacent molecules are similar in both forms **2A** and **2B**. Figure 6B shows this interaction in the case of the major form **2A**. The allyl group is inserted into the cavity of the adjacent molecule from the secondary face. The C(17), C(18) and C(19) atoms of the allyl group in **2A** are situated respectively at 2.455, 1.206 and 0.094 Å below the plane through the six O-4 atoms of the host macrocycle (Table 3, part I). In **2B**, the C(17), C(18) and C(19) atoms are situated respectively at 2.455, 1.169 and 0.489 Å below the same plane (Table 3, part I). These results indicate that the allyl group in **2A** appears to be included in the cavity to a greater extent, while in **2B**, the space in the host cavity is shared between the allyl group and W3 and W5.

The important interaction contributing to the tail to tail stacking in **2** is a strong hydrogen bonding between O(3, G2) and O(3, G6) (2.762 Å), and between O(3, G5) and O(3, G1) (2.819 Å). Van der Waals interactions between the allyl group and the H-3, H-5 and O-4 atoms of the adjacent α-CD macrocycle, in **2A** and **2B**, and between the allyl group and W5 also in **2B**, contribute to this interaction (Table 3, part II). A helical arrangement of the macrocycles along the two-fold screw axis *a* with an inclination of 41.3° to this axis is found in **2** (Figure 7B).

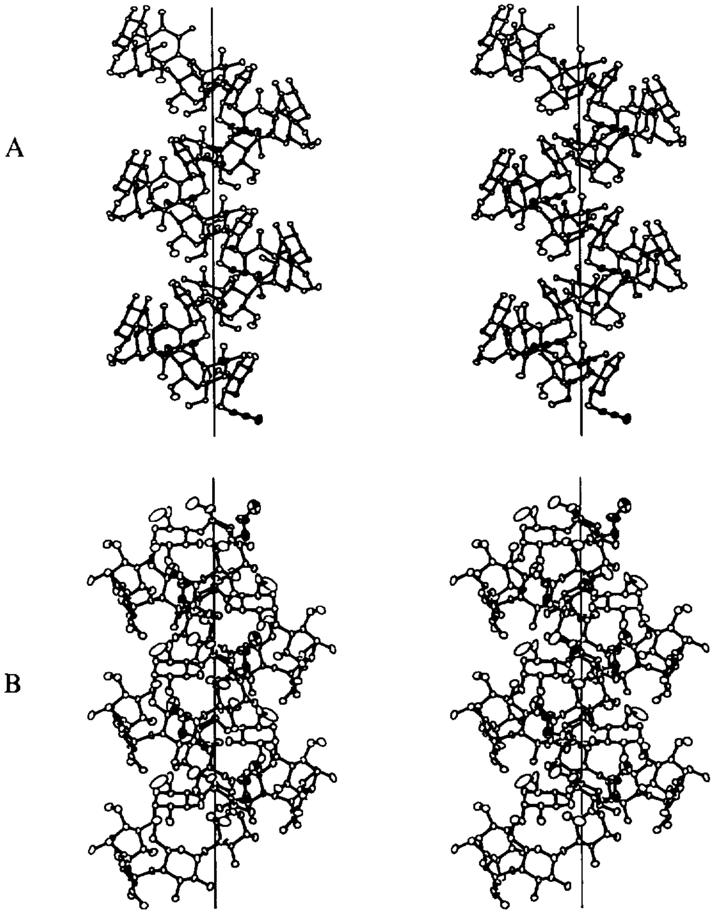


Fig. 7. Stereodrawing of the helical polymer penetrated by 2_1 screw axis shown by a straight line, A. compound **1**, B. compound **2**.

The water molecules included in the α-CD cavity are in an unfavorable hydrophobic environment and are at high energy if they cannot satisfy their hydrogen bonding potentials[14]. The displacement of these water molecules by hydrophobic guest molecules during formation of inclusion complexes is energetically favored[14]. The allyl group in **2** displaces the water molecule W5 from the cavity in spite of the fact that it is fully coordinated and it has the lowest temperature factor among the five water molecules of the asymmetric unit (Figure 4B). In compound **1**, the cavity space is shared between the azide group and two water molecules since the azide group is too small to displace water molecules from the cavity.

In conclusion, we have demonstrated that mono-azido and mono-O-allyl-α-CDs are capable of forming crystalline helical polymeric inclusion complexes in association with water molecules. Other aspects of this phenomenon are under investigation and will be reported in due course.

EXPERIMENTAL

The preparation and purification of compounds **1** and **2** are described separately.[11] For X-ray analysis, a crystal of 0.30x0.34x0.36x0.50 mm for **1** and of 0.16x0.16x0.29 mm for **2** were used for intensity measurements. The cell dimensions were obtained from 25 reflections with $39°\leq 2\theta \leq 45°$ on a Nonius diffractometer using graphite monochromated CuKα radiation (λ = 1.54056 Å) with a scan rate of 16.5° min^{-1} at 220° K for **1** and 295° K for **2**. Then a total of 19939 reflections with 5083 unique reflections were measured for **1** and 32385 total reflections with 5244 unique reflections were mesured for **2** with a limiting 2θ value of 140° and using $\omega/2\theta$ scan mode. From these reflections, 4806 for **1** and 3002 for **2** were considered to be observed with $I>1.96\sigma(I)$. No absorption correction was applied.

Crystal data. Compound **1** : $C_{36}H_{59}O_{29}N_3$. $6H_2O$, Mr 1105.96, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 11.990(2), b = 13.621(6), c = 29.449(12) Å, V = 4809(3) Å^3, D_c = 1.527 Mg m^{-3}, μ = 1.15 mm^{-1}, Compound **2** : $C_{39}H_{64}O_{30}$. $4.36H_2O$, Mr 1091.47, orthorhombic, space group $P2_12_12_1$, Z = 4, a = 10.419(2), b = 19.280(3), c = 24.760(3) Å, V = 4973(14) Å^3, D_c = 1.458 Mg m^{-3}, μ = 1.09 mm^{-1}.

The structure of **1** and **2** were solved by direct method using SHELX-86 and subsequent difference Fourier synthesis using NRCVAX for **1** and SHELX-76 for **2**. The refinement of the structures to a final R value of 0.031 for **1** and of 0.044 for **2** was realized by block diagonal least-squares for **1** and full-matrix least-squares for **2**, with anisotropic temperature factors for all non-hydrogen atoms and isotropic temperature factors for all hydrogen atoms. For **2** partial disorder (occ. = 0.64, major; 0.36, minor) located for the allyl group was found to be related to the water contains. Disorder model was adjusted using constrained distances and angles retained in last cycles. Tables of final atomic coordinates, anisotropic temperature factors, distances, angles, torsion angles and hydrogen bond distances and angles have been deposited at the Cambridge Crystallographic Data Centre.

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