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Neutron Diffraction Study of the Hydrogen Bonding in Partially Deuterated γ-Cyclodextrin·15.7D_2O at T = 110 K[†]

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Abstract: A single-crystal neutron diffraction study of partially deuterated γ-cyclodextrin (γ-CD) hydrate, $(C_6D_3H_7O_5)_8\cdot 15.7D_2O$, was carried out at T = 110 K. The crystal is monoclinic, space group $P2_1$, with cell dimensions a = 16.899 (7) Å, b = 10.891 (5) Å, c = 20.226 (6) Å, β = 105.06 (2)°, Z = 2, and V = 3595 (2) Å^3. A total of 10688 reflections were collected with λ = 1.3196 Å on an area detector to the nominal resolution of 0.92 Å, yielding 4906 unique reflections with an R_{merge} = 0.064 on F^2. All H and D atoms for the cyclodextrin molecule and most of the D atoms for the water molecules were located, and the structure was refined to an R factor of 0.093 for 4538 observed reflections ($F^2 \geq \sigma(F^2)$). In the crystal structure, the γ-CD molecules are arranged in a herringbone pattern forming a cage-type packing. A narrow intermolecular interstitial channel, which is filled with water molecules, runs along the crystallographic b axis at $a \sim {}^1/_2$ and $c \sim 0$. Compared with the β-CD hydrate, which crystallizes in a similar packing arrangement, the cavities of the γ-CD molecules are not as completely closed at the narrow O(6) hydroxyl group end by adjacent molecules and are connected with the interstitial channel. All glucose residues are in the usual $^4C_1$ chair conformation with a relatively strong distortion of glucose residue **1** (θ_2 = 14.5°). Glucose residue **8**, which closes the cavity of a symmetry-related γ-CD molecule at the wider O(2),O(3) end, and even slightly intrudes into it, is somewhat disordered as a whole. The 15.7 water molecules in the asymmetric unit are distributed over 25 positions. A total of 8.8 water molecules are located in the hydrophobic γ-CD cavity; they are all positionally disordered and distributed over 17 positions with occupation factors in the range 0.31–0.95. The hydrogen-bond network in the cavity is very complicated due to the severe disorder of the water molecules and could not be reliably assigned in any detail. One water molecule acts as a bridge connection and has hydrogen bonds both to water molecules enclosed in the γ-CD cavity and to water molecules in the intermolecular interstice, and one water molecule donates a hydrogen bond to glycosidic O(4) of the cavity wall. There are 6.9 water molecules located over 8 sites in the intermolecular interstitial channel, 5 of them are fully occupied, the others are partially occupied, with occupation factors in the range 0.13–0.88. The water molecules in the interstice are better ordered than those in the γ-CD cavity and have a clearer hydrogen-bonding scheme. One water molecule, which is 2-fold disordered, is isolated from all other water molecule sites and forms hydrogen bonds only to hydroxyl groups of γ-CD molecules; the others have hydrogen bonds to adjacent water molecules and/or to γ-CD hydroxyl groups or donate hydrogen bonds to ring oxygen atoms O(5). Of 71 symmetry-independent hydrogen bonds in this crystal structure, 25 (=35%) are of the three-center type, if a 2.8-Å cutoff criterion is used. All O(2) and O(3) hydroxyl groups of neighboring glucose units form interresidue, intramolecular hydrogen bonds, which are major components of unsymmetrical three-center hydrogen bonds donating relatively strong intramolecular components to the corresponding glycosidic O(4) atoms. One primary hydroxyl group donates a minor intraglucose hydrogen-bonding component to O(5) of the same residue; O(5) and O(6) of two glucose accept chelated three-center hydrogen bonds, and in two glucose residues, O(2) and O(3) of the same glucose accept three-center hydrogen bonds. All O–D···O hydrogen bonds are interconnected to form an infinite spatial network, with infinite chains, cycles, and finite chains as motifs, reminiscent of α-CD and β-CD hydrates. Homodromic arrangements of hydrogen bonds dominate in the network and indicate the strong influence of the cooperative effect.

Introduction

The cyclodextrins (CD) are a family of macrocyclic oligosaccharides consisting of six (α-CD), seven (β-CD), eight (γ-CD), or nine (δ-CD) D-glucose units in the $^4C_1$ chair conformation linked by α-1,4-interglycosidic bonds.[1–3] They have a "round", slightly conical form with all the secondary hydroxyl groups O(2)–H and O(3)–H located on the wider end and all the primary hydroxyl groups O(6)–H on the narrower end and an intramolecular, relatively hydrophobic cavity, the surface of which is dominated by C–H hydrogen atoms and glycosidic O(4) oxygen atoms. In aqueous solution, they accommodate guest molecules of suitable size in their central cavities and thereby form inclusion complexes that readily crystallize and can be used for X-ray and neutron diffraction studies. If cyclodextrins are crystallized from a pure water solution, the uncomplexed hydrates are formed with water molecules included in their cavities and located in interstices between the cyclodextrin macrocycles. In these crystals, the

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[†] Topography of Cyclodextrin Inclusion Complexes. 28. Part 27: Steiner, Th.; Mason, S. A.; Saenger, W. *J. Am. Chem. Soc.* **1991**, *113*, 5676–5687. Part 26: Ding, J.; Steiner, Th.; Saenger, W. *Acta Crystallogr., Sect. B*, in press.

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Table I. Crystallographic Data[a] for γ-Cyclodextrin Hydrate in Space Group $P2_1$

	a, Å	b, Å	c, Å	β, deg	V, Å^3
X-ray I[17] (T = 295 K)[b]	16.847 (2)	11.098 (2)	20.271 (2)	104.97 (1)	3661.4 (9)
X-ray II[18] (T = 120 K)[b]	16.892 (6)	10.949 (5)	20.253 (8)	105.32 (1)	3613 (3)
Neutron I[19] (T = 298 K)[c]	16.858 (12)	11.079 (7)	20.287 (10)	105.07 (4)	3659 (4)
Neutron II (T = 298 K)[d]	16.810 (3)	11.197 (3)	20.520 (5)	105.23 (1)	3727 (2)
Neutron III (T = 110 K)[e]	16.899 (7)	10.891 (5)	20.226 (6)	105.06 (2)	3595 (2)

[a] Standard deviations are given in parentheses; the setting of the unit cell ($a < c$) is chosen according to Harata.[17] [b] Nondeuterated. [c] Nondeuterated; structure refinement not finished. [d] Partially deuterated; ORNL experiment, structure not refined. [e] This work; same crystal as for Neutron II, ILL, experiment.

hydration number increases with the ring size: α-CD·6H_2O, β-CD·11H_2O, β-CD·12H_2O, and γ-CD·(14–17)H_2O. The water content may also depend on the method of crystallization and on the history of the crystals, as was shown for β-CD hydrates.[4,5] Owing to their hydroxyl groups and hydrate molecules, crystal structures of CDs and their complexes display a great number of O–H···O hydrogen bonds forming extended networks.[6]

In the crystal structures of α-CD·6H_2O (form I[7] and form II[8]) and of α-CD·7.57H_2O,[9] the most prominent hydrogen-bonding motifs are well-ordered systems of hydrogen-bonding chains and rings formed by four or more directly linked O–H···O–H···O–H interactions. Depending on the direction of the O–H bonds in these chains and rings, three different types can be distinguished. When all hydrogen bonds point in the same direction, the arrangement is called homodromic; if all point in opposite directions, it is called antidromic; and if there is no preferred orientation, it is called heterodromic.[10] In most cases, the hydrogen bonds are formed with the homodromic orientation due to the cooperative effect that increases the hydrogen-bonding affinity of an O–H group when it is engaged in a hydrogen bond.[11,12]

In the crystal structure of β-CD·11H_2O, the hydrogen-bonding pattern is even more complex. The neutron diffraction study at room temperature (T = 293 K)[13,14] has shown that the 11 water molecules per asymmetric unit are statistically disordered over 16 positions, of which only 3 are fully occupied. Among the 53 hydrogen bonds per asymmetric unit, 35 are of the normal type O–H···O and 18 are of the flip-flop type O–$^1/_2$H···$^1/_2$H–O. In the flip-flop type hydrogen bonds, the O···O distance is in the normal range 2.7–3.0 Å, but the $^1/_2$H···$^1/_2$H distance of ~1 Å is so short that these H positions are mutually exclusive. Therefore, the crystallographic observation of these hydrogen bonds has to be a space and time average over the two states

$$\text{O–H}\cdots\text{O–H} \rightleftharpoons \text{H–O}\cdots\text{H–O} \qquad (1)$$

where hydrogen atoms are in one or the other position. At low temperature (T = 120 K), all O–H groups are ordered so that the flip-flop type hydrogen bonds disappear and the ordered O–H···O hydrogen bonds form extended patterns with homodromic orientation.[15] This indicates that the disorder of O–H groups at room temperature is of dynamic nature and the homodromic arrangements of hydrogen bonds show the strong influence of the cooperative effect. Similar effects and hydrogen-bond networks are also observed in the crystal structures of the deuterated β-CD inclusion complex β-CD·EtOD·8D_2O,[5,16] indicating that these characteristics are not unique but are a feature of numerous β-CD complexes.

X-ray crystal structures of γ-CD hydrate determined at room temperature[17] and at T = 120 K[18] have shown that the γ-CD molecule adopts a round shape but is somewhat distorted from the ideal octagonal symmetry and that O(2)···O(3) hydrogen bonds form between adjacent glucose residues. As H atoms were not located, a neutron diffraction study was carried out (for a preliminary report, see ref 19). In the present contribution, we report the crystal structure of γ-CD hydrate at T = 110 K and give a detailed analysis of the hydrogen-bonding network.

Experimental Section

Commercially available γ-CD was dissolved in hot (T ~ 70 °C) D_2O. After cooling, the solvent was removed by a rotary evaporator. This process was repeated three times in order to exchange the hydroxyl H atoms with D and hence to reduce the incoherent neutron-scattering contribution of ^{1}H nuclei. The crystal used for the neutron diffraction study was grown at room temperature by slow evaporation of a saturated solution of γ-CD in D_2O in a desiccator.

A crystal of dimensions 1.6 × 3.8 × 1.1 mm^3, volume 4.85 mm^3, was sealed with some mother liquor in a quartz capillary in order to prevent dehydration, which leads to cracking of the crystals. After measurements of two incomplete room-temperature neutron diffraction data sets at the high-flux reactors of Oak Ridge National Laboratory (ORNL) and the Institut Laue-Langevin (ILL), the crystal was remounted for a low-temperature experiment. By use of the D19 four-circle area-detector diffractometer (ILL) equipped with a cryorefrigerator, the crystal was slowly (over several hours) cooled to T = 110 K. Diffraction data of 10 688 reflections were collected with λ = 1.3196 Å to $2\theta_{max}$ = 91°, corresponding to a nominal resolution of $\lambda/(2 \sin \theta)$ = 0.92 Å. The unit cell parameters measured by neutron diffraction are consistent with those determined earlier with a conventional X-ray source. Upon cooling, however, the cell constants changed anisotropically: the b and c axis lengths reduced, while the a axis length increased significantly, and the cell volume decreased by about 3.5%; see Table I. Absorption corrections were applied; minimum and maximum transmission factors are 0.72 and 0.87, respectively, with μ_{calc} = 1.57 cm^{-1}. Symmetry-equivalent reflections were averaged to yield 4906 unique reflections; $R_{merge}(F^2)$ = 0.064.

During or after sample preparation (deuteration by addition of D_2O, evaporation of solvent), substantial back-exchange of the solvent with H_2O must have taken place, leading to a partial reexchange of D → H in the deuterated cyclodextrin molecule. This became obvious only during structure refinement. Due to the limited accessibility of neutron diffraction devices and the long measurement times required, it was not possible to repeat the experiment as would have been desirable.

Structure Determination and Refinement. The crystallographic calculations were based on F_{hkl} of all 4538 reflections with $F^2 \geq \sigma(F^2)$ and the neutron-scattering lengths of C, O, H, and D taken from ref 20. The structure was refined by blocked full-matrix least-squares techniques employing the program SHELX-76[21] on blocks of about 500 variables. The function minimized was $\sum w(|F_o| - |F_c|)^2$ with unit weights w = 1.0. The refinement was guided by use of the computer graphics program FRODO,[22,23] version E2.3,[24] which was frequently used to inspect $2F_o - F_c$ and

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$F_o - F_c$ Fourier maps prepared with the CCP4 program package[25] and to locate new atom sites. All calculations were performed on a Micro-VAX 3500 computer. Molecular parameters were calculated with the program PARST7;[26] all plots were drawn with the program ORTEPII.[27]

To compare this structure determination with the previous X-ray study,[17] the same unit cell setting ($a < c$; see Table I) was chosen, which is contrary to our preliminary report.[19] The C and O atom positions of the γ-CD molecule from the X-ray study[17] were used to initiate refinement. After several cycles of isotropic refinement, all C–H hydrogen atoms were located in Fourier maps as negative peaks in the expected positions. The interpretation and assignment of the positive peaks in the difference Fourier maps to deuterium atoms and water oxygen atoms was complicated and difficult, especially within the γ-CD cavity. Reasons for this are the disorder of hydroxyl O and D atoms, extensive disorder of water molecules, and most seriously incomplete H/D exchange. In a series of refinements followed by difference Fourier syntheses, minor sites of hydroxyl O atoms and all of the D atoms for the γ-CD molecule and most of the O and D atoms for water molecules could be assigned. After isotropic refinement had converged, the thermal parameters of all atoms were refined anisotropically, except for atoms with occupancy less than 0.4. Due to the limited number of reflection data available, it was not possible to refine all atoms anisotropically. In the final stages of refinement, occupation parameters of all D and of most water O atoms were allowed to vary, and occupation parameters for all C and H atoms, except H(6)1B, were kept at 1.0.

The CH$_2$(6)–O(6) group of glucose residue **1** is 3-fold disordered. The O atom occupation factors were refined independently, and their sum totals 0.82; two D atom sites were located for two disordered O positions. Among the disordered H atom sites, one position is fully occupied and the other is partially occupied (occ = 0.64). The remaining minor sites of O, D, and H atoms are occupied so weakly that they cannot be assigned unambiguously. The O(6)–D(6) group of glucose residue **4** is 2-fold disordered. Most atoms of glucose residue **8** are severely disordered. All attempts to resolve the disorder of this residue by locating and refining different alternative positions of the disordered atoms, except for H(1)A/B, H(2)A/B, and D(2)A/B, were unsuccessful due to the limited resolution of the data set (0.92 Å).

Refinement and interpretation of the sites of water molecules, especially for those in the cavity of the γ-CD molecule, were complicated since there are many partially occupied atomic positions with distances closer than or near the O···O covalent distance. These atomic positions were labeled as disordered A and B, and the occupation factors were not constrained. The density peaks outside the γ-CD cavity could in most cases be unambiguously assigned to O or D, guided by stereochemical considerations. For most of the water molecules enclosed in the γ-CD cavity, however, the assignment to O or D was very difficult due to disorder and overlapping molecular sites. The atomic positions for which the assignments as O or D is not absolutely reliable are OW1B, DW1B, DW6A2, OW6B, OW11B, DW11B, OW13A, DW13A, OW17B, and DW17B.

During refinement, the covalent geometry (bond distances and angles) of several disordered groups had to be constrained to ideal values, but thermal parameters were refined individually. These atomic groups are CH$_2$(6)1–O(6)1, O(6)4–D(6)4A/B, C(1)8–H(1)8A/B, C(2)8–H(2)8A/B, O(2)8–D(2)8A/B, C(6)8–O(6)8–D(6)8, water molecules W3, W7, W8, W14, and water positions W1A/B, W9A/B, W10A/B, W11A/B, W13A/B, W17A/B.

The occupation factors of the D positions were refined by using the coherent scattering length of D.[20] Because of the imperfect deuteration, this resulted in occupation factors of D atoms much smaller than 1.0, as ^{1}H has a scattering length of negative sign. The "apparent" occupation factors occ$_{\text{app}}$(D) were determined with rather low accuracy. For hydrogen atoms, which are positionally ordered, they are scattered around occ$_{\text{app}}$(D) ~ 0.4, corresponding to a degree of deuteration of only ≈0.62 according to a simple estimation for positionally ordered but isotopically disordered hydrogen atoms (occ(D) + occ(H) = 1.0)

$$\frac{\text{occ(D)}}{\text{occ(D)} + \text{occ(H)}} = \frac{b_{\text{coh}}(\text{D})\ \text{occ}_{\text{app}}(\text{D}) - b_{\text{coh}}(\text{H})}{b_{\text{coh}}(\text{D}) - b_{\text{coh}}(\text{H})} \tag{2}$$

where b_{coh}(D) and b_{coh}(H) are the coherent scattering lengths. We refrained from estimating "effective" hydrogen occupation factors from the apparent ones with occ$_{\text{eff}}$ = (const)occ$_{\text{app}}$, as the accuracy of the results is expected to be low; the occupation factors given in Table II (supplementary material) therefore are the apparent ones.

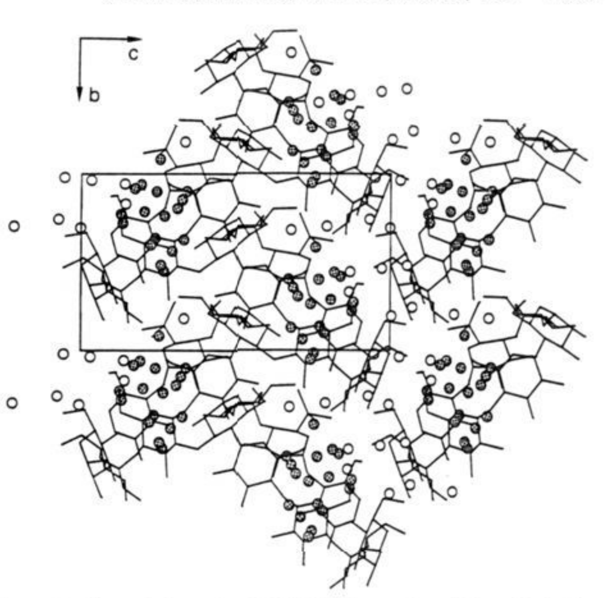

Figure 1. General view of γ-CD·15.7D$_2$O crystal packing. Projection is along the crystallographic *a* axis; for clarity, hydrogen atoms are not drawn. Water molecules are shown as circles; water molecules enclosed in the γ-CD cavities are shaded.

In the last cycle of refinement, the average parameter shifts were less than one-fourth of the average errors determined from the correlation matrix. The final *R* factor ($R = \sum||F_o| - |F_c||/\sum|F_o|$) is 0.093 for 4538 observed reflections with $F^2 \geq \sigma(F^2)$. A total of 15.7 water molecules are distributed over 25 sites. In the final difference Fourier map, significant positive peaks are found close to the severely disordered glucose residue **8** and around the disordered water molecules in the cavity of the γ-CD molecule; the residual density, however, could not be interpreted in terms of stereochemistry. This indicates that some unassigned minor water sites are still present in the γ-CD cavity.

Results and Discussion

Final fractional atomic coordinates and occupational and equivalent isotropic temperature factors with standard deviations are given in Table II (supplementary material). The anisotropic temperature factors, bond lengths, bond angles, and selected torsion angles are given in Tables III–VIa (supplementary material). The Cremer and Pople puckering parameters[28] of the glucose residues, deviations of O(4) atoms from their least-squares plane, and tilt angles of the glucose residues are given in Tables VII–IX. The bond lengths and bond angles for water molecules are listed in Table X (supplementary material). The hydrogen bond parameters and parameters of three-center hydrogen bonds are listed in Tables XI and XII. Measured and calculated structure factor amplitudes for all unique reflections are deposited in Table XIII (supplementary material). The atom numbering in the glucose residues is the same as used in our previous publications:[14,15,29] C(5)2 means carbon atom 5 of glucose number 2.

(a) Crystal Packing. The packing of γ-CD molecules in the crystal is the same as in the X-ray structures[17] (see Figure 1) which have already been described. The γ-CD molecules are stacked in a herringbone pattern to form a cage-type packing. The angle between the least-squares plane through the eight O(4) atoms and the crystallographic *b* axis is 46.0° and differs very little from the value of 46.5° derived on the basis of X-ray data.[17,18] Both ends of the γ-CD cavity are closed by neighboring molecules. This packing is similar to that of the hydrates of β-CD[30] and δ-CD.[31] Unlike the case of β-CD hydrate, a narrow interstitial channel, which is filled with water molecules, runs along the *b* axis in the

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Table VIb. Torsion Angles (deg)[a] Defining the Linkage Bonds between the Glucose Residues and the Orientations of the Primary Hydroxyl Groups[b]

torsion angles	G1	G2	G3	G4	G5	G6	G7	G8
C(3)–C(4)–O(4)–C(1)″	133 (1)	139 (1)	104 (1)	135.1 (9)	119.8 (9)	128.0 (8)	130 (1)	119 (1)
C(5)–C(4)–O(4)–C(1)″	−109 (1)	−100 (1)	−134.0 (9)	−102 (1)	−120.9 (9)	−112.3 (9)	−109 (1)	−124 (1)
O(5)–C(1)–O(4)′–C(4)′	114 (1)	109 (1)	120 (1)	105 (1)	110.2 (9)	107 (1)	105 (1)	108 (2)
C(2)–C(1)–O(4)′–C(4)′	−127 (1)	−129 (1)	−118.8 (9)	−136.9 (9)	−130.3 (8)	−133 (1)	−131 (1)	−134 (1)
O(5)–C(5)–C(6)–O(6)A	59 (2)	−57 (1)	−55 (1)	−64 (1)	73 (1)	−60 (1)	−65 (1)	69 (2)
O(5)–C(5)–C(6)–O(6)B	−102 (2)							
O(5)–C(5)–C(6)–O(6)C	115 (2)							

[a] Standard deviations are given in parentheses. Atoms marked with a single prime belong to next higher glucose units. Atoms marked with a double prime belong to next lower glucose units. [b] For a more complete selection of torsion angles, see Table VIa (supplementary material).

Table VII. Cremer and Pople Puckering Parameters[a–c] for the Glucose Subunits

ring no.	q_2	q_3	ϕ_2	Q	θ
1	0.136	0.523	70.4	0.54	14.5
2	0.013	0.530	90.7	0.53	1.4
3	0.012	0.565	−3.4	0.57	1.2
4	0.024	0.564	−49.6	0.57	2.5
5	0.050	0.574	−42.8	0.58	5.0
6	0.098	0.577	−72.7	0.59	9.6
7	0.008	0.570	−103.8	0.57	0.8
8	0.039	0.581	−103.3	0.58	3.9

[a] ϕ_2 and θ in degrees, Q (total puckering amplitude) in Å, $q_2 = Q \sin \theta$, $q_3 = Q \cos \theta$. [b] The standard deviations of ϕ_2 become very large if θ is small. The values of ϕ_2 given therefore are of limited significance. [c] Atom sequence in the ring is O(5)–C(1)–C(2)–C(3)–C(4)–C(5).

region where $a \sim {}^1/_2$ and $c \sim 0$. On the narrow O(6) end, the cavities of the γ-CD molecules are not as completely closed by adjacent molecules as in β-CD hydrate and are connected with the interstitial channel. Glucose residues 7 and 8 are partially inserted into the wider end of the neighboring γ-CD molecule related by the 2-fold screw axis. Such close contact between γ-CD molecules reduces the effective space of the γ-CD cavity so that fewer water molecules than expected are accommodated.

(b) Conformation of the γ-CD Molecule. The bond distances (Table IV, supplementary material), bond angles (Table V, supplementary material), and torsion angles (Table VIa, supplementary material) observed for the γ-CD molecule are in no way unusual. A selection of torsion angles, which define the linkage bonds beween the glucose residues and the orientation of the primary hydroxyl groups, is given in Table VIb. The Cremer and Pople puckering parameters of the glucose subunits, which are in the usual ${}^4C_1$ chair conformation with some degree of flexibility, are listed in Table VII. Parameter θ_2, which measures the deviation from "ideal" chair conformation, is conspicuously large only for glucose **1** with $\theta_2 = 14.5°$, indicating a relatively strong distortion of this residue. For the other residues, θ_2 has values between 0.8 and 9.6°, with an average of 3.5°. In the hydrated complex of γ-CD with 1-propanol, values of θ_2 vary between 1.7 and 7.1°, with an average of 4.6°,[29] and in β-CD ethanol octahydrate, they are between 1.2 and 7.5°, with an average of 4.5°.[16] A similar abnormally high value of $\theta_2 = 16.3°$ was observed for one residue in α-CD hydroquinone hexahydrate.[32]

The C(6)–O(6) bonds of the five glucose residues **2**, **3**, **4**, **6**, and **7** point "away" from the macrocyclic axis with the torsion angles O(5)–C(5)–C(6)–O(6) in the (−)gauche range, and those of the two residues **5** and **8** point "inward" with torsion angles O(5)–C(5)–C(6)–O(6) in the (+)gauche range (Table VIb); also see Figure 2. The CH_2(6)–O(6) group of residue **1** is disordered over three positions, with the major orientation (+)gauche and with two minor orientations, one pointing "inside" and one "outside". The minor orientations are, however, refined less reliably than the major orientation due to steric overlap. This parallels the situation at room temperature, except for C(6)1–O(6)1, which is ordered in the (+)gauche orientation, and C(6)6–O(6)6, which is (+)gauche/(−)gauche 2-fold disordered.[17]

Glucose residue **8** is somewhat disordered as a whole. Almost all atoms display more or less irregular nuclear density distributions, which are typical for disorder over two or more positions with distances shorter than the limit of resolution (0.92 Å) or even "continuous" disorder. As this could not be resolved, refinement yielded "average" positions with apparently much higher temperature factors of the atoms involved. Only for hydrogen atoms H(1)8, H(2)8, and D(2)8 could two alternative positions be located and refined. Similar disorder was observed with X-ray diffraction at $T = 120$ K,[18] but not at room temperature.[17] A detailed study of this disorder would require diffraction data of significantly higher resolution.

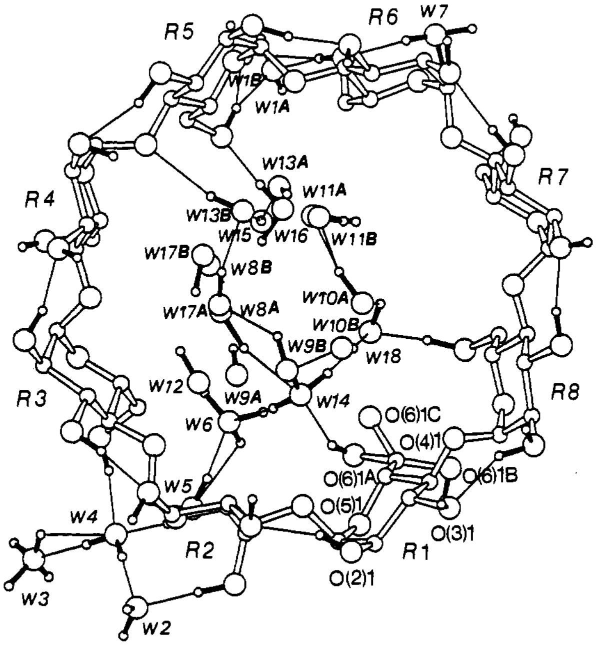

Figure 2. View of one asymmetric unit in the crystal structure of γ-CD·15.7D_2O. Projection is along the γ-CD molecular axis; C–H hydrogen atoms of the γ-CD molecules are omitted for clarity; O–D bonds are drawn solid, and hydrogen bonds are indicated by thin lines.

Table VIII. Deviations of O(4) Atoms from Their Least-Squares Plane[a]

atom	dev, Å	atom	dev, Å
O(4)1	0.08 (1)	O(4)5	−0.09 (1)
O(4)2	−0.25 (1)	O(4)6	−0.026 (9)
O(4)3	0.03 (1)	O(4)7	−0.03 (1)
O(4)4	0.16 (1)	O(4)8	0.16 (1)

[a] Standard deviations are given in parentheses.

The C(4)–O(4)–C(1)′ interglucose bond angles (Table V (supplementary material)) range from 114.9 (8) to 118 (1)° with an average value of 116.4 (10)°, which is similar to the 117 (1)° value at room temperature[17] and the 116.8° value for γ-CD 1-propanol hydrate[29] but a little smaller than for β-CD (117.7°)[30] and for α-CD (119.0°),[33] indicating that the widening of the CD macrocycle from six to eight glucoses is accompanied by a reduction of curvature. The glycosidic O(4) atoms form a nearly

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(32) Steiner, Th.; Saenger, W. Unpublished result.

(33) Hingerty, B.; Saenger, W. *J. Am. Chem. Soc.* **1976**, *98*, 3357–3365.

Table IX. Tilt Angles[a]

residue	tilt angle, deg	residue	tilt angle, deg
G1	17.1	G5	18.9
G2	−4.2	G6	14.5
G3	23.3	G7	12.9
G4	6.5	G8	25.7

[a] The tilt angle is defined as the angle between the least-squares plane through the O(4) atoms and the least-squares plane through C(1), C(4), O(4), and O(4)′ of each residue.

ideal octagon and are almost coplanar with a maximum deviation from the least-squares plane of 0.25 Å for O(4)2; see Table VIII. For each O(4) atom, the deviation is similar to that at room temperature[17] but in most cases has a slightly higher value. The tilt angles between the least-squares planes through the atoms C(1), C(4), O(4), and O(4)′ and the least-squares O(4)-plane have values between −4.2 and +25.7°, with an average of 14.5° (Table IX). This means that all residues are inclined with their O(6) side turned to the inside of the macrocycle except residue **2**, which has a negative inclination; see Figure 2. For all glucoses, this value is very similar to the one at room temperature.[17] The spread of the tilt angles is much larger than in the highly symmetrical γ-CD molecule in the tetragonal crystal structures of the complexes γ-CD 1-propanol hydrate, 11.8–18.0°, with an average of 14.9°,[29] and γ-CD·12-crown-4·NaCl, 11.3–17.6°, with an average of 14.7°,[34] reflecting a more irregular shape of the γ-CD molecule.

(c) General Remarks on the Cocrystallized Water Molecules. The shrinkage of the unit cell volume upon cooling to T = 110 K, 3.5% (Table I), is relatively very large. For comparison, the cooling of β-CD·11D_2O to T = 120 K leads to a shrinkage of 2.8% and is accompanied by ordering of cocrystallized water molecules;[15] the cooling of β-CD·ethanol·8D_2O to T = 15 K leads to a shrinkage of 3.5% and is also accompanied by a similar solvent-ordering process,[16] while the cell volume of the fairly well-ordered α-CD·6D_2O shrinks only by 1.9% upon cooling to T = 50 K.[35] This suggested initially that in γ-CD hydrate the cooling should also lead to substantial ordering of water molecules. Actually, however, the water molecules in the γ-CD hydrate do *not* order upon cooling: in this crystal structure, 15.7 water molecules were located in an asymmetric unit, distributed over 25 positions. Of these sites, 8 are placed outside the cavity with $\sum$occ(O) = 6.9 and 17 are inside the cavity with $\sum$occ(O) = 8.8. Only 5 water sites outside the γ-CD cavity are fully occupied; the other sites display occupation factors between 0.13 and 0.95; see Table II (supplementary material). In the X-ray diffraction study at room temperature, 23 water sites were located with a total occupancy of 14.1 molecules, of which 7.1 are distributed over 14 sites in the cavity.[17] In the X-ray study at T = 120 K, a total of 17 water molecules were found in 19 sites, 12 of which are situated in the cavity.[18] These variations may be due to the different methods of crystallization used, as well as to the notorious inaccuracy of counting total occupations by summing a number of partially occupied sites. For a more systematic study, we have labeled the water sites outside the cavity W1–W7 and those inside W8–W18. This labeling differs for some molecular sites from that used in the X-ray structure.[17] The major sites of water molecules found in the room-temperature X-ray structure, especially those outside the γ-CD cavity, are located in virtually identical positions in the present structure. The corresponding labelings are as follows: W1 → W9, W2 → W4, W3 → W5, W4 → W7, W5 → W1, W7 → W3; W8 → W2, W9A → W23, W10A → W17, W11A → W22, W12 → W6, W13B → W18, W14 → W20, W16 → W11, W17A → W21, W18 → W16. Here the former is the labeling used in this structure and the latter is the labeling used in the room-temperature structure.[17]

The bond lengths and angles for the water molecules are not unusual; see Table X (supplementary material). From a geometrical viewpoint, the alternative A and B positions of disordered water molecules cannot be occupied at the same time. If they appear in position A, position B is excluded and vice versa.

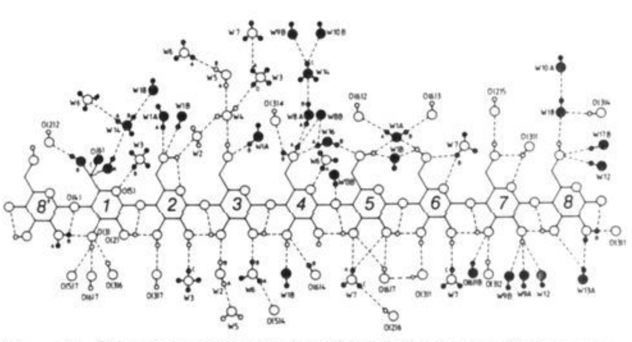

Figure 3. Schematic representation of the hydrogen-bonding arrangement around the γ-CD molecule. Large circles represent O atoms and small circles D atoms. Hydrogen bonds are indicated by dashed lines. D and O atoms, which are found to be disordered, are shaded. Numbers in the glucoses show the residue numbering.

(d) General Remarks about Hydrogen Bonding. We define an O–D···O interaction as a hydrogen bond if the D···O distance is <2.8 Å and the angle O–D···O is >90°. All hydroxyl groups and water molecules take part in hydrogen-bonding interactions in each of their alternative positions. The geometrical hydrogen-bond parameters are listed in Table XI. The hydrogen-bonding arrangement around the γ-CD molecule is schematically shown in Figure 3.

Most of the γ-CD hydroxyl groups are ordered and hence donate and accept hydrogen bonds with defined orientations. By way of exception, O(6)4–D and O(2)8–D are disordered with two well-defined D positions and donate hydrogen bonds to two alternative acceptors each; see Figure 3. O(2)1 donates a hydrogen bond to O(3)2 but is not an acceptor. The D position located for O(2)4 behaved reasonably in refinement, but is very questionable due to a short contact of 1.64 Å to the ordered D atom D(3)5 and was therefore excluded from the analysis of hydrogen bonding. For the 3-fold disordered O(6)1, none of the three sites has been identified as a hydrogen-bond acceptor. For both O(2)2–D and O(2)6–D, only one D position each was located, but these are involved in orientationally disordered hydrogen bonds, where both oxygen atoms act as donors and acceptors with partially occupied D positions (see Figure 3), and consequently alternative sites for D(2)2 and D(2)6 must exist. These, however, could not be located in the difference Fourier maps.

Interresidue, intramolecular hydrogen bonds are formed between all O(2) and O(3) hydroxyl groups of neighboring glucose units. These bonds are all ordered, with a distribution of O(2)–D···O(3) to O(2)···D–O(3) of 4 to 4, indicating that they are equally probable. All intramolecular O(2)···O(3) hydrogen bonds are major components of unsymmetrical three-center hydrogen bonds donating the minor component to the corresponding glycosidic O(4) atom; see Figure 3 and Table XII. The O(2) and O(3) hydroxyl groups, which accept these intramolecular bonds, donate hydrogen bonds to neighboring γ-CD or water molecules. This parallels the case of β-CD hydrate,[14,15] where a similar "ring" of interresidue hydrogen bonds, which stabilizes the conformation of the macrocyclic molecule, is observed in all crystal structures. As in γ-CD hydrate, in hydrated β-CD complexes all O(2)···O(3) hydrogen bonds systematically donate a minor component to O(4)[5,15,16] and have equally probable O(2)–H···O(3) and O(2)···H–O(3) orientations.[16]

(e) Water Molecules in the γ-CD Cavity. In the hydrophobic cavity of the γ-CD molecule, all 8.8 water molecules are positionally disordered and distributed over 17 positions with occupation factors between 0.31 and 0.95, with an average of 0.52. Due to the severe disorder of the water molecules and the resulting steric overlap, only three D atom positions for W14 and two D atom positions for W8A and W16 could be assigned unambiguously. For the other water sites, only one D atom position was identified. The resulting system of hydrogen bonds in the cavity is very complicated. As the alternative positions of the water

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(34) Kamitori, S.; Hirotsu, K.; Higuchi, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 3825–3830.

(35) Koellner, G.; Steiner, Th.; Mason, S. A.; Saenger, W. Unpublished results.

Table XI. Hydrogen Bond Parameters[a]

bond	O–D	D···O	O···O	O–D···O	symm (acceptor)
O(2)1–D(2)1···O(3)2	0.98 (4)	1.96 (4)	2.90 (2)	158 (3)	*x*, *y*, *z*
O(3)1–D(3)1···O(6)7	1.01 (3)	1.70 (3)	2.70 (2)	166 (2)	−*x*, 0.5 + *y*, 1 − *z*
O(6)1A–D(6)1A···OW14	0.80 (3)	1.71 (6)	2.41 (6)	145 (3)	*x*, *y*, *z*
O(6)1B–D(6)1B···O(2)2	0.91 (6)	2.15 (5)	2.91 (4)	142 (4)	*x*, *y* − 1, *z*
O(2)2–D(2)2···OW3	1.04 (7)	1.70 (7)	2.70 (2)	158 (6)	−1 − *x*, 0.5 + *y*, −*z*
O(3)2–D(3)2···O(3)7	1.05 (3)	1.62 (3)	2.67 (2)	173 (3)	−*x*, 0.5 + *y*, 1 − *z*
O(6)2–D(6)2···OW2	1.03 (3)	1.74 (3)	2.77 (2)	172 (3)	*x*, *y*, *z*
O(2)3–D(2)3···O(3)4	1.00 (4)	1.84 (4)	2.81 (1)	164 (4)	*x*, *y*, *z*
O(3)3–D(3)3···O(2)2	0.97 (3)	1.78 (3)	2.75 (3)	170 (3)	*x*, *y*, *z*
O(6)3–D(6)3···OW4	0.95 (3)	1.81 (3)	2.74 (2)	167 (3)	*x*, *y*, *z*
O(3)4–D(3)4···OW18	1.09 (4)	1.39 (5)	2.45 (4)	161 (3)	*x*, 1 + *y*, *z*
O(6)4–D(6)4A···OW8A	0.93 (3)	2.30 (4)	2.75 (3)	110 (2)	−*x*, 0.5 + *y*, −*z*
O(6)4–D(6)4A···OW8B	0.93 (3)	2.34 (7)	3.07 (7)	136 (2)	−*x*, 0.5 + *y*, −*z*
O(6)4–D(6)4B···O(3)4	0.93 (3)	1.89 (3)	2.79 (2)	160 (3)	−*x*, 0.5 + *y*, −*z*
O(2)5–D(2)5···O(3)6	1.05 (3)	1.74 (3)	2.75 (1)	162 (2)	*x*, *y*, *z*
O(3)5–D(3)5···O(2)4	1.01 (2)	1.97 (3)	2.73 (2)	160 (2)	*x*, *y*, *z*
O(6)5–D(6)5···OW1A	0.97 (3)	1.81 (3)	2.75 (2)	162 (3)	*x*, *y*, *z*
O(6)5–D(6)5···OW1B	0.97 (3)	1.51 (7)	2.42 (7)	154 (3)	*x*, *y*, *z*
O(2)6–D(2)6···OW7	1.09 (3)	1.82 (3)	2.85 (1)	158 (3)	1 − *x*, 0.5 + *y*, 1 − *z*
O(3)6–D(3)6···O(3)1	1.04 (3)	1.79 (3)	2.81 (1)	165 (2)	−*x*, 0.5 + *y*, 1 − *z*
O(6)6–D(6)6···OW1A	1.16 (5)	1.63 (5)	2.75 (2)	158 (4)	*x*, *y*, *z*
O(6)6–D(6)6···OW1B	1.16 (5)	2.15 (9)	3.00 (9)	128 (4)	*x*, *y*, *z*
O(2)7–D(2)7···OW9A	0.88 (4)	1.80 (7)	2.64 (5)	160 (4)	−*x*, *y* − 0.5, 1 − *z*
O(2)7–D(2)7···OW9B	0.88 (4)	2.22 (7)	2.88 (5)	132 (3)	−*x*, *y* − 0.5, 1 − *z*
O(2)7–D(2)7···OW12	0.88 (4)	1.99 (6)	2.43 (3)	109 (3)	−*x*, *y* − 0.5, 1 − *z*
O(3)7–D(3)7···O(2)6	0.91 (3)	1.96 (3)	2.87 (2)	169 (2)	*x*, *y*, *z*
O(6)7–D(6)7···O(2)5	0.95 (4)	2.13 (3)	3.00 (2)	151 (3)	*x*, *y* − 1, *z*
O(2)8–D(2)8A···OW13A	1.08 (4)	2.05 (5)	2.41 (4)	96 (3)	−*x*, *y* − 0.5, 1 − *z*
O(2)8–D(2)8B···O(3)1	1.09 (4)	1.98 (3)	2.95 (2)	146 (3)	*x*, *y*, *z*
O(3)8–D(3)8···O(2)7	1.02 (4)	1.80 (4)	2.75 (2)	155 (3)	*x*, *y*, *z*
O(6)8–D(6)8···OW18	1.11 (4)	1.63 (5)	2.74 (5)	174 (3)	*x*, *y*, *z*
OW1A–DW1A1···O(6)2	0.96 (3)	1.77 (3)	2.72 (2)	170 (2)	1 + *x*, *y*, *z*
OW1A–DW1A2···O(6)3	0.94 (4)	1.95 (5)	2.86 (2)	160 (5)	−*x*, *y* − 0.5, −*z*
OW1B–DW1B···O(6)2	0.86 (7)	1.95 (5)	2.43 (9)	114 (3)	1 + *x*, *y*, *z*
OW2–DW2A···OW5	0.99 (4)	1.83 (4)	2.80 (2)	167 (4)	−1 − *x*, 0.5 + *y*, −*z*
OW2–DW2B···O(3)3	0.99 (3)	1.77 (3)	2.75 (1)	169 (3)	−1 − *x*, *y* − 0.5, −*z*
OW3–DW3A···OW7	1.06 (3)	1.63 (3)	2.66 (2)	161 (3)	−*x*, 0.5 + *y*, −*z*
OW3–DW3B···O(5)1	1.11 (3)	1.77 (3)	2.84 (2)	160 (3)	−1 − *x*, 0.5 + *y*, −*z*
OW3–DW3C···O(2)2	0.86 (3)	1.96 (3)	2.70 (2)	142 (3)	−1 − *x*, *y* − 0.5, −*z*
OW3–DW3D···OW4	0.91 (4)	2.28 (4)	2.81 (2)	117 (3)	*x*, *y*, *z*
OW4–DW4A···OW3	0.96 (3)	1.85 (4)	2.81 (2)	173 (3)	*x*, *y*, *z*
OW4–DW4B···OW2	0.98 (4)	1.77 (4)	2.73 (2)	165 (4)	*x*, *y*, *z*
OW5–DW5A···OW4	1.01 (3)	1.81 (3)	2.81 (2)	166 (2)	*x*, *y*, *z*
OW5–DW5B···OW6	1.01 (3)	1.70 (3)	2.70 (2)	167 (3)	*x*, *y*, *z*
OW6–DW6A···O(5)4	1.13 (3)	1.80 (3)	2.92 (2)	170 (2)	−*x*, *y* − 0.5, −*z*
OW6–DW6B···O(2)3	1.15 (3)	1.46 (3)	2.60 (2)	171 (3)	*x*, *y* − 1, *z*
OW6–DW6C···O(2)3	1.15 (4)	2.30 (4)	2.60 (2)	92 (3)	*x*, *y* − 1, *z*
OW6–DW6C···OW5	1.15 (4)	2.23 (4)	2.70 (2)	101 (3)	*x*, *y*, *z*
OW7–DW7A···O(3)5	1.06 (2)	1.73 (2)	2.76 (1)	162 (2)	*x*, *y* − 1, *z*
OW7–DW7B···O(6)6	0.98 (2)	1.89 (3)	2.85 (1)	167 (3)	*x*, *y*, *z*
OW7–DW7C···O(2)6	1.05 (6)	1.96 (5)	2.85 (1)	141 (4)	1 − *x*, *y* − 0.5, 1 − *z*
OW8A–DW8A1···O(6)4	1.11 (5)	1.67 (4)	2.75 (3)	163 (3)	−*x*, *y* − 0.5, −*z*
OW8A–DW8A2···OW14	1.23 (6)	2.05 (8)	3.19 (6)	153 (4)	*x*, *y*, *z*
OW9B–DW9B···OW17A	0.98 (2)	1.90 (8)	2.63 (5)	129 (6)	*x*, *y*, *z*
OW10A–DW10A···OW11A	1.17 (9)	1.63 (9)	2.69 (4)	147 (8)	*x*, *y*, *z*
OW10A–DW10A···OW11B	1.17 (9)	2.27 (9)	2.69 (4)	158 (8)	*x*, *y*, *z*
OW10B–DW10B···OW18	1.02 (9)	2.03 (8)	3.03 (6)	166 (5)	*x*, *y*, *z*
OW12–DW12···O(6)8	1.00 (2)	2.03 (4)	2.80 (4)	132 (3)	*x*, 1 + *y*, *z*
OW13A–DW12A···O(2)8	0.89 (6)	1.74 (3)	2.41 (4)	130 (4)	−*x*, 0.5 + *y*, 1 − *z*
OW13B–DW13B···O(4)5	1.00 (8)	2.34 (7)	3.32 (6)	166 (6)	*x*, *y*, *z*
OW14–DW14A···OW6	0.96 (7)	2.21 (6)	3.10 (5)	154 (6)	*x*, *y*, *z*
OW14–DW14B···OW18	1.03 (8)	1.65 (7)	2.65 (6)	163 (7)	*x*, *y*, *z*
OW14–DW14C···OW9B	1.06 (8)	1.56 (8)	2.46 (6)	135 (5)	*x*, *y*, *z*
OW14–DW14C···OW10B	1.06 (8)	2.15 (8)	2.87 (6)	123 (5)	*x*, *y*, *z*
OW15–DW15···OW13A	1.10 (7)	2.06 (7)	3.06 (4)	150 (6)	*x*, *y*, *z*
OW15–DW15···OW13B	1.10 (7)	1.96 (7)	3.03 (3)	164 (6)	*x*, *y*, *z*
OW16–DW16A···O(6)4	1.20 (5)	1.82 (6)	3.01 (2)	169 (7)	−*x*, *y* − 0.5, −*z*
OW16–DW16B···O(6)5	0.92 (4)	1.69 (4)	2.60 (2)	175 (4)	*x*, *y*, *z*
OW17A–DW17A···OW13B	1.04 (5)	1.81 (4)	2.78 (3)	153 (3)	*x*, *y*, *z*
OW17B–DW17B···O(6)8	1.04 (4)	2.34 (4)	2.78 (5)	104 (3)	*x*, 1 + *y*, *z*
OW18–DW18···OW10A	0.98 (4)	2.04 (5)	2.62 (4)	116 (4)	*x*, *y*, *z*

[a] Distances in angstroms; angles in degrees; standard deviations given in parentheses. Hydrogen bonding within the γ-CD cavity is only determined with limited reliability.

molecules could not be determined in any detail, it is not possible to describe the hydrogen bonding in terms of alternative networks, as for vitamin B_{12} hydrate[36] and for β-CD·EtOD·$8D_2O$.[5] Out of the 17 water sites, W10A/B, W11A/B, W15, and W17A form

Table XII. Parameters of Three-Center Hydrogen Bonds[a] (D···A2 Shorter Than 2.8 Å)[b]

bond	O–D	D···A	O···A	O–D···A	A1···A2	A1···D···A2	sum[c]	symm (acceptor)
O(2)1–D(2)1···O(3)2	0.98 (4)	1.96 (4)	2.90 (2)	158 (3)	2.76 (2)	83 (1)	353	x, y, z
O(2)1–D(2)1···O(4)2		2.18 (4)	2.71 (2)	112 (3)				x, y, z
O(3)1–D(3)1···O(6)7	1.01 (3)	1.70 (3)	2.70 (2)	166 (2)	2.81 (2)	78 (9)	360	$-x, 0.5 + y, 1 - z$
O(3)1–D(3)1···O(5)7		2.63 (2)	3.20 (1)	116 (2)				$-x, 0.5 + y, 1 - z$
O(6)2–D(6)2···OW2	1.03 (3)	1.74 (3)	2.77 (2)	172 (3)	2.92 (1)	87 (1)	357	x, y, z
O(6)2–D(6)2···O(5)2		2.44 (3)	2.78 (2)	98 (2)				x, y, z
O(2)3–D(2)3···O(3)4	1.00 (4)	1.84 (4)	2.81 (1)	164 (4)	2.87 (2)	85 (2)	350	x, y, z
O(2)3–D(2)3···O(4)4		2.38 (4)	2.74 (2)	101 (3)				x, y, z
O(3)3–D(3)3···O(2)2	0.97 (3)	1.78 (3)	2.75 (3)	170 (3)	2.86 (2)	82 (1)	360	x, y, z
O(3)3–D(3)3···O(4)3		2.50 (3)	2.95 (2)	108 (2)				x, y, z
O(6)4–D(6)4B···O(3)4	0.93 (3)	1.89 (3)	2.79 (2)	160 (3)	3.47 (2)	94 (1)	349	$-x, 0.5 + y, -z$
O(6)4–D(6)4B···OW16		2.77 (4)	3.01 (2)	95 (2)				$-x, 0.5 + y, -z$
O(2)5–D(2)5···O(3)6	1.05 (3)	1.74 (3)	2.75 (1)	162 (2)	2.79 (1)	89 (1)	360	x, y, z
O(2)5–D(2)5···O(4)6		2.21 (2)	2.74 (1)	109 (2)				x, y, z
O(3)5–D(3)5···O(2)4	1.01 (2)	1.97 (3)	2.73 (2)	160 (2)	2.82 (2)	80 (1)	344	x, y, z
O(3)5–D(3)5···O(4)5		2.41 (3)	2.83 (1)	104 (2)				x, y, z
O(2)7–D(2)7···OW12	0.88 (4)	1.99 (6)	2.43 (3)	109 (3)	2.17 (5)	70 (3)	339	$-x, y - 0.5, 1 - z$
O(2)7–D(2)7···OW9A		1.80 (7)	2.64 (5)	160 (3)				$-x, y - 0.5, 1 - z$
O(2)7–D(2)7···OW12	0.88 (4)	1.99 (6)	2.43 (3)	109 (3)	3.50 (5)	113 (2)	354	$-x, y - 0.5, 1 - z$
O(2)7–D(2)7···OW9B		2.22 (7)	2.88 (4)	132 (3)				$-x, y - 0.5, 1 - z$
O(3)7–D(3)7···O(2)6	0.91 (3)	1.96 (3)	2.87 (2)	169 (2)	2.74 (1)	79 (1)	360	x, y, z
O(3)7–D(3)7···O(4)7		2.31 (3)	2.79 (1)	112 (2)				x, y, z
O(6)7–D(6)7···O(2)5	0.95 (4)	2.13 (3)	3.00 (2)	151 (3)	2.87 (1)	74 (1)	355	$x, y - 1, z$
O(6)7–D(6)7···O(3)5		2.61 (3)	3.30 (2)	130 (2)				$x, y - 1, z$
O(2)8–D(2)8B···O(3)1	1.09 (4)	1.98 (3)	2.95 (2)	146 (3)	2.75 (2)	79 (1)	322	x, y, z
O(2)8–D(2)8B···O(4)1		2.33 (4)	2.69 (2)	97 (2)				x, y, z
O(3)8–D(3)8···O(2)7	1.02 (4)	1.80 (4)	2.75 (2)	155 (3)	2.69 (2)	75 (1)	322	x, y, z
O(3)8–D(3)8···O(4)8		2.52 (4)	2.75 (2)	92 (2)				x, y, z
OW6-DW6C···OW5	1.15 (4)	2.23 (4)	2.70 (2)	101 (3)	4.47 (2)	161 (2)	354	x, y, z
OW6–DW6C···O(2)3		2.30 (4)	2.60 (2)	92 (2)				$x, y - 1, z$
OW7–DW7A···O(3)5	1.06 (2)	1.73 (2)	2.76 (2)	162 (2)	2.87 (1)	80 (1)	357	$x, y - 1, z$
OW7–DW7A···O(2)5		2.61 (3)	3.21 (2)	115 (2)				$x, y - 1, z$
OW7–DW7B···O(6)6	0.98 (2)	1.89 (3)	2.85 (1)	167 (3)	2.82 (2)	73 (1)	357	x, y, z
OW7–DW7B···O(5)6		2.72 (5)	3.28 (2)	117 (3)				x, y, z
OW7–DW7C···O(2)6	1.05 (6)	1.96 (5)	2.85 (1)	141 (4)	3.13 (1)	90 (2)	360	$1 - x, y - 0.5, 1 - z$
OW7–DW7C···O(2)5		2.45 (5)	3.21 (2)	129 (4)				$x, y - 1, z$
OW9B–DW9B···OW17A	0.98 (2)	1.90 (8)	2.63 (5)	129 (6)	4.02 (4)	130 (3)	356	x, y, z
OW9B–DW9B···OW10A		2.53 (7)	2.82 (4)	97 (4)				x, y, z
OW10B–DW10B···OW18	1.02 (9)	2.03 (8)	3.03 (6)	166 (5)	2.65 (6)	74 (2)	351	x, y, z
OW10B–DW10B···OW14		2.35 (6)	2.87 (6)	111 (3)				x, y, z
OW13A–DW13A···O(2)8	0.89 (6)	1.74 (3)	2.41 (4)	130 (4)	2.86 (2)	76 (1)	325	$-x, 0.5 + y, 1 - z$
OW13A–DW13A···O(3)8		2.72 (2)	3.26 (4)	119 (5)				$-x, 0.5 + y, 1 - z$
OW14–DW14C···OW9B	1.06 (8)	1.56 (8)	2.46 (6)	138 (6)	3.45 (5)	105 (3)	352	x, y, z
OW14–DW14C···OW8A		2.69 (7)	3.19 (6)	109 (5)				x, y, z
OW14–DW14C···OW10B	1.06 (8)	2.15 (8)	2.87 (6)	123 (5)	4.23 (6)	122 (3)	354	x, y, z
OW14–DW14C···OW8A		2.69 (7)	3.19 (6)	109 (4)				x, y, z
OW14–DW14C···OW10B	1.06 (8)	2.15 (8)	2.87 (6)	123 (5)	3.06 (5)	79 (2)	337	x, y, z
OW14–DW14C···OW9A		2.63 (8)	3.46 (6)	135 (5)				x, y, z
OW16–DW16A···O(6)4	1.20 (5)	1.82 (6)	3.01 (2)	169 (7)	3.07 (7)	90 (3)	357	$-x, y - 0.5, -z$
OW16–DW16A···OW8B		2.46 (3)	2.95 (4)	98 (5)				x, y, z

[a] Distances in angstroms; angles in degrees; standard deviations given in parentheses. Hydrogen bonding within the γ-CD cavity is determined only with limited reliability. [b] A = acceptor oxygens. [c] sum = sum of the angles around D.

hydrogen bonds with other included water molecules; the others are hydrogen-bonded to γ-CD hydroxyl groups; see Figures 2 and 3. W14 acts as a bridge and has hydrogen bonds both to water molecules (W8A, W9B, W10B, W18) in the γ-CD cavity and to water molecule W6 in the interstitial channel. W13B donates a hydrogen bond to a glycosidic oxygen atom of the cavity wall: W13B–D···O(4)5, with $d_{D\cdots O}$ = 2.34 (7) Å. Such hydrogen bonds between water molecules enclosed in the cavity and glycosidic oxygen atoms O(4) seem to be common in cyclodextrin hydrates, as they have been previously observed in β-CD·11D$_2$O at T = 293 K[14] (OW8–DW8A···O(4)3 with $d_{D\cdots O}$ = 2.12 (3) Å) and at T = 120 K[15] (OW9–DW9A···O(4)6 with $d_{D\cdots O}$ = 2.04 (1) Å) and in β-CD·EtOD·8D$_2$O at T = 295 K[5] (OW6–DW6B···O(4)7 with $d_{D\cdots O}$ = 2.18 (6) Å).

(f) Water Molecules in the Interstices between γ-CD Molecules. Of the 6.9 water molecules distributed over 8 interstitial sites between γ-CD molecules, 5 sites (W2, W4, W5, W6, W7) are fully occupied; W1 has a major and a minor site with occ = 0.87 and 0.13, respectively, and for W3, occ = 0.88. W3 has four partially occupied hydrogen positions in nearly tetrahedral arrangement; W6 and W7 have three D positions; W1A, W2, W4, and W5 have two D positions; for the minor position W1B, only one D position was located.

The hydrogen-bonding scheme in this region is clearer than in the γ-CD cavity; see Figures 4 and 5. W1A and W1B are isolated from other water molecules and form hydrogen bonds only with hydroxyl groups of γ-CD molecules. The other six water molecular sites are interconnected and fill the interstitial channel between the γ-CD molecules. They also have hydrogen-bonding contact with the water molecules enclosed in the γ-CD cavity via OW6···DW14A–OW14. W5 is only hydrogen-bonded to water molecules W2, W4, and W6. The other water molecules form hydrogen bonds both to adjacent water molecules and to γ-CD hydroxyl groups or donate hydrogen bonds to O(5) ring oxygen atoms of γ-CD molecules. No water molecule is found in the region $c \sim {}^1/_2$; see Figures 1 and 4. All water molecules, except W5 and the minor site of disordered water molecule W1B, have an almost tetrahedral coordination geometry, as expected for the two-donor and two-acceptor functions. W5 and W1B are only 3-fold coordinated.

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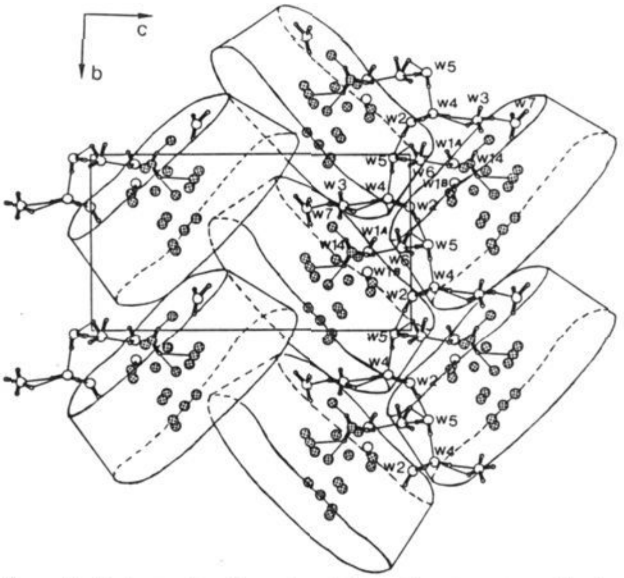

Figure 4. Hydrogen-bonding network formed by the water molecules located in the interstitial channel between the γ-CD molecules. Projection is as in Figure 1; γ-CD molecules are drawn schematically; the water molecules enclosed in the γ-CD cavities are drawn as shaded circles.

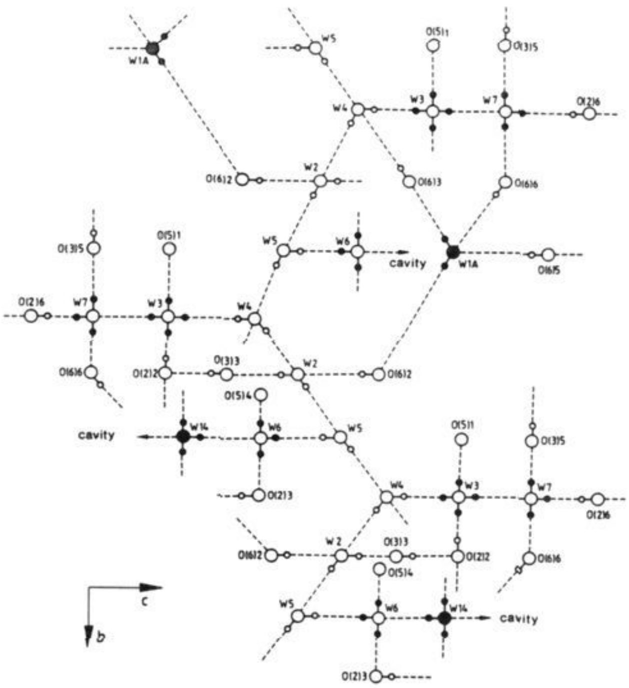

Figure 5. Schematic view of the hydrogen-bonding network formed by the water molecules situated in the intermolecular interstices and their surroundings. D and O atoms, which are found disordered, are shaded.

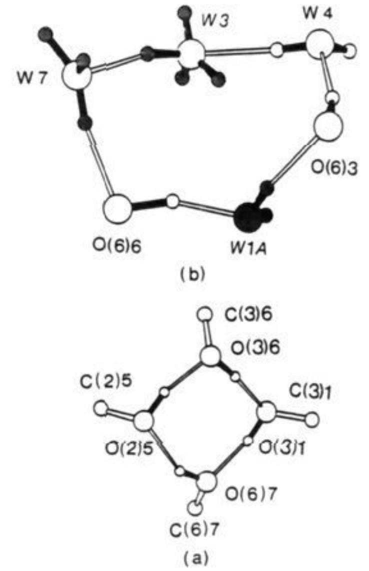

Figure 6. Two examples of circular arrangements of hydrogen bonds in homodromic orientation: (a) a four-membered hydrogen-bonding ring of almost square geometry; (b) a six-membered hydrogen-bonding ring. D and O atoms, which are found to be disordered, are shaded.

In this crystal structure, the water positions in the intermolecular interstices, which are predominantly of hydrophilic character, are more densely occupied and better ordered than those situated in the hydrophobic γ-CD cavity. This is similar to the situation in the γ-CD 1-propanol complex.[29] We assume that the hydrophilic environment and the formation of numerous hydrogen bonds between water molecules and hydroxyl groups of the γ-CD molecules stabilize these water molecules.

(g) Three-Center Hydrogen Bonds. In the following description, we define a hydrogen bond as three-centered if, for a given donor group, two acceptor atoms satisfy the criteria for a hydrogen bond ($d_{D\cdots O} < 2.8$ Å, $O-D\cdots O > 90°$) and if the D atom lies within or close to the plane defined by the three O atoms, i.e., if the sum of angles with D as their vertex is close to 360°. If both hydrogen-bond components have comparable D$\cdots$O distances, the three-center hydrogen bond is called symmetric; if one D$\cdots$O distance is significantly shorter than the other, it is called unsymmetric, with the shorter the "major" and the longer the "minor" component. According to these criteria, of the 71 symmetry-independent hydrogen bonds in the crystal structure, 25 (=35%) are three-centered; their parameters are listed in Table XII.

Of the 25 three-center hydrogen bonds, O(2)7 donates a symmetric three-center bond to W9A and W12, and W6 donates a symmetric three-center bond to W5 and O(2)3; the others are largely asymmetric. All O(2)$\cdots$O(3) interresidue hydrogen bonds donate relatively strong minor components to the corresponding glycosidic O(4) atoms. The D$\cdots$O(4) distances range from 2.18 to 2.52 Å, with an average of 2.36 Å. They are on the average slightly shorter for O(2)–D$\cdots$O(4) hydrogen bonds (2.28 Å) than for O(3)–D$\cdots$O(4) hydrogen bonds (2.44 Å). This completely parallels the situation in the β-CD·EtOD·8D_2O complex, where all O(2)$\cdots$O(3) *interresidue bonds donate minor components to* O(4) with very similar lengths: $\bar{d}_{D\cdots O(4)} = 2.38$ Å; $\bar{d}_{D(2)\cdots O(4)} = 2.32$ Å; $\bar{d}_{D(3)\cdots O(4)} = 2.43$ Å.[5]

The O(6)2 hydroxyl group forms an intraglucose three-center hydrogen bond donating the major component to W2 and the minor component to O(5)2 of the same residue. W7 and O(3)1 donate chelated three-center hydrogen bonds to glucoses **6** and **7** with O(6) the major and O(5) the minor components, respectively. W7 also donates two asymmetric three-center hydrogen bonds to hydroxyl groups of γ-CD molecules, one to O(2) (minor) and O(3) (major) of glucose **5** and the other to O(2)6 (major) and O(2)5 (minor) of two neighboring γ-CD molecules. The O(6)7 hydroxyl group donates a three-center bond to O(2) (major) and O(3) (minor) of glucose **5** of the neighboring γ-CD molecule. *W13A donates a three-center bond to O(2) (major) and O(3)* (minor) of glucose **8**.

(h) Some Features of the Hydrogen-Bonding Network. All O–D$\cdots$O hydrogen bonds are interconnected to form an infinite spatial network. As in the crystal structures of the α-CD and β-CD hydrates, where infinite chains, cycles, and finite chains of hydrogen bonds were frequently observed to form structural motifs, in the γ-CD hydrate structure, several such chain and circular arrangements of hydrogen bonds are also observed. Because of the severe disorder in the γ-CD cavity, it is not possible to describe the hydrogen-bonding network in terms of infinite structural elements extending through the whole crystal. In the following, we consider only some local arrangements of hydrogen bonds as representative examples.

In the intermolecular interstice, two screw chains wind along the crystallographic *b* axis direction. One, W2→W5→W4→W2′, is homodromic, with all water molecules acting as donors and acceptors; see Figures 4 and 5. The other, W1A→O(6)2→W2←W4←O(6)3←W1A′, is antidromic, with W1A donating two hydrogen bonds and W2 acting as double acceptor; see Figure 5.

Two of the circular hydrogen-bond arrangements, a four-membered and a six-membered ring, are shown in Figure 6; see also Figure 5. The four-membered ring is formed by hydroxyl groups of neighboring γ-CD molecules, O(3)1→O(6)7→O(2)5→O(3)6→O(3)1, and is of almost square geometry. The six-membered ring is formed by four water molecules and two hydroxyl groups, W7→O(6)6→W1A→O(6)3→W4→W3→W7. Both are homodromic, indicating the strong influence of the cooperative effect on the directionality of O–D···O hydrogen bonds. A five-membered ring is also observed in this structure, W2→O(3)3→O(2)2→←W3→←W4→W2 (see Figure 5), in which W3 is orientationally disordered with four D positions and acts as both donor and acceptor; because W4 is a double donor, this ring is antidromic. An eight-membered hydrogen-bonding ring is formed by the interconnection of the two screw chains mentioned above, W1A→O(6)3→W4→W2→W5→W4′→W2′←O(6)2←W1A, of which four water molecules, W2, W2′, W4, and W4′, are symmetry related by the screw axis 2_1. It is antidromic: W1A donates two hydrogen bonds and W2′ accepts two hydrogen bonds; see Figure 5.

An example of a finite homodromic chain is O(2)1→O(3)2→O(3)7→O(2)6→W7. In initiates at O(2)1, which acts only as a hydrogen-bond donor, and leads to the cluster of interstitial water molecules.

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Supplementary Material Available: Tables II–VIa, listing fractional coordinates and equivalent isotropic temperature factors, anisotropic temperature factors for all atoms, individual bond lengths, bond angles, and selected torsion angles for the γ-CD molecule, and Table X, giving bond lengths and bond angles for the water molecules (20 pages); Table XIII, listing measured and calculated structure factor amplitudes (55 pages). Ordering information is given on any current masthead page.

Studies on the Mechanism and Origin of Stereoselective Opening of Chiral Dioxane Acetals

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Abstract: A systematic examination of the mechanism and origin of stereoselection in the reaction of dioxane acetals with allyltrimethylsilane was undertaken. Experimental tests for two limiting mechanisms, synchronous (S_N2-like) and dissociative (S_N1-like) substitution processes, were investigated. The meso 2,4,6-trisubstituted 1,3-dioxane acetals *cis*- and *trans*-**1** provided an interesting opportunity to test the timing of bond breaking and making in the substitution reaction. The modest and C(2)-substituent-dependent selectivity excluded the possibility of a direct S_N2-type attack on a complexed acetal. Further, the enol ethers **3** and **5** and acyclic acetal **7** were studied as precursors of the putative oxocarbenium ion intermediate in the dissociative limit. The weak and inverted selectivity observed with these substrates ruled out the intermediacy of the extended, separated ion in reactions of the cyclic acetals under similar conditions. A unified mechanistic scheme involving three distinct ion pairs is proposed to explain the dependence of allylation selectivity on structural and experimental variables. The three species are analogous to those proposed in the classic Winstein scheme: (1) an intimate ion pair, (2) an external ion pair, and (3) a separated ion. Each of these proposed intermediates has a different stereochemical profile and the ultimate outcome is a composite of those factors that balance the contribution of the different intermediates. The influence of C(2) substituent, acetal configuration, Lewis acid type and stoichiometry, allylsilane stoichiometry, concentration, solvent, and temperature were investigated and integrated in the proposed mechanistic scheme.

Introduction

Due to their stability under basic conditions, acetals are generally employed as the ideal protecting groups for the ketone and aldehyde functions against nucleophiles. Nonetheless, it has been known for some time that acetals can also undergo carbon–carbon bond-forming reactions ostensibly by nucleophilic addition at the carbonyl carbon.[1] Most of the classical examples of these reactions require vigorous conditions and are not generally synthetically useful.[2] However, over the past 15 years the reaction chemistry of acetals has been greatly expanded by the use of Lewis acidic promoters particularly in conjunction with silicon-containing nucleophiles[3] (Scheme I). This reaction evolved in parallel with the related addition of organosilicon nucleophiles to aldehydes in the presence of Lewis acids[4] and has found unique applications

Scheme I

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