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(4) [Cp*Ru(η^6-3,5-Me$_2$C$_6$H$_3$OMe)]CF$_3$SO$_3$ (13). 3,5-Dimethylphenol (68 mg, 0.56 mmol) was added to a solution of CF$_3$SO$_3$H (57 μL, 0.60 mmol) and [Cp*RuOMe]$_2$ (150 mg, 0.28 mmol) in dichloromethane (10 mL). The resulting solution was stirred for 2 h, CH$_3$I (34 μL, 0.56 mmol) was added, and the mixture was stirred for another 2 h. **12** was obtained as a white microcrystalline solid upon recrystallization from dichloromethane/diethyl ether. Yield: 90%. Anal. Calcd for $C_{20}H_{27}F_3O_4SRu{\cdot}H_2O$: C, 44.52; H, 5.42. Found: C, 44.75; H, 5.66. ^{1}H NMR (Me$_2$CO-d_6): 2.08 (s, 15 H, C$_5$Me$_5$), 2.40 (s, 6 H, Me), 3.99 (s, 3 H), 5.94 (s, 1 H), 6.32 (s, 2 H). ^{13}C NMR (Me$_2$CO-d_6): 9.50 (q, C$_5$*Me*$_5$), 17.73 (q, C*Me*), 57.0 (s, CO*Me*), 77.85 (d, *C*H), 87.35 (d, *C*H), 94.57 (s, *C*$_5$Me$_5$), 99.52 (s, *C*Me), 130.00 (s, *C*OMe).

Disordered Guest and Water Molecules. Three-Center and Flip-Flop O–H···O Hydrogen Bonds in Crystalline β-Cyclodextrin Ethanol Octahydrate at T = 295 K: A Neutron and X-ray Diffraction Study[†]

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Abstract: A single crystal neutron diffraction study of partially deuterated β-cyclodextrin ethanol octahydrate was carried out at T = 295 K, composition $(C_6H_7D_3O_5)_7{\cdot}C_2D_5OD{\cdot}8D_2O$, space group $P2_1$, cell constants a = 21.125 (2) Å, b = 10.212 (1) Å, c = 15.215 (2) Å and β = 111.47 (1)°; 4138 unique neutron data (λ = 1.3167 Å) with nominal resolution 0.93 Å ($2\theta \leq 90°$). All H and D atoms were located and the structure was refined to R = 6.6%. In the β-CD molecule, 2-fold orientational disorder is found for two of the seven CH$_2$(6)–O(6) groups and for 15 of the 21 hydroxyl groups; one hydroxyl group is 3-fold disordered. Five water molecules are located between the β-CD macrocycles; two of them have four partially occupied hydrogen atom sites, two have three hydrogen sites, and only one is ordered. One ethanol and three water molecules are enclosed in the β-CD cavity, the ethanol molecule occupying two and the water molecules occupying four alternative discrete sites. The ethanol hydroxyl orientation and the water orientations are disordered for all these sites. In both positions, the ethanol molecule has a well-defined site for the oxygen atom, which is determined by hydrogen bond formation, while the CH$_2$–CH$_3$ group vibrates extensively. The two hydrogen-bonding networks in the cavity were assigned individually for both ethanol sites. Hydrogen bonding in the cavity is geometrically disadvantageous, and thermal parameters are higher than for the rest of the structure, indicating considerable solvent mobility in this region. One water molecule forms a hydrogen bond with a glycosidic O(4) oxygen atom of the cavity wall. Out of the 68 symmetry independent hydrogen bonds, 22 (=32%) are of the three-center and two (=3%) of the four-center type (based on a 2.8 Å-cutoff criterion for $d_{D\cdots O}$), and 44 are engaged in O–$^1/_2$D···$^1/_2$D–O flip-flop type disorder. The latter comprise the seven intramolecular, interglucose O(2)···O(3) interactions with a three-center minor component to the corresponding O(4) atoms. There are minor three-center components O(6)–D···O(5) in four glucoses, and O(5) and O(6) of two glucoses accept a three-center chelated hydrogen bond from a hydroxyl group. In two cases, there are weak minor hydrogen bond components between O(2) and O(3) of the *same* glucose. An X-ray study of a different crystal of the same partially deuterated compound showed a significantly different arrangement of the solvent molecules in the β-CD cavity. This implies that in biological crystal structures even of this moderate size hydrogen bonding networks can be reliably determined only for individual single crystals and may be different in others.

Introduction

The torus-shaped cyclodextrins are a family of cyclic oligosaccharides consisting of six (α-CD), seven (β-CD), eight (γ-CD), or nine (δ-CD) D-glucoses connected by α(1–4) interglucose bonds. They readily form inclusion complexes with guest molecules of suitable size, which are of interest in the study of noncovalent interactions and are used for certain industrial applications.[1-3] Many of the complexes crystallize so well that they can be studied by X-ray and neutron diffraction techniques. As each of the glucoses has three free hydroxyl groups and the crystal structures always contain several hydration water molecules, a large number of O–H···O hydrogen bonds are formed, which are interconnected into complicated three-dimensional networks. The guest molecules enclosed in the cyclodextrin cavities tend to be more or less disordered. In our laboratory we use crystalline cyclodextrin complexes as model systems to study their ordered and disordered hydrogen bonding networks, which are of biological interest.

In the room-temperature crystal structure of α-CD·6H$_2$O, a well-ordered system of cycles and chains of hydrogen bonds is observed.[4,5] In β-CD·11H$_2$O the situation is more complex. Neutron diffraction disclosed that at room temperature the 11 water molecules per asymmetric unit are disordered over 16 positions, of which only three are fully occupied.[6,7] Five water molecules and 15 (out of 21) hydroxyl groups of the β-CD molecule display orientational disorder, where the hydrogen (deuterium) atoms are found in partially occupied discrete sites.

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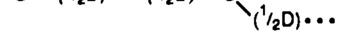
Table I. Crystallographic Data[a] for β-Cyclodextrin Ethanol Octahydrate, Space Group $P2_1$

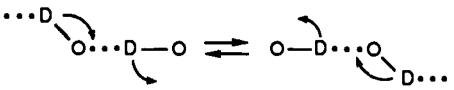
	a (Å)	b (Å)	c (Å)	β (deg)	V (Å^3)
X-ray I (nondeut)[b]	21.115	10.190	15.214	111.4	3048
X-ray II (deut)[c]	21.146 (4)	10.216 (2)	15.185 (4)	111.64 (2)	3049
neutron (deut)[d]					
T = 295 K	21.125 (2)	10.212 (1)	15.215 (2)	111.47 (1)	3054
T = 15 K[17]	20.460 (1)	10.003 (1)	15.227 (1)	109.023 (4)	2946

[a] Estimated standard deviations in parentheses. [b] Nondeuterated, room temperature, Tokuoka et al.[16] [c] Partially deuterated, room temperature, this work. [d] Partially deuterated, this work.

Many of these disordered groups are interconnected to form structures of the type



They were called "flip-flop" hydrogen bonds[6] and interpreted as a dynamical equilibrium



The dynamic nature of the disorder was disclosed by a neutron diffraction study at T = 120 K,[8] well below a phase transition observed at T = 227 K.[9,10] It showed that the water molecules and hydroxyl groups order upon cooling, which is unlikely for static disorder. Molecular dynamics computer simulations predicted water mobility in the β-CD cavity[11] and changes in hydrogen bond orientations[12] on a time scale of 10^{-11} s. This was experimentally supported by quasielastic neutron scattering experiments, which showed strong local diffusive motions of hydrogen atoms in a powder sample.[13,14] A dielectric study suggested that gradual ordering of hydrogen bonds is initiated around T = 226 K and continues down to T = 150 K, where some disorder remains frozen in.[15]

In order to check whether these properties are specific to β-CD$\cdot$11H$_2$O or if they are characteristic of other cyclodextrin complexes as well, we have performed neutron diffraction analyses of the related complex β-CD ethanol octahydrate, $(C_6H_7D_3O_5)_7\cdot C_2D_5OD\cdot 8D_2O$, at T = 295 K and T = 15 K. To complement these studies, we have also performed an X-ray structure analysis of the same compound at room temperature. In the original X-ray structure of β-CD ethanol octahydrate, 2-fold disorder of the ethanol molecule included in the β-CD cavity was observed, but no hydrogen atoms were located.[16] A calorimetric study (DTA and DSC) has shown an exothermic phase transition at T = 236 K[9] (in the nondeuterated compound). In a recent contribution we have already described the neutron structure of $(C_6H_7D_3O_5)_7\cdot C_2D_5OD\cdot 8D_2O$ at T = 15 K,[17] which shows almost perfectly ordered solvent molecules and hydroxyl groups. In the present contribution we describe the neutron and X-ray structures at room temperature and give a detailed analysis of the hydrogen bond pattern.

Experimental Section

To reduce the incoherent scattering contribution from ^{1}H nuclei, partially deuterated β-CD with all hydroxyl H atoms replaced by D and fully deuterated water and ethanol were used for crystallization. The sample preparation was described previously.[17] The neutron experiments were performed in the D19 diffractometer[18] equipped with an area-detector (4° × 64° aperture) at the high-flux reactor of the Institut Laue-Langevin, Grenoble. A 6-mm^3 crystal was used for the data collection first at T = 295 K and then at T = 15 K.[17] At T = 295 K, diffraction data of 6658 reflections were measured in equatorial and normal-beam geometry with a wavelength of λ = 1.3167 Å within 14 days (starting about eight weeks after crystallization). Intensities and profiles of three reference reflections monitored daily showed no significant changes during the data collection. Symmetry-equivalent reflections were merged to yield 4138 unique data (merging R factor $R_{\text{merge}}(F^2)$ = 3.8%), of which 218 have values of $F^2 < \sigma(F^2)$. The data are essentially complete to a nominal resolution of $\lambda/2 \sin \Theta$ = 0.93 Å (2Θ = 90°), with some 80 additional reflections to 2$\Theta \approx$ 92°. Extinction corrections were not applied.

For X-ray data collection, a crystal with dimensions 0.5 × 0.3 × 0.2 mm^3 was selected from a batch prepared in parallel at the same time, with the same method and from the same deuterated material as the one used for the neutron experiment. The crystal was mounted in a glass capillary with some mother liquor. X-ray intensities of 4002 unique reflections to 2$\Theta_{\max}$ = 120° or a nominal resolution of 0.89 Å were measured about 23 weeks after crystallization on a STOE four-circle diffractometer employing Ni-filtered Cu K$_\alpha$ radiation (λ = 1.542 Å) and an ω/2Θ scan mode with stationary background measurements on both sides of each scan. The diffraction data were corrected for background, Lorentz and polarization effects, and for absorption with the ψ-scan method.[19]

Structure Determination and Refinement

Neutron Structure. The initial structure solution was obtained with the Patterson search program PATSEE,[20] by using the C and O atomic coordinates of the β-CD molecule from the β-CD$\cdot$11D$_2$O complex[7] as an input model. The setting of the unit cell ($a > c$, see Table I) and the atom labeling are the same as in our previous publications on isomorphous β-CD complexes,[7,8,21,22] with O(2)3 meaning oxygen atom O(2) of glucose number 3 in the β-CD molecule. The crystallographic calculations were based on F_{hkl} of all reflections measured, and neutron scattering lengths b_{coh}(C) = 6.6484, b_{coh}(O) = 5.805, b_{coh}(H) = −3.7423, b_{coh}(D) = 6.674 fm from reference 23. Several cycles of consecutive isotropic least-squares refinement (program SHELX76,[24] slightly modified for neutron crystallography,[25] blocks of about 500 variables, function minimized = $\sum w(|F_o| - |F_c|)^2$, w = 1.0 for all reflections) and difference Fourier analyses gradually revealed the atomic positions of all β-CD H atoms, of most β-CD D atoms, many of which were found to be 2-fold disordered, and of five water molecules.

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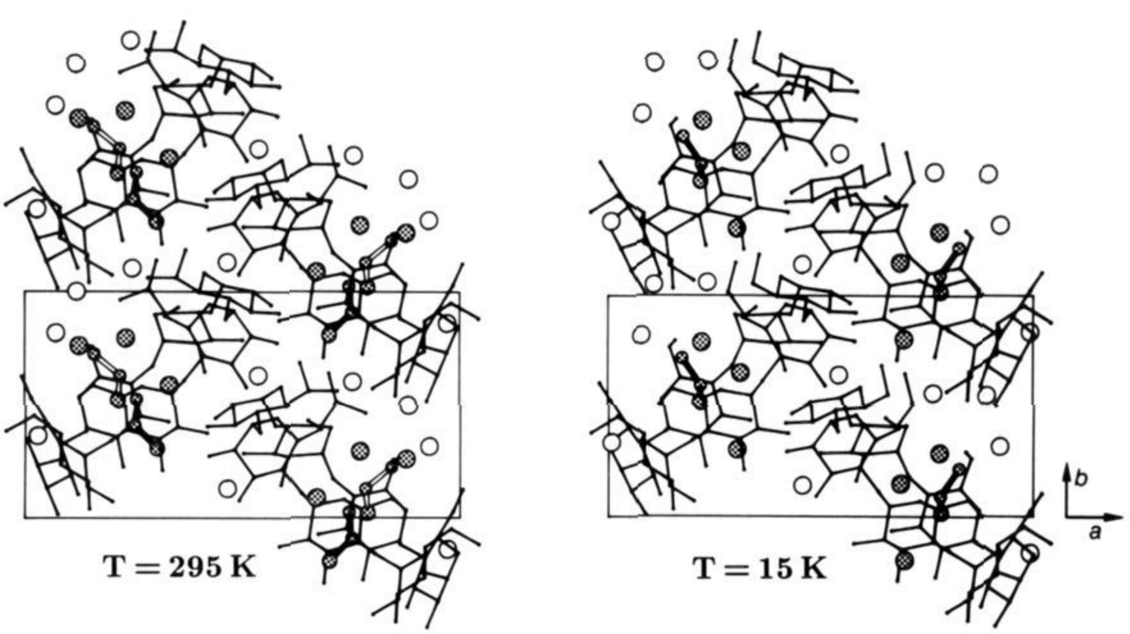

Figure 1. General view of the crystal packing, with projection along the crystallographic *c*-axis and hydrogen atoms omitted for clarity. Large spheres represent water molecules; the major site of the ethanol molecule (occ = 0.61) is drawn with solid, the minor site (occ = 0.32) with open bonds. The molecules enclosed in the β-CD cavity are shaded.

After convergence of isotropic refinement, the thermal parameters of all atoms were varied anisotropically, except for the C(1) to C(5) and O(2) to O(5) atoms of the glucose residues, which exhibit the smallest thermal motions. Due to the relatively limited number of measured reflections it was not feasible to refine all atoms anisotropically. Unlike the $T = 15$ K neutron structure,[17] the limited number of reflections, the moderate resolution of 0.93 Å, and the disorder (vide infra) caused considerable problems in the refinement.

The most difficult parts of the structure to refine were the ethanol and three water molecules, which are enclosed in the β-CD cavity, and two of the $CH_2(6)$–O(6) groups. The ethanol molecule has two alternative sites which partially overlap, and the water molecules are positionally and orientationally disordered. The two $CH_2(6)$–O(6)–D groups are disordered such that partially occupied H and O positions are situated very close to each other and partially "extinguish" each other's density peaks in the Fourier maps due to the opposite sign of the coherent scattering lengths of H and O.

In these regions the covalent geometries (bond distances and angles) of the disordered groups had to be restricted to more or less ideal values, but thermal parameters could be refined individually. We attempted, however, to use as few and as weak constraints as possible for covalent geometries and occupation factors. The atomic groups for which geometrical constraints were applied in the refinement are as follows: $CH_2(6)1$–O(6)1A, $CH_2(6)1$–O(6)1B, $CH_2(6)2$–O(6)2A, $CH_2(6)2$–O(6)2B (D(6)1A, D(6)1B, and D(6)2A were refined independently, D(6)2B could not be located), O(6)4–D(6)4A/B, O(3)6–D(3)6B/C, water positions W6, W8, and W9, and both ethanol positions. Furthermore, all atom positions for the disordered $CH_2(6)$–O(6) groups and the ethanol molecule were refined with a common occupation factor for each alternative site; those for the CH_2-(6)–O(6) groups were constrained to have a sum of 1.0.

The refinement was guided by the computer graphics program FRODO,[26,27] version E 2.3,[28] which was used to inspect $2F_o - F_c$ and $F_o - F_c$ Fourier maps prepared with the CCP4[29] program package.

In the final difference Fourier map, several minor nuclear density peaks were still present in the β-CD cavity and could not be assigned. The sum of the occupation factors of the ethanol positions is 0.93 (it is 1.0 at $T = 15$ K, measured on the same crystal[17]), and for the water–oxygen positions in the cavity it is 2.52 (3.0 at $T = 15$ K[17]); the O occupations of the water sites W3, W5, and W7, which are situated outside the β-CD cavity, are smaller than 1.0. The sum of occupation factors for all water oxygen atoms is only 7.13 (7.95 at $T = 15$ K) and indicates that there must be sites too weakly occupied to be identified. The disorder of the water sites W6 and W8 seems to be, to a certain degree, "continuous", as the corresponding nuclear densities are larger than expected for single water molecules. In the refinement this results in apparently too long O–D bond distances for W6 (OW6–D2W6 = 1.17 Å, OW6–D3W6 = 1.24 Å, see Table XII in the supplementary material).

Refinement finally converged with $R = 6.6\%$ for all measured data ($R = \sum|(|F_o| - |F_c|)|/\sum|F_o|$).

X-ray Structure. To avoid any bias from the already determined β-CD ethanol hydrate structures, the C and O atomic coordinates of the β-CD molecule in the isomorphous crystal structure β-CD·11D_2O were used as the initial model in the structure refinement with the X-ray data (SHELX76, F_{hkl} of 3787 reflections with $F_o < \sigma(F_o)$). Refinement was guided by computer graphics (FRODO). A fully occupied ethanol and eight water positions were located; the sum of water occupation factors is 7.56. The ethanol molecule shows high thermal motion and had to be constrained in ideal covalent geometry. Two C(6)–O(6) groups are disordered. In the anisotropic refinement, the C–H hydrogen atoms were placed in their calculated ideal positions. Refinement converged with $R = 7.0\%$.

Results and Discussion

The crystallographic data for β-CD ethanol octahydrate is shown in Table I. Atomic coordinates, equivalent isotropic temperature factors, and occupation factors of the neutron and the X-ray structures are given in Tables V.1. and V.2. in the supplementary material, which also contains tables of anisotropic temperature factors, bond distances, bond angles, and torsion angles of all molecules, Cremer and Pople ring puckering parameters[30] for the glucose subunits, and measured and calculated structure factor amplitudes for both structures. Corresponding

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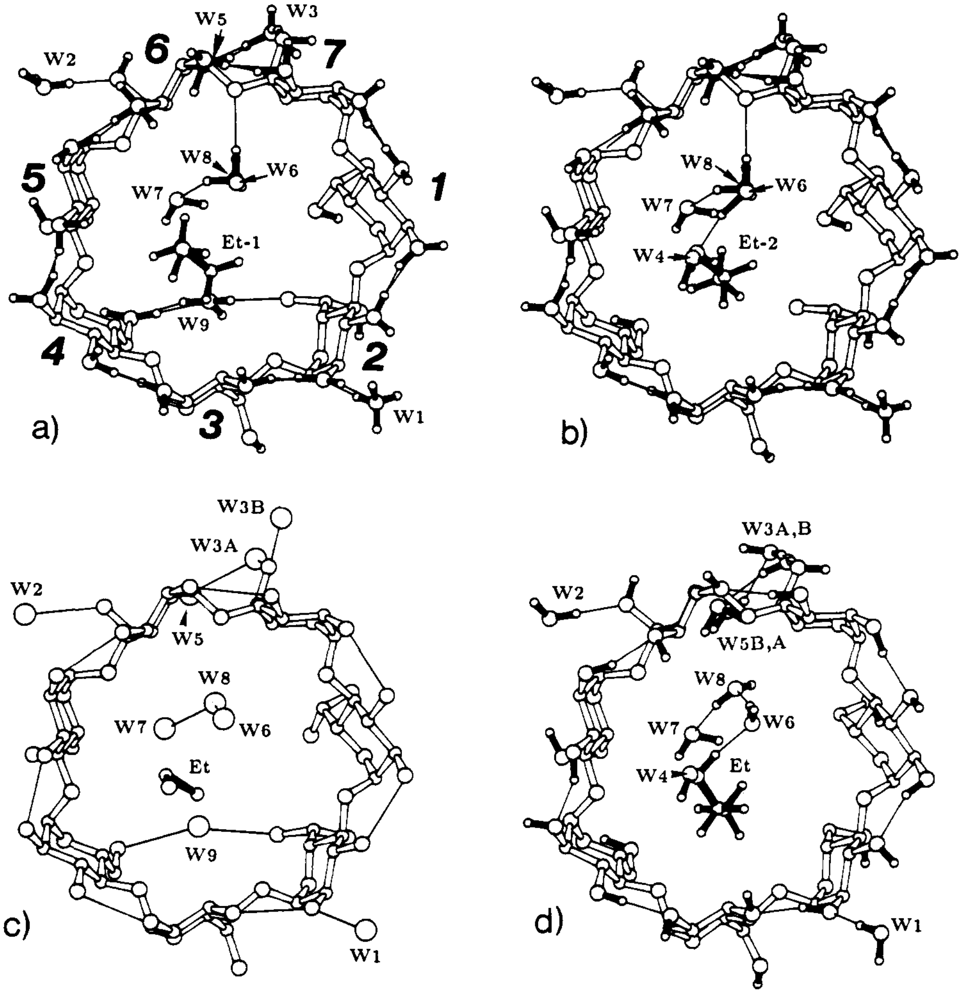

Figure 2. One asymmetric crystal unit of the inclusion complex β-CD·EtOD·8D_2O, with projection along the β-CD molecular axis. C–H hydrogen atoms in the β-CD molecule are omitted for clarity, O–D and C–D bonds are drawn solid, and hydrogen bonds are shown as thin lines: (a) neutron structure, T = 295 K, major site of the ethanol molecule (occ = 0.61), all alternative sites are drawn for disordered groups outside the β-CD cavity; (b) as in (a), but minor site of the ethanol molecule (occ = 0.32); (c) X-ray structure, T = 295 K, the site of the ethanol molecule is fully occupied; and (d) neutron structure, T = 15 K, the site of the ethanol molecule is fully occupied.

data for the structure at T = 15 K is included in the supplementary material to our previous report.[17]

(a) Crystal Packing. In the crystal, the β-CD molecules are arranged in a herringbone pattern, see Figure 1, whereby the cavity of each molecule is closed on both ends by neighboring β-CD molecules. This results in a cage-type packing where the molecular cavities are geometrically isolated from each other. As this packing scheme has already been described in the original X-ray paper[16] and for the isomorphous complex β-CD dodecahydrate,[21] it needs not be discussed any further. Each cavity contains one ethanol and three water molecules; the other five water molecules are placed between the β-CD macrocycles. The structure of one asymmetric unit is shown in Figure 2 for the neutron and X-ray structure determinations.

(b) Orientational Disorder of CH_2(6)–O(6) Groups. In cyclodextrins, the CH_2(6)–O(6) groups may rotate around the C(5)–C(6) bond. In crystal structures, O(5)–C(5)–C(6)–O(6) torsion angles are observed in the (–)-gauche and the (+)-gauche ranges, the former being usually preferred. In the present crystal structures, at room temperature four C(6)–O(6) groups (**3**, **5**, **6**, and **7**) are oriented (–)-gauche, one (**4**) (+)-gauche, and two (**1** and **2**) show disorder (–)-gauche/(+)-gauche (Table II). If disordered, the alternative O(6)–D sites engage in different hydrogen-bonding patterns. Upon cooling to T = 15 K, the two disordered groups order in the preferred (–)-gauche orientation.[17] In the original X-ray structure, also a third C(6)–O(6) group (**4**) was found to be disordered.[16] Table II shows slightly different occupation factors for the alternative sites of the disordered groups (**1** and **2**) in the neutron and the X-ray structure. This means that not only the arrangement of solvent molecules (see next sections) but also fine details in the structure of the β-CD macrocycle may be different in different single crystals of the same composition. In Table II, the C(6)–O(6) orientations of some other isomorphous β-CD complexes are compiled; considerable variations are observed only for glucoses **1** and **2**.

(c) Five Water Molecules Are Placed between the β-CD Macrocycles. As the water molecules W1, W2, W3, W5, and W7 between the β-CD molecules are in virtually identical places as in β-CD·11D_2O,[7] the same labeling is used as in that paper. W1 forms hydrogen bonds with β-CD hydroxyl groups only, W2 has hydrogen bonding contact with W7 and three β-CD hydroxyl groups, W7 is placed directly "above" the β-CD cavity and accepts a hydrogen bond of the water molecule W8 enclosed therein, see Figures 2 and 3, and W3 and W5 have adjacent positions with contacts only to β-CD hydroxyl groups.

W1 and W3 are orientationally disordered with four partially occupied D positions in roughly tetrahedral arrangement, W2 and W5 have one fully occupied and one 2-fold disordered D atom each, and W7 is fully ordered. W3 is partially occupied, occ(OW3) = 0.79, in the neutron structure, with some weak nuclear density peaks in its vicinity, which could not be assigned on stereochemical grounds. In the X-ray structure a minor site W3B, occ = 0.27, could be located. For W5 and W7 the total occupations are slightly below 1.0 in the neutron structure, occ(OW5) = 0.89, $\sum$occ(DW5) = 2.05 and occ(OW7) = 0.93, $\sum$occ(DW7) = 1.87, but it is 1.0 both in the X-ray and 15 K neutron structures.

At room temperature, all five interstitial water sites have an almost tetrahedral coordination geometry.

Table II. Orientation[a] of the CH_2(6)–O(6) Groups in β-Cyclodextrin Ethanol Octahydrate and Some Isomorphous Complexes

	glucose number[i]						
	1	2	3	4	5	6	7
β-CD·EtOH·$8H_2O$							
X-ray I[b]	(−)-g/(+)-g[c]	(−)-g/(+)-g[c]	(−)-g	(−)-g/(+)-g[c]	(−)-g	(−)-g	(−)-g
X-ray II 295 K[d]	47% (−)-g/53% (+)-g	80% (−)-g/20% (+)-g	(−)-g	(+)-g	(−)-g	(−)-g	(−)-g
neutron 295 K[d]	41% (−)-g/59% (+)-g	69% (−)-g/31% (+)-g	(−)-g	(+)-g	(−)-g	(−)-g	(−)-g
neutron 15 K[d,17]	(−)-g	(−)-g	(−)-g	(+)-g	(−)-g	(−)-g	(−)-g
β-CD·$11D_2O$							
neutron 293 K[e]	(+)-g	46% (−)-g/54% (+)-g	(−)-g	(+)-g	(−)-g	(−)-g	(−)-g
neutron 120 K[f]	(+)-g	(+)-g	(−)-g	(+)-g	(−)-g	(−)-g	(−)-g
β-CD·MeOH·$6.5H_2O$[g]	(−)-g	(−)-g/(+)-g[c]	(−)-g	(+)-g	(−)-g	(−)-g	(−)-g
β-CD·2HI·$8H_2O$[g,h]	(−)-g	(−)-g	(−)-g	(+)-g	(−)-g	(−)-g	(−)-g

[a] Range of the torsion angle O(5)–C(5)–C(6)–O(6). [b] Nondeuterated, room temperature, Tokuoka et al.[16] [c] No occupation factors given in the original paper. [d] Partially deuterated, this work. [e] Partially deuterated.[7] [f] Partially deuterated.[8] [g] X-ray, room temperature.[22] [h] The same conformation of the C(6)–O(6) groups is also observed in the isomorphous crystal structures of β-CD benzyl alcohol pentahydrate,[31] if the different labeling of the glucose residues in this publication is taken into account, and β-CD·1,4-butanediole·$6.25H_2O$[32]. [i] Abbreviation for gauche: g.

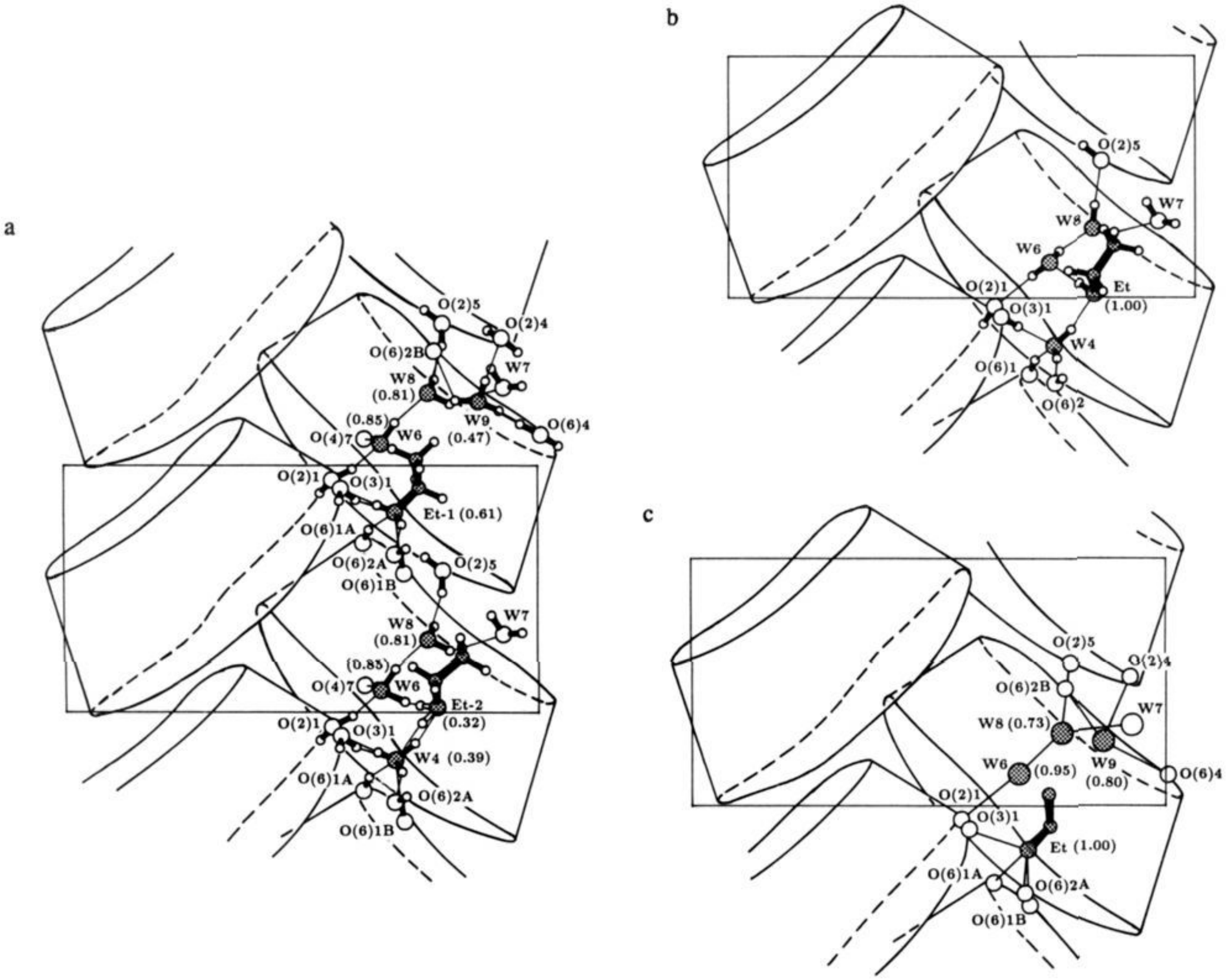

Figure 3. Hydrogen-bonding network of the molecules included in the β-CD cavity. The projection is the same as in Figure 1, β-CD molecules are drawn schematically, molecules included in the β-CD cavity are shaded, occupation factors are given in parentheses. (a) Neutron structure, $T = 295$ K, the arrangement for the major site of the ethanol molecule is drawn in one cavity (top), that for the ethanol minor site in the other (bottom). For the latter, the ethanol hydroxyl D atom could not be located and the positions drawn are hypothetical; this is indicated by open O–D bonds. (b) Neutron structure, $T = 15$ K, all occupation factors are 1.0. (c) X-ray structure, $T = 295$ K.

(d) Positions of One Ethanol and Three Water Molecules in the β-CD Cavity. At room temperature the molecules enclosed in the β-CD cavity are extensively disordered, and significant differences are seen in the neutron and X-ray structures, Figure 3. This shows that the arrangement and disorder of solvent molecules can be different in different crystals, even if they were prepared the same way. This may be due to some slight differences in the conditions of crystallization, which can never be completely avoided, and to the different history after crystallization. Similar observations were made with β-CD hydrate[9] and with vitamin B_{12} hydrate.[33] This implies that even in biological structures of this

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(31) Harata, K.; Uekama, K.; Otagiri, M.; Hirayama, F.; Ohtani, Y. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 1234–1238.
(32) Steinger, Th.; Koellner, G.; Saenger, W., submitted for publication.
(33) Savage, H. *Biophys. J.* **1986**, *50*, 947–965, 967–980.

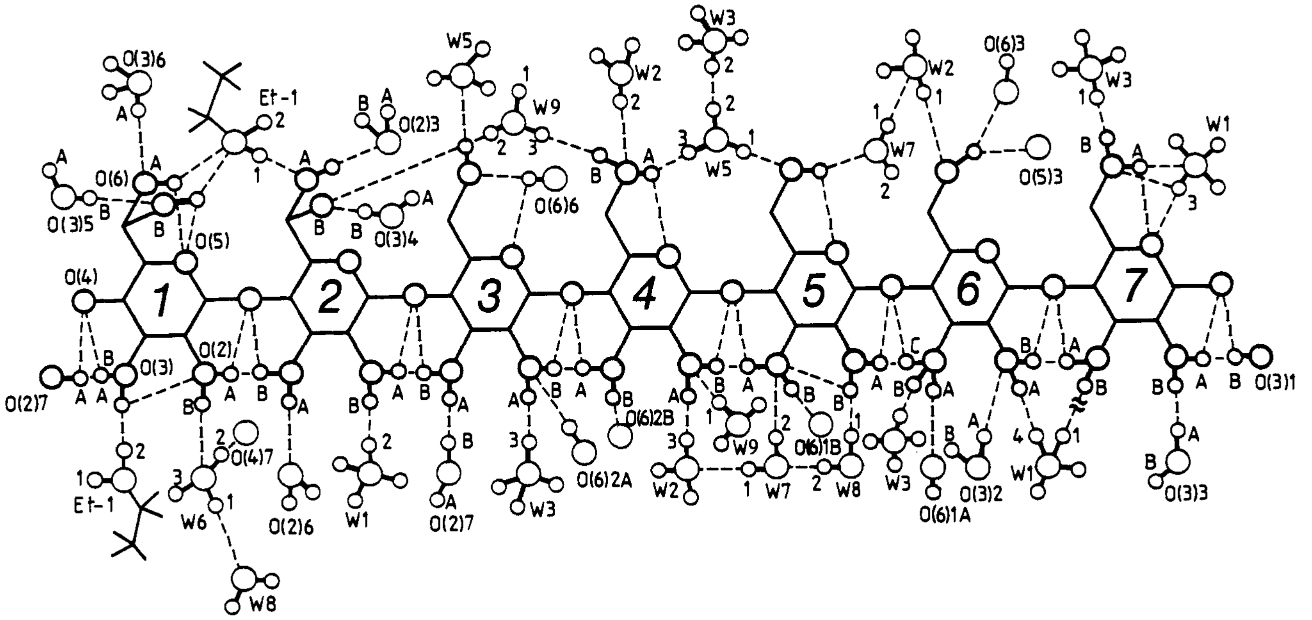

Figure 4. Schematic representation of the hydrogen-bonding arrangement around the β-CD molecule. Large spheres represent O and small spheres D atoms. For the ethanol molecule, only the major site is drawn; as this excludes W4, this water site is not in the figure. The corresponding scheme for $T = 15$ K is given in reference 17.

moderate size, details of hydrogen-bonding networks may be unique in individual crystals and differ from one crystal to another.

In the neutron structure (Figure 3a), the ethanol molecule has two partially overlapping alternative positions. In the main site, occ = 0.61, the ethanol hydroxyl group is placed roughly in the O(2)/O(3) plane of the host β-CD molecule and is 2-fold orientationally disordered. It is held in a well-defined position by a system of hydrogen bonds formed with hydroxyl groups at the rims of neighboring β-CD molecules, which close the cage. The CH_2–CH_3 group projects into the cavity and vibrates extensively, the thermal parameters of the atoms gradually becoming larger with increasing distance from the hydroxyl group. The occupation factor of the CH_2–CH_3 group is 0.61 but 1.0 for the hydroxyl oxygen atom, indicating that a water molecule (W4, occ = 0.39) substitutes for it when the ethanol is not there.

In the minor site, occ = 0.32, the ethanol hydroxyl group is placed in the central part of the cavity and accepts hydrogen bonds from two included water molecules, W4 and W6 (Figure 3a). The hydroxyl D atom could not be located. As both water molecules are orientationally disordered and therefore can also accept hydrogen bonds from the ethanol, and as there is no other possible acceptor atom at an appropriate distance, it is likely that the ethanol hydroxyl group is also 2-fold disordered to donate hydrogen bonds to W4 and W6 with occupation factors around 0.15 for the alternative D sites. Two corresponding hypothetical D positions are included in the final coordinate set (not used in the refinement); these sites are shown in Figure 3a and indicated by open O–D bonds.

For the minor ethanol site, the CH_2–CH_3 group is arranged almost parallel to the β-CD molecular axis. Due to hydrogen bonding, the hydroxyl oxygen atom has a defined position, which could be well-refined, while the CH_2–CH_3 group vibrates strongly and consequently is the least reliably determined part of the whole crystal structure.

In the neutron structure, four water sites were found in the β-CD cavity: W4, occ(O) = 0.39; W6, occ(O) = 0.85; W8, occ(O) = 0.81; and W9, occ(O) = 0.47. Due to sterical overlap, position W4 cannot be occupied if the ethanol molecule is in its major site, and W9 cannot be occupied if the ethanol is in its minor site. W4, W6, and W9 are orientationally disordered with three hydrogen positions each. For W8 the sum of the two D occupation factors is only 1.31, indicating the existence of at least one other hydrogen position, which, however, could not be unambiguously located. Such a third D position is also demanded by the orientational disorder of the hydrogen bond W8–D1W8···D(2)5B–O(2)5, see Figure 3a, which forces the D1W8 to be elsewhere, if D(2)5 is in position B. The nuclear density distributions of W6 and W8 are, though well-defined in their main characteristics, somewhat diffuse and larger than expected for single water molecules. For W6, the distance between hydrogen positions D2W6 and D3W6 is 2.2 Å, and therefore there must be at least two oxygen sites for W6, which are situated too close together to be separated with the given resolution of 0.93 Å. This indicates, apart from strong thermal vibrations, either the existence of different discrete sites placed very close to each other or disorder which is to some extent "continuous". In any event, we see only one "mean" position.

In the X-ray structure, a fully occupied site for the ethanol molecule was found, which corresponds to the major site of the neutron structure. The water positions W6, W8, and W9 in the β-CD cavity are almost the same as in the neutron structure, but the occupation factors are significantly different, see Figure 3c.

In the original X-ray analysis, 2-fold disorder of the enclosed ethanol molecule was reported.[16] One of the two ethanol sites corresponds to our major site, while the other is equivalent to our minor site, with O and CH_3 exchanged. As it is difficult to distinguish between these groups with X-rays, especially if they are disordered, we suppose that the earlier interpretation is erroneous and the ethanol should be reoriented. This structure then is consistent with ours.

Upon cooling to $T = 15$ K, the molecules in the cavity order perfectly,[7] and all occupation factors become 1.0. The β-CD cavity contains 1.0 ethanol which, surprisingly, occupies the room temperature *minor* site, see Figure 3b, and 3.0 water molecules. In the room-temperature studies, sums of occupation factors are significantly smaller: $\sum$occ(Et) = 0.93 and $\sum$occ(water) = 2.52 for the neutron structure and $\sum$occ(water) = 2.48 for the X-ray structure. The "missing" solvent molecules must be assigned to continuous residual density distributions observed in the β-CD cavity.

(e) General Remarks about Hydrogen Bonding. Most of the hydroxyl groups and water molecules are orientationally disordered as in β-CD·11D_2O.[7] All hydroxyl and water hydrogen atoms form hydrogen bonds with neighboring acceptor atoms in each alternative position. The geometrical parameters of the hydrogen bonds are listed in Table III; the hydrogen bonding arrangement around the β-CD molecule is schematically represented in Figure 4.

The O–D···O hydrogen bond geometries cover the whole range observed in biological structures (see, for instance, references 34 and 35), as shown by the distribution of D···O distances for both temperatures in Figure 5. The mean D···O distance reduces upon

Table III. Hydrogen Bond Parameters[a,b] (Neutron Structure)

bond	C[c]	O–D	D···O	O···O	O–D···O	symm	occ(O/D/O)[d]	F[e]
O(2)1–D(2)1A···O(3)2		0.90 (2)	2.14 (2)	3.00 (1)	161 (2)	*x*, *y*, *z*	1.0/0.44/1.0	F
O(2)1–D(2)1B···OW6	**b**	0.95 (3)	1.65 (6)	2.58 (5)	164 (3)	1 − *x*, *y* − 0.5, −*z*	1.0/0.59/1.0	
O(3)1–D(3)1A···O(E1)	**b**	0.96 (3)	1.84 (3)	2.74 (3)	158 (2)	1 − *x*, *y* − 0.5, −*z*	1.0/0.36/1.0	F
O(3)1–D(3)1B···O(2)7		0.94 (2)	1.98 (2)	2.91 (1)	171 (2)	*x*, *y*, *z*	1.0/0.57/1.0	F
O(6)1A–D(6)1A···O(E1)	**c**	0.87 (4)	2.23 (4)	3.07 (3)	159 (3)	*x*, *y* − 1, *z*	0.41/0.45/1.0	
O(6)1B–D(6)1B···O(E1)	**c**	0.97 (5)	1.88 (4)	2.85 (4)	173 (3)	*x*, *y* − 1, *z*	0.59/0.59/1.0	
O(2)2–D(2)2A···O(3)3		0.88 (2)	1.97 (2)	2.82 (1)	164 (1)	*x*, *y*, *z*	1.0/0.49/1.0	F
O(2)2–D(2)2B···OW1		0.87 (2)	1.97 (2)	2.83 (2)	170 (2)	*x*, *y*, *z*	1.0/0.60/1.0	F
O(3)2–D(3)2A···O(2)6		0.79 (3)	2.44 (2)	3.22 (1)	169 (3)	1 − *x*, *y* − 0.5, −*z*	1.0/0.46/1.0	F
O(3)2–D(3)2B···O(2)1		0.87 (2)	2.14 (2)	3.00 (1)	166 (2)	*x*, *y*, *z*	1.0/0.56/1.0	F
O(6)2A–D(6)2A···O(2)3	**a**	0.92 (2)	1.92 (2)	2.83 (2)	173 (2)	*x*, *y* − 1, *z*	0.69/0.57/1.0	
O(2)3–D(2)3A···OW3		1.00 (2)	1.77 (2)	2.74 (2)	162 (1)	*x*, *y* + 1, *z* − 1	1.0/0.79/0.79	F
O(2)3–D(2)3B···O(3)4	**b**	0.97 (5)	1.97 (5)	2.89 (1)	158 (4)	*x*, *y*, *z*	1.0/0.17/1.0	F
O(3)3–D(3)3A···O(2)7		0.83 (2)	1.97 (2)	2.79 (1)	166 (2)	1 − *x*, *y* + 0.5, −*z*	1.0/0.45/1.0	F
O(3)3–D(3)3B···O(2)2		0.96 (3)	1.88 (3)	2.82 (1)	164 (2)	*x*, *y*, *z*	1.0/0.56/1.0	F
O(6)3–D(6)3···OW5		0.93 (2)	1.96 (2)	2.88 (2)	172 (2)	*x*, *y*, *z* − 1	1.0/1.0/0.89	
O(2)4–D(2)4A···OW2		0.93 (2)	1.97 (3)	2.88 (2)	166 (2)	2 − *x*, *y* + 0.5, −*z*	1.0/0.54/1.0	F
O(2)4–D(2)4B···O(3)5		0.98 (2)	1.87 (3)	2.80 (1)	157 (2)	*x*, *y*, *z*	1.0/0.43/1.0	F
O(3)4–D(3)4A···O(2)3		0.94 (2)	1.95 (2)	2.89 (1)	176 (1)	*x*, *y*, *z*	1.0/0.78/1.0	F
O(3)4–D(3)4B···O(6)2B	**b**	0.88 (4)	2.05 (6)	2.85 (3)	150 (4)	*x*, *y* + 1, *z*	1.0/0.20/0.31	
O(6)4–D(6)4A···OW5	**a**	0.96 (2)	2.07 (3)	3.03 (3)	172 (2)	2 − *x*, *y* + 0.5, −*z*	1.0/0.49/0.89	F
O(6)4–D(6)4B···OW9	**c**	0.97 (2)	1.97 (5)	2.93 (5)	178 (3)	*x*, *y*, *z*	1.0/0.51/0.49	F
O(2)5–D(2)5A···O(3)6	**b**	0.92 (1)	1.91 (1)	2.80 (1)	161 (1)	*x*, *y*, *z*	1.0/0.74/1.0	F
O(2)5–D(2)5B···OW8	**b**	1.00 (6)	2.36 (8)	3.33 (5)	165 (5)	*x*, *y* + 1, *z*	1.0/0.12/0.81	F
O(3)5–D(3)5A···O(2)4		0.92 (1)	1.92 (1)	2.80 (1)	161 (2)	*x*, *y*, *z*	1.0/0.64/1.0	F
O(3)5–D(3)5B···O(6)1B	**b**	1.16 (2)	1.53 (3)	2.68 (2)	174 (3)	*x*, *y* + 1, *z*	1.0/0.39/0.59	
O(6)5–D(6)5···OW7		1.01 (2)	1.78 (2)	2.79 (2)	176 (1)	2 − *x*, *y* + 0.5, −*z*	1.0/1.0/0.93	
O(2)6–D(2)6A···OW1		0.92 (2)	1.84 (2)	2.75 (1)	173 (1)	1 − *x*, *y* + 0.5, −*z*	1.0/0.61/1.0	F
O(2)6–D(2)6B···O(3)7		0.76 (4)	2.16 (4)	2.90 (1)	169 (3)	*x*, *y*, *z*	1.0/0.35/1.0	F
O(3)6–D(3)6A···O(6)1A	**b**	1.07 (3)	2.05 (4)	3.04 (3)	153 (2)	*x*, *y* + 1, *z*	1.0/0.45/0.41	
O(3)6–D(3)6B···OW3	**a**	0.96 (8)	2.22 (8)	3.18 (2)	172 (6)	*x*, *y* + 1, *z*	1.0/0.12/0.79	F
O(3)6–D(3)6C···O(2)5	**a**	0.96 (2)	1.84 (3)	2.80 (1)	171 (3)	*x*, *y*, *z*	1.0/0.20/1.0	F
O(6)6–D(6)6···O(6)3		0.95 (2)	1.98 (2)	2.87 (2)	154 (1)	*x*, *y*, *z* + 1	1.0/1.0/1.0	
O(2)7–D(2)7A···O(3)1		0.86 (2)	2.07 (2)	2.91 (1)	164 (2)	*x*, *y*, *z*	1.0/0.48/1.0	F
O(2)7–D(2)7B···O(3)3		1.00 (2)	1.86 (2)	2.79 (1)	152 (2)	1 − *x*, *y* − 0.5, −*z*	1.0/0.51/1.0	F
O(3)7–D(3)7A···O(2)6		0.97 (1)	1.96 (2)	2.90 (1)	163 (1)	*x*, *y*, *z*	1.0/0.63/1.0	F
O(3)7–D(3)7B···OW1		1.00 (2)	1.83 (1)	2.83 (1)	172 (2)	*x*, *y*, *z* + 1	1.0/0.38/1.0	F
O(6)7–D(6)7A···OW1		1.02 (2)	2.00 (2)	3.00 (1)	165 (1)	1 − *x*, *y* − 0.5, −*z*	1.0/0.55/1.0	F
O(6)7–D(6)7B···OW3		0.88 (3)	1.98 (3)	2.80 (2)	154 (3)	*x*, *y*, *z*	1.0/0.34/0.79	F
O(E1)–DO(E1)A···O(6)2A	**c**	1.11 (2)	2.11 (4)	3.16 (3)	156 (3)	*x*, *y* + 1, *z*	0.61/—/0.69	
O(E1)–DO(E1)B···O(3)1	**a**	0.86 (5)	1.89 (4)	2.74 (3)	176 (4)	1 − *x*, *y* + 0.5, −*z*	0.61/—/1.0	F
OW1–D1W1···O(3)7		0.97 (2)	1.86 (2)	2.83 (1)	172 (1)	*x*, *y*, *z* − 1	1.0/0.68/1.0	F
OW1–D2W1···O(2)2		0.85 (3)	2.01 (3)	2.83 (2)	163 (2)	*x*, *y*, *z*	1.0/0.45/1.0	F
OW1–D3W1···O(5)7		1.03 (2)	2.12 (3)	3.03 (1)	147 (2)	1 − *x*, *y* + 0.5, −*z*	1.0/0.38/1.0	F
OW1–D4W1···O(2)6		0.85 (3)	1.91 (4)	2.75 (1)	169 (2)	1 − *x*, *y* − 0.5, −*z*	1.0/0.50/1.0	F
OW2–D1W2···O(6)6		0.90 (3)	1.72 (2)	2.62 (2)	177 (2)	*x*, *y*, *z*	1.0/0.63/1.0	
OW2–D2W2···O(6)4	**b**	1.03 (3)	2.01 (3)	3.03 (2)	170 (3)	2 − *x*, *y* + 0.5, −*z*	1.0/0.77/1.0	
OW2–D3W2···O(2)4		0.89 (4)	2.00 (4)	2.88 (2)	169 (3)	2 − *x*, *y* − 0.5, −*z*	1.0/0.47/1.0	F
OW3–D1W3···O(6)7		1.02 (3)	1.82 (3)	2.80 (2)	158 (2)	*x*, *y*, *z*	0.79/0.48/1.0	F
OW3–D2W3···OW5		1.06 (3)	1.70 (3)	2.76 (2)	176 (2)	*x*, *y*, *z*	0.79/0.35/0.89	F
OW3–D3W3···O(2)3		0.87 (5)	1.95 (5)	2.74 (2)	151 (4)	*x*, *y* − 1, *z* + 1	0.79/0.15/1.0	F
OW3–D4W3···O(3)6	**b**	1.13 (4)	2.07 (4)	3.18 (2)	168 (3)	*x*, *y* − 1, *z*	0.79/0.27/1.0	F
OW4–D1W4···O(6)2A	**c**	1.11 (5)	2.11 (4)	3.16 (3)	156 (3)	*x*, *y* − 1, *z*	0.39/—/0.69	
OW4–D2W4···O(3)1	**a**	0.86 (5)	1.89 (4)	2.74 (3)	176 (4)	1 − *x*, *y* + 0.5, −*z*	0.39/—/1.0	F
OW4–D3W4···O(E2)	**c**	1.06 (4)	1.90 (6)	2.83 (5)	144 (4)	*x*, *y*, *z*	0.39/0.29/0.32	F?
OW5–D1W5···O(6)5		1.07 (3)	1.81 (2)	2.82 (2)	157 (2)	2 − *x*, *y* − 0.5, −*z*	0.89/0.98/1.0	
OW5–D2W5···OW3		0.96 (6)	1.82 (5)	2.76 (2)	164 (4)	*x*, *y*, *z*	0.89/0.29/0.79	F
OW5–D3W5···O(6)4	**b**	1.08 (5)	1.98 (5)	3.03 (3)	161 (4)	2 − *x*, *y* − 0.5, −*z*	0.89/0.78/1.0	F
OW6–D1W6···OW8	**c**	1.05 (6)	1.93 (6)	2.93 (6)	157 (4)	*x*, *y*, *z*	0.85/0.84/0.81	
OW6–D2W6···O(4)7	**a**	1.17 (8)	2.18 (6)	3.34 (5)	173 (5)	*x*, *y*, *z*	0.85/0.30/1.0	
OW6–D3W6···O(E2)	**c**	1.24 (7)	1.73 (6)	2.95 (5)	164 (6)	*x*, *y*, *z*	0.85/0.41/0.32	F?
OW7–D1W7···OW2		0.97 (2)	2.05 (2)	2.99 (2)	162 (2)	2 − *x*, *y* − 0.5, −*z*	0.93/0.98/1.0	
OW7–D2W7···O(3)5		0.97 (3)	1.94 (2)	2.92 (2)	178 (2)	*x*, *y* − 1, *z*	0.93/0.89/1.0	
OW8–D1W8···O(2)5	**a**	1.02 (7)	2.46 (4)	3.33 (5)	143 (4)	*x*, *y* − 1, *z*	0.81/0.47/1.0	F
OW8–D2W8···OW7	**a**	1.04 (8)	2.34 (5)	3.15 (4)	134 (5)	*x*, *y*, *z*	0.81/0.84/0.93	
OW9–D1W9···O(2)4	**a**	1.00 (6)	2.16 (5)	2.84 (5)	123 (4)	*x*, *y* − 1, *z*	0.47/0.47/1.0	
OW9–D2W9···O(6)2B	**c**	0.98 (7)	2.22 (6)	2.81 (6)	117 (5)	*x*, *y*, *z*	0.47/0.13/0.31	
OW9–D3W9···O(6)4	**c**	0.96 (9)	2.00 (7)	2.93 (5)	164 (8)	*x*, *y*, *z*	0.47/0.17/1.0	F

[a] Distances in Å, angles in deg, estimated standard deviations in parentheses. [b] For three-center hydrogen bonds only the parameters of the major component are given. [c] Symbol **a**, geometrical constraints during refinement applied on the donor group; **b**, geometrical constraints during refinement applied on the acceptor atom; and **c**, geometrical constraints during refinement applied on the donor group and the acceptor atom. [d] Occupation factors of donor oxygen atom, hydrogen atom, and acceptor atom. [e] Symbol F indicates hydrogen bonds which are involved in flip–flop disorder.

Table IV. Parameters of Three-Center Hydrogen Bonds[a] (D···O < 2.8 Å, Angle O–D···O > 90°)

bond	C[b]	O–D	D···A	O···A	O–D···A	A1···A2	A1··D··A2	sum[c]	symm
O(2)1–D(2)1A···O(3)2		0.90 (2)	2.14 (2)	3.00 (1)	161 (2)	2.84 (1)	79.9 (6)	352.9	x, y, z
O(2)1–D(2)1A···O(4)2			2.28 (2)	2.75 (1)	112 (1)				x, y, z
O(3)1–D(3)1A···O(E1)	b	0.96 (3)	1.84 (3)	2.74 (3)	158 (2)	3.37 (2)	96 (1)	350	$1 - x, y - 0.5, -z$
O(3)1–D(3)1A···O(2)1			2.64 (2)	2.91 (1)	96 (2)				x, y, z
O(3)1–D(3)1B···O(2)7		0.94 (2)	1.98 (2)	2.91 (1)	171 (2)	2.814 (9)	78.1 (6)	352.1	x, y, z
O(3)1–D(3)1B···O(4)1			2.45 (2)	2.82 (1)	103 (1)				x, y, z
O(6)1A–D(6)1A···O(E1)	c	0.87 (4)	2.23 (4)	3.07 (3)	159 (3)				$x, y - 1, z$
O(6)1A–D(6)1A···O(2)1	a		2.59 (3)	3.03 (2)	113 (3)	3.36 (2)	88 (1)	360	$1 - x, y - 0.5, -z$
O(6)1A–D(6)1A···O(5)1	a		2.69 (4)	2.86 (3)	93 (3)	3.16 (2)	79 (1)	331	x, y, z
O(6)1B–D(6)1B···O(E1)	c	0.97 (5)	1.88 (4)	2.85 (4)	173 (3)	3.16 (2)	87 (1)	335	$x, y - 1, z$
O(6)1B–D(6)1B···O(5)1	a		2.63 (2)	2.88 (2)	95 (2)				x, y, z
O(2)2–D(2)2A···O(3)3		0.88 (2)	1.97 (2)	2.82 (1)	164 (1)	2.78 (1)	82.2 (7)	355.2	x, y, z
O(2)2–D(2)2A···O(4)3			2.25 (2)	2.67 (1)	109 (1)				x, y, z
O(3)2–D(3)2B···O(2)1		0.87 (2)	2.14 (2)	3.00 (1)	166 (2)				x, y, z
O(3)2–D(3)2B···O(4)2			2.50 (2)	2.84 (1)	104 (1)	2.75 (1)	72.1 (6)	342.1	x, y, z
O(3)2–D(3)2B···O(6)1A	b		2.65 (2)	3.11 (2)	114 (2)	3.03 (2)	77.6 (8)	357.6	$1 - x, y + 0.5, -z$
O(2)3–D(2)3B···O(3)4		0.97 (5)	1.97 (5)	2.89 (1)	158 (4)	2.87 (1)	86 (2)	358	x, y, z
O(2)3–D(2)3B···O(4)4			2.25 (2)	2.79 (1)	114 (3)				x, y, z
O(3)3–D(3)3B···O(2)2		0.96 (3)	1.88 (3)	2.82 (1)	164 (2)	2.67 (1)	78.4 (8)	352.4	x, y, z
O(3)3–D(3)3B···O(4)3			2.30 (3)	2.78 (1)	110 (2)				x, y, z
O(2)4–D(2)4B···O(3)5		0.98 (2)	1.87 (3)	2.80 (1)	157 (2)	2.82 (1)	85 (1)	354	x, y, z
O(2)4–D(2)4B···O(4)5			2.29 (2)	2.81 (1)	112 (2)				x, y, z
O(3)4–D(3)4A···O(2)3		0.94 (2)	1.95 (2)	2.89 (1)	176 (1)	2.79 (1)	76.0 (5)	354.0	x, y, z
O(3)4–D(3)4A···O(4)4			2.52 (1)	2.87 (1)	102 (1)				x, y, z
O(6)4–D(6)4A···OW5	a	0.96 (2)	2.07 (3)	3.03 (3)	172 (2)	3.17 (2)	85.1 (9)	356.1	$2 - x, y + 0.5, -z$
O(6)4–D(6)4A···O(5)4	a		2.58 (2)	2.89 (2)	99 (1)				x, y, z
O(2)5–D(2)5A···O(3)6		0.92 (1)	1.91 (1)	2.80 (1)	161 (1)	2.803 (9)	82.0 (5)	350.0	x, y, z
O(2)5–D(2)5A···O(4)6			2.34 (1)	2.76 (1)	107 (1)				x, y, z
O(2)5–D(2)5B···OW8	b	1.00 (6)	2.36 (8)	3.33 (5)	165 (5)	3.16 (4)	81 (2)	345	$x, y + 1, z$
O(2)5–D(2)5B···O(3)5			2.51 (6)	2.85 (1)	99 (4)				x, y, z
O(3)5–D(3)5A···O(2)4		0.91 (1)	1.92 (1)	2.80 (1)	161 (2)	2.81 (1)	79.3 (6)	346.3	x, y, z
O(3)5–D(3)5A···O(4)5			2.43 (2)	2.82 (1)	106 (1)				x, y, z
O(6)5–D(6)5···OW7		1.01 (2)	1.78 (2)	2.79 (2)	176 (1)	3.14 (2)	87.6 (7)	359.6	$2 - x, y + 0.5, -z$
O(6)5–D(6)5···O(5)5			2.67 (1)	2.95 (1)	96.2 (8)				x, y, z
O(2)6–D(2)6B···O(3)7		0.76 (4)	2.16 (4)	2.90 (1)	169 (3)	2.833 (9)	76 (1)	350	x, y, z
O(2)6–D(2)6B···O(4)7			2.45 (4)	2.74 (1)	105 (3)				x, y, z
O(3)6–D(3)6C···O(2)5	a	0.96 (2)	1.84 (3)	2.80 (1)	171 (3)	2.76 (1)	81 (1)	360	x, y, z
O(3)6–D(3)6C···O(4)6	a		2.36 (3)	2.803 (9)	108 (3)				x, y, z
O(6)6–D(6)6···O(6)3		0.95 (2)	1.98 (2)	2.87 (2)	154 (1)	2.73 (1)	77.5 (5)	359.5	$x, y, z + 1$
O(6)6–D(6)6···O(5)3			2.36 (1)	3.04 (1)	128 (1)				$x, y, z + 1$
O(2)7–D(2)7A···O(3)1		0.86 (2)	2.07 (2)	2.91 (1)	164 (2)	2.82 (1)	78.4 (6)	355.4	x, y, z
O(2)7–D(2)7A···O(4)1			2.37 (2)	2.814 (9)	113 (2)				x, y, z
O(3)7–D(3)7A···O(2)6		0.97 (1)	1.96 (2)	2.90 (1)	163 (1)	2.74 (1)	76.0 (5)	342.1	x, y, z
O(3)7–D(3)7A···O(4)7			2.45 (1)	2.833 (9)	103.1 (9)				x, y, z
O(6)7–D(6)7A···OW1		1.02 (2)	2.00 (2)	3.00 (1)	165 (1)	3.03 (1)	89.0 (7)	358	$1 - x, y - 0.5, -z$
O(6)7–D(6)7A···O(5)7			2.31 (2)	2.75 (1)	104 (1)				x, y, z
OW1–D3W1···O(5)7		1.03 (2)	2.12 (3)	3.03 (1)	147 (2)	2.75 (1)	78.7 (9)	358.8	$1 - x, y + 0.5, -z$
OW1–D3W1···O(6)7			2.21 (3)	3.00 (1)	133 (2)				$1 - x, y + 0.5, -z$
OW7–D1W7···OW2		0.97 (2)	2.05 (2)	2.99 (2)	162 (2)	3.33 (2)	87.7 (9)	357.7	$2 - x, y - 0.5, -z$
OW7–D1W7···O(5)5			2.70 (2)	3.14 (2)	108 (2)				$2 - x, y - 0.5, -z$

[a] Distances in Å, angles in deg, estimated standard deviations in parentheses. [b] Symbol **a**, geometrical constraints during refinement applied on the donor group; **b**, geometrical constraints during refinement applied on the acceptor atom; **c**, geometrical constraints during refinement applied on the donor group and the acceptor atom. [c] Sum of the angles at D (=360° for a planar arrangement).

cooling from 1.98 Å ($T = 295$ K) to 1.87 Å ($T = 15$ K), indicating increased strength of the hydrogen bonds.

A list of short O···O contacts <3.5 Å, which would be suggestive of hydrogen bonds in an X-ray study but definitely are *not* engaged in a hydrogen bond in our neutron structure, is given in Table XII (supplementary material). They indicate that one has to be careful in the interpretation of hydrogen bonds from O···O distances if the hydrogen atoms are not located.[35]

The X-ray structure was analyzed for hydrogen bonds employing the usual 3.2-Å cutoff criterion for $d_{O\cdots O}$, Table XIV (supplementary material).

(f) Hydrogen Bonding in the β-CD Cavity. For both positions of the ethanol molecule, individual networks of hydrogen bonds can be assigned in the β-CD cavity. The arrangements are energetically disadvantageous due to sterical restrictions of the cavity and lead to considerable mobility of the enclosed molecules in the

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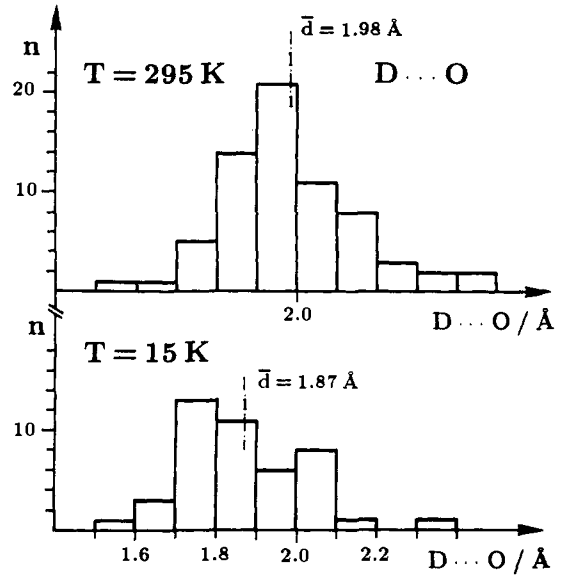

Figure 5. Distribution of the D···O distances for all hydrogen bonds at T = 295 K (top) and T = 15 K (bottom). For three-center hydrogen bonds, only the major components were included.

crystalline state, as indicated by relatively high temperature factors (Table V.1, supplementary material).

In the major site the ethanol molecule has only van der Waals contacts with the three enclosed water molecules W6, W8, and W9, see Figures 2 and 3. Two of these, W6 and W8, form a short hydrogen-bonded chain parallel to the β-CD molecular axis, which at both ends terminates at rims of neighboring β-CD molecules. W8 also donates a hydrogen bond to W7, which is located outside the cavity, and W6 donates a hydrogen bond to the glycosidic oxygen atom O(4)7 of the cavity wall with $d_{D\cdots O}$ = 2.18 (6) Å (Table III). This bond is not observed in the X-ray structure, where OW6···O(4)7 is 3.65 Å. Similar hydrogen bonds between water molecules and O(4) atoms have been observed in β-CD·11D$_2$O at T = 293 K[7] (OW8–DW8A···O(4)3 with $d_{D\cdots O}$ = 2.12 (3) Å) and T = 120 K[8] (OW9–DW9A···O(4)6 with $d_{D\cdots O}$ = 2.04 (1) Å) and very recently in γ-CD·15.7D$_2$O at T = 110 K[36] (OW13B–DW13B···O(4)5 with $d_{D\cdots O}$ = 2.34 (7) Å), indicating that such bonds to the cavity wall are not as rare as previously assumed. The third water molecule, W9, forms no hydrogen bonds with other solvent molecules but with the primary hydroxyl groups O(6)2B–D and O(6)4–D of the host molecule, which are turned "inward" ((+)-gauche conformation), and with O(2)4–D of a neighboring β-CD molecule.

For the minor site of the ethanol there are more hydrogen-bonding interactions within the cavity, see Figure 3. On the average these hydrogen bonds are relatively weak; for the chain W4–O(Et)–W6–W8–W7 a mean O···O distance of 2.97 Å is observed. Upon cooling to T = 15 K the enclosed molecules approach each other, and we observe a mean O···O distance of 2.80 Å.

(g) Three-Center Hydrogen Bonds. Three-center hydrogen bonds can be either symmetrical with two comparable H···O distances or unsymmetrical, with the shorter distance called the major component and the longer distance the minor component. In this analysis we have included minor components with $d_{D\cdots O}$ < 2.8 Å, which is slightly larger than the sum of van der Waals radii, 2.6 Å, and angles O–D···O > 90°. As weak hydrogen bond interactions have a major Coulombic component, such a cutoff criterion inevitably is somewhat arbitrary and will exclude some weak minor components. According to our criterion, out of 68 symmetry independent hydrogen bonds in this crystal structure, 22 (=32%) are defined as three-center and two (=3%) as four-center, with parameters listed in Table IV; several examples are shown in Figures 6 and 7. The proportion of three-centered hydrogen bonds is slightly higher than the 25% in crystal structures of simple carbohydrates,[37] which in most cases do not contain water molecules (in reference 37 a 2.85-Å cutoff criterion was used). All of the oxygen atoms accept major or minor hydrogen-bonding components except for O(5)2 and O(5)6, which do not act as acceptors.

The intramolecular interglucose O(2)···O(3) hydrogen bonds have a relatively strong minor component to the corresponding glycosidic O(4) atom, see Figures 4 and 6. The D···O(4) distances vary from 2.25 to 2.52 Å and are on average slightly shorter for O(2)2–D···O(3) bonds ($\bar{d}$ = 2.32 Å) than for O(3)–D···O(2) bonds ($\bar{d}$ = 2.43 Å). The three-center character of interglucose O(2)···O(3) hydrogen bonds is inherent to the stereochemistry of the β-CD molecule.

Due to stereochemical restrictions, major intraresidue hydrogen bonding components between O(2) and O(3) of the *same* glucose cannot be formed. In this crystal structure, two corresponding minor components of three-center hydrogen bonds are found: O(2)1 accepts a minor component from O(3)1–D(A), see Figure 4, and O(3)5 accepts a minor component from O(2)5–D(B), see Figures 4 and 6. Minor components of this kind were not observed at T = 15 K.

If the primary hydroxyl group O(6)–D is oriented appropriately, an intraresidue minor hydrogen-bonding component to the ring oxygen O(5) of the same glucose residue can be formed, as we reported earlier[17] for the first time in a crystalline cyclodextrin complex. In the present structure, five such three-center bonds are found, see Figures 4, 6, and 7. This type of minor component occurs in both orientations of the C(6)–O(6) bond, (−)-gauche for O(6)1A, O(6)5, and O(6)7 and (+)-gauche for O(6)1B and O(6)4.

There are only three three-center bonds where both components are intermolecular: O(6)6–D···O(6)3 major, O(5)3 minor; the almost symmetrical OW1–D···O(5)7 major, O(6)7 minor; and OW7–D1W7···OW2 major, O(5)5 minor (Table IV).

In two cases three acceptor atoms satisfy our criterion for a hydrogen bond, with the donor groups O(6)1A–D and O(3)2–D(B), see Table IV. In both cases all three components have D···O distances over 2.1 Å and hence are relatively weak.

(h) Short Contacts of O Atoms to O(5) and O(6) of the Same Glucose Are Indicative of Three-Center Hydrogen Bonding. To our surprise, we noticed that all contacts <3.5 Å between hydroxyl or water oxygen atoms to O(5) and O(6) of the *same* glucose are three-center hydrogen bonds. In order to see whether this is systematic, the available five other cyclodextrin neutron structures[5,7,8,17,36] were analyzed (Table XV, supplementary material). Out of 31 such contacts, 28 (=90%) are actually of the three-center type, two are purely two-center, and only one, with O···O(5) = 3.33 Å and O···O(6) = 3.12 Å, shows no hydrogen bond. Of the 28 three-center hydrogen bonds, 11 (=39%) have "strong" minor components with D···O < 2.6 Å shorter than the sum of van der Waals radii, and 17 (=61%) have weak minor components with 2.6 < D···O < 2.8 Å.

In 16 (=57%) of the 28 three-center interactions, O(6) is donor and O(5) accepts an intraresidue minor component (as O(6)5 in Figure 4), and in 10 (=36%) the contacting hydroxyl or water oxygen donotes a chelating three-center bond (as O(6)6 to glucose O(5)3, O(6)3 in Figure 4) with the major component seven times to O(6) and three times to O(5); in two cases (=7%) there is orientational disorder, as for O(6)7···W1 in Figure 4 (left).

In all six structures there are only two exceptional cases, where a water molecule bridges O(6) and O(5) by acting simultaneously as donor and acceptor, as O(6)5–D···OW7–D(A)···O(5)5 in Figure 6 (left), with D(A)···O(5), 2.70 Å the minor component of a three-center bond.

These observations suggest that simultaneous contacts <3.5 Å of a hydroxyl or water oxygen to O(5) and O(6) of a given glucose residue in cyclodextrins are indicative for a corresponding three-center hydrogen bond with a probability of about 90%. This

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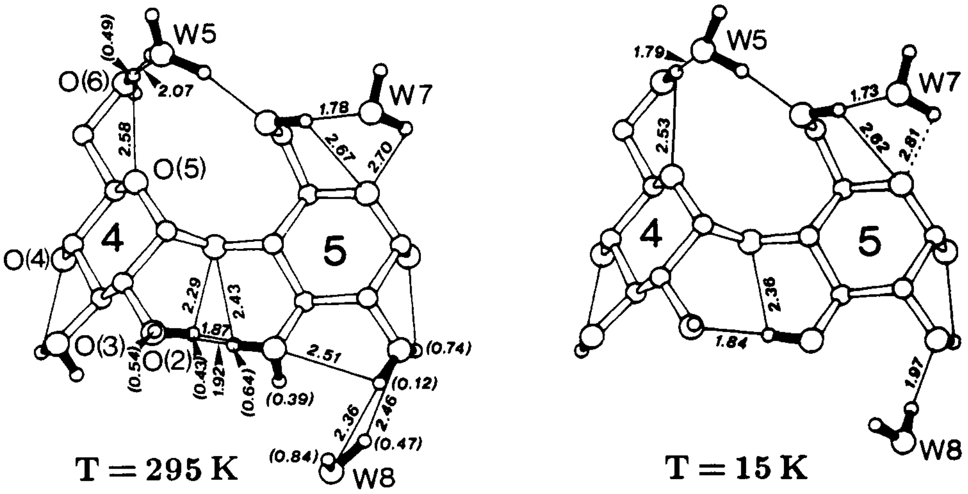

Figure 6. One example of flip-flop and three-center hydrogen bonds: the glucose residues 4 and 5 at T = 295 K (left) and T = 15 K (right). For disordered D atoms, occupation factors are given in parentheses, numbers give D···O distances in Å units. Note the flip-flop hydrogen bonds O(6)4–$^1/_2$D···$^1/_2$D–OW5, O(2)4–$^1/_2$D···$^1/_2$D–O(3)5 and the intraglucose component O(2)5–$^1/_2$D···O(3)5, which disappears at T = 15 K.

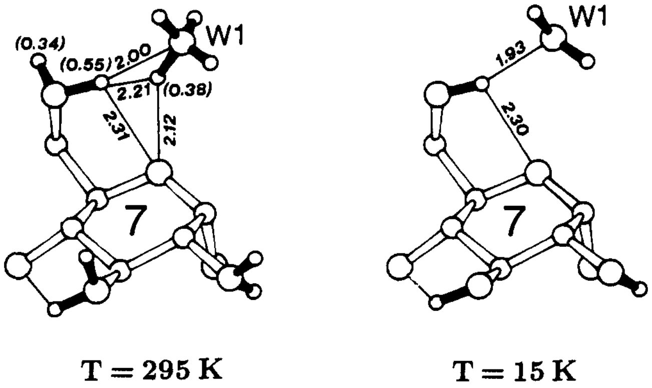

Figure 7. The three-center hydrogen bond between W1, O(6)7, and O(5)7 at T = 295 K (left) and T = 15 K (right). At T = 295 K, W1 and O(6)7-D are orientationally disordered and engaged in a flip-flop hydrogen bond; occupation factors are given in parentheses. The three-center bond donated from W1 to O(5)7 and O(6)7 at T = 295 K is almost symmetrical. Numbers give D···O distances in Å units.

might be helpful for X-ray analyses of cyclodextrin complexes, where the hydrogen positions often cannot be located, and simultaneous short contacts to O(5) and O(6) were thus far disregarded.

Short simultaneous contacts of oxygen atoms to O(5) and O(6) are not specific for cyclodextrin complexes but have also been observed, for example, in the crystal structure of the linear hexasaccharide (p-nitrophenyl α-maltohexaoside)$_2$·Ba(I$_3$)$_2$·27H$_2$O, where this effect was called *chelation* of water molecules between O(6) and O(5).[38] As H atoms could not be located, the nature of the hydrogen bonding was not clear. As the O(5)···O···O(6) geometries (see Table XV, supplementary material) are practically identical in the hexasaccharide and the cyclodextrin neutron structures, we suppose that this *chelation* in most cases is due to the formation of three-center hydrogen bonds rather than to bonding of the type O(6)–H···O(X)–H···O(5). We also suggest that this type of three-center hydrogen bonds is a more general structural characteristic of related, hydrated oligo-(and poly-)saccharides.

(i) Orientational Flip-Flop Disorder of Hydroxyl Groups and Water Molecules. Of the 21 β-CD hydroxyl groups, 16 display orientational flip-flop disorder. These are two O(6)–D groups, of glucoses 4 and 7, and all seven O(2), O(3) hydroxyls. Fifteen of these O–D groups have two and O(3)6–D has three discrete positions for the hydrogen atom. The D occupation factors, which were refined independently with accuracies around ±0.03, sum up to about 1.0, Table III. Of the nine water sites, two have four partially occupied hydrogen positions in roughly tetrahedral arrangement (W1 and W3); five have three D positions (W2, W4, W5, W6, and W9), and of these, three have one D position with the same occupation as the oxygen (W5, W6, and W9); for W7 and W8 only two D positions were located; the latter, however, must have at least one more D position, see section (e). In this crystal structure, *all* D positions are engaged in hydrogen bonds.

The alternative sites are not exactly half-occupied, and for many of the disordered groups one orientation is significantly preferred to the other(s). In order to determine the distribution of occupation factors shown in Figure 8 (supplementary material), a weighted occupation factor occ$_w$(D) = occ(D)/occ(O) was introduced, because some donor groups are positionally disordered as a whole. The spread of the occupation factors around the average of occ$_{mean}$(D) = 0.48 (2) is symmetrical with a root-mean-square deviation (rms deviation) of 0.17.

Reorientational motions for this kind of disorder are rotational jumps of water molecules and of hydroxyl groups. Each disordered group has its own specific jump angle and jump distance of the hydrogen atoms; this is illustrated by the distribution of D···D jump distances in Figure 9 (supplementary material), which peaks around a mean jump distance $\bar{d}$ = 1.56 (3) Å, rms deviation = 0.18 Å, and the corresponding mean jump angle $\bar{\alpha}$ is 110 (3)°, rms deviation = 17°. These results parallel those for β-CD·11D$_2$O,[7] where further analysis of the published data yields a similar but slightly sharper distribution of D occupation factors, occ$_{mean}$(D) = 0.49 (2), rms deviation = 0.12, and a mean jump distance $\bar{d}$ = 1.55 (2) Å, rms deviation = 0.13 Å.

(j) The Hydrogen Bonding Network. All hydrogen bonds of this crystal structure are interconnected to form an infinite spatial network. Due to the extensive disorder, it is not feasible to describe this network in terms of infinite structural elements extending through the whole crystal, as we have done for the structure determined at T = 15 K.[17] It is better to consider local arrangements of hydrogen bonds, as shown in Figure 3 for the molecules enclosed in the β-CD cavity. Another interesting arrangement is the combination of two four-membered hydrogen-bonding rings with almost square geometries shown in Figure 10. Four-membered rings are frequently found in crystal structures of cyclodextrin complexes.

Two examples of hydrogen-bonding networks are schematically shown in Figure 11 for both temperatures. Figure 11a represents the surrounding of an "infinite" chain of flip-flop hydrogen bonds winding along the crystallographic screw axis at $x = {}^1/_2$, $z = {}^1/_2$ (W1 ↔ O(3)7 ↔ O(2)6 ↔ W1′). All oxygen atoms are ordered, but the O–D bonds are disordered at T = 295 K. Upon cooling to T = 15 K, the disorder disappears, the oxygen atoms remain in very similar positions, and an ordered system of cooperative hydrogen bonds in homodromic[4] arrangement is formed. Figure 11b shows the two four-membered rings and their surroundings

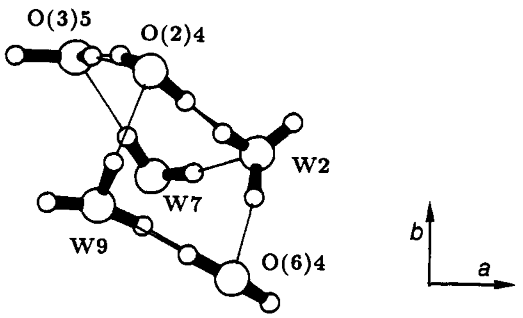

Figure 10. A system of two four-membered hydrogen bonding rings of almost square geometry. Also see Figure 11b. Water position W9 is only 47% occupied.

involving ordered, orientationally disordered, and positionally disordered groups. It is the average of several local hydrogen-bonding networks, which are determined by the various combinations of the occupationally disordered groups being present or not. Upon cooling to T = 15 K, the three partially occupied sites O(6)1B, O(6)2B, W9, and the flip-flop disorder disappear, leading to a much simpler and ordered arrangement.

(k) Summary. (1) With two different crystals, a neutron and an X-ray crystal structure of partially deuterated β-CD ethanol octahydrate were determined at room temperature with resolution ~0.9 Å.

(2) The β-CD molecules are arranged in a herringbone fashion; the molecular cavities are isolated from each other and form separate cages. Each cage contains one ethanol and three water molecules; five water molecules per β-CD molecule are placed in interstices between the macrocycles.

(3) In the neutron structure, the ethanol molecule is disordered over two discrete sites with occupation factors ~0.61 and ~0.32, and the three water molecules enclosed in the β-CD cage over are disordered four discrete sites. For both ethanol sites, the hydrogen-bonding network in the cage was assigned. A water molecule forms a hydrogen bond with a glycosidic O(4) atom of the cavity wall.

(4) Orientational disorder of the *flip-flop* type is observed for 16 of the 21 β-CD hydroxyl groups and for seven of the nine water sites. Furthermore, two $CH_2(6)$–O(6) groups are orientationally disordered.

(5) The different types of disorder parallel those found in β-CD undecahydrate. In both crystal structures, they almost completely disappear upon cooling.

(6) If a 2.8-Å cutoff criterion is used for $d_{D\cdots O}$, 32% of the hydrogen bonds are of the three-center and 3% of the four-center type.

(7) The analysis of six cyclodextrin neutron structures showed that simultaneous contacts <3.5 Å of a hydroxyl or water oxygen atom to O(5) and O(6) of the same glucose are indicative of three-center hydrogen bonding with ~90% reliability. If in such a three-center bond O(6) is the donor, O(5) accepts the minor component; if the contacting oxygen is the donor, O(5) can accept a major component as well as O(6).

(8) Significant differences were found between the neutron and the X-ray structure. For the ethanol molecule enclosed in the β-CD cavity, a fully occupied site was observed in the X-ray structure, while two partially occupied sites were found in the neutron structure. This correlates with different hydrogen-bonding patterns in the β-CD cavity. The hydrogen bond of an enclosed

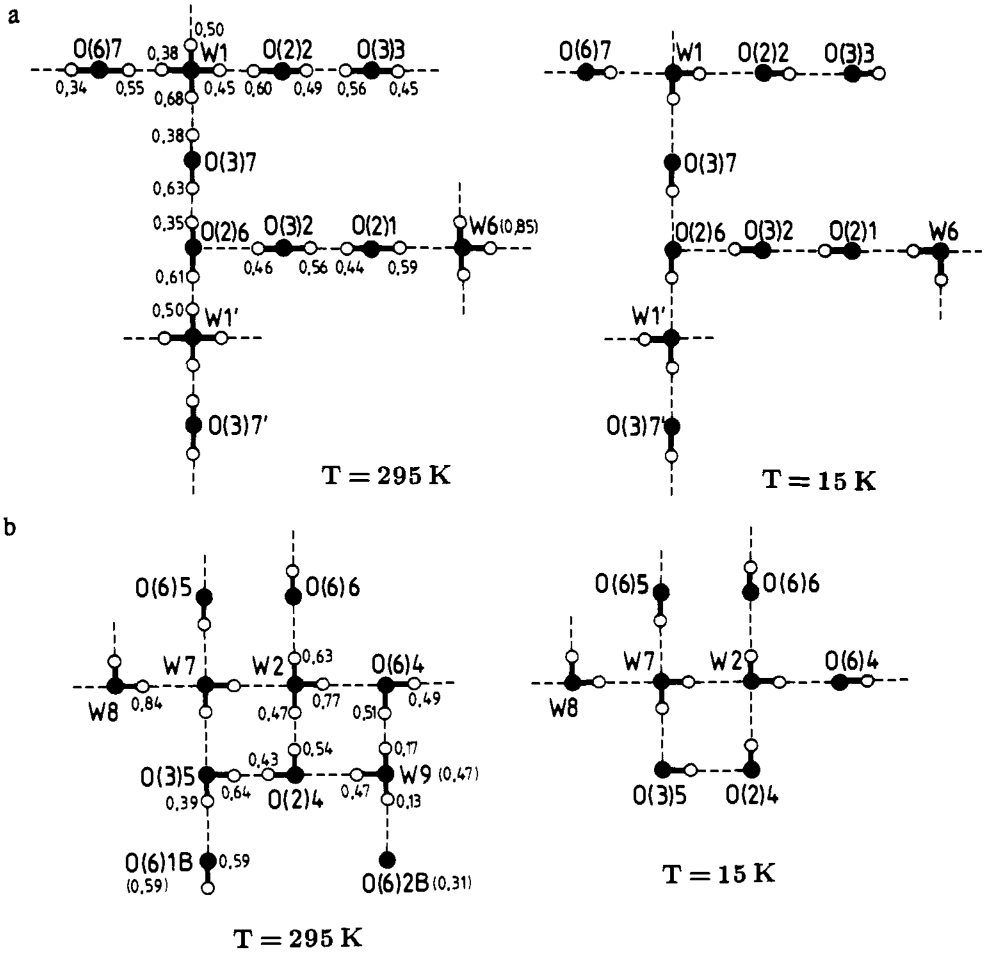

Figure 11. Two sections of the hydrogen-bonding network at T = 295 K (left) and T = 15 K (right), with occupation factors in parentheses. (a) The infinite flip-flop chain W1···O(3)7···O(2)6···W1′ (in our previous report[17] called chain D) and its surroundings: Adjacent symmetry-equivalent atoms are produced by the $P2_1$ screw operation. (b) The two four-membered rings and their surroundings: see also Figure 10 (W7···O(3)5···O(2)4···W2···W7 was called ring H in our previous report[17]). At T = 15 K (right), atom sites W9, O(6)1B, and O(6)2B have disappeared.

water molecule to an O(4) atom of the cavity wall was not found in the X-ray structure, and the occupation factors for the disordered $CH_2(6)$–O(6) groups are different. These differences may be due to slight variations in the conditions of crystallization or to the different history after crystallization. They show that even in crystal structures of this size hydrogen-bonding networks may be unique to each individual crystal.

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Supplementary Material Available: Listings of atomic coordinates, equivalent isotropic temperature factors, occupation factors, anisotropic temperature factors, individual bond distances and angles, torsion angles, Cremer and Pople ring puckering parameters for both the neutron and X-ray structures, a list of short O···O contacts not involved in hydrogen bonding, hydrogen bond parameters for the X-ray structure, a list of short contacts of oxygen atoms to O(5) and O(6) of the same glucose for six neutron and two X-ray structures, and figures showing the distributions of D occupation factors and D···D jump distances (37 pages); tables of measured and calculated structure factor amplitudes for the neutron and the X-ray structure (49 pages). Ordering information is given on any current masthead page.

Calibration of a New Horologery of Fast Radical "Clocks". Ring-Opening Rates for Ring- and α-Alkyl-Substituted Cyclopropylcarbinyl Radicals and for the Bicyclo[2.1.0]pent-2-yl Radical[1]

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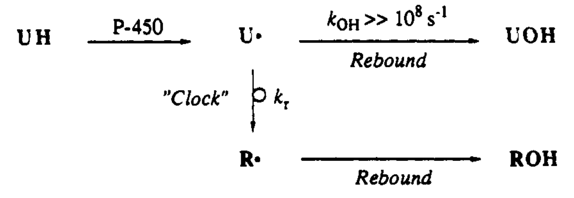
Abstract: Rate constants have been determined at 37 °C for the ring opening of a variety of alkyl-substituted cyclopropylcarbinyl radical "clocks" by nitroxide radical trapping (NRT) using TEMPO. Relative yields of unrearranged and rearranged trialkylhydroxylamines were measured at various TEMPO concentrations, and these data were then combined with absolute rate constants for the reactions of structurally appropriate alkyl radicals with TEMPO as determined by laser flash photolysis. Cyclopropylcarbinyl radicals, including the bicyclo[2.1.0]pent-2-yl radical, were generated by H-atom abstraction from the parent hydrocarbon and, in a few cases, also from the appropriate diacyl peroxide. Twelve substrates yielded sixteen clock reactions because some cyclopropylcarbinyls can undergo two different ring-opening reactions. For six methyl-substituted cyclopropylcarbinyls rate constants ranged from 0.8×10^8 s^{-1} for 1-methylcyclopropylcarbinyl to 47×10^8 s^{-1} for pentamethylcyclopropylcarbinyl. Rate constants for the ring opening of cyclopropylcarbinyl, α-methyl- and α,α-dimethylcyclopropylcarbinyl are 1.2, 0.70, and 0.88×10^8 s^{-1}, respectively. Rate constants for H-atom abstraction by *tert*-butoxyl from various positions in the 12 cyclopropane substrates relative to the rate of H-atom abstraction from cyclopentane have also been determined by using competitive NRT.

In connection with an investigation[3] of the detailed mechanism of the cytochrome P-450-catalyzed hydroxylation of alkanes, we required a number of very fast radical rearrangements ($U^\bullet \rightarrow R^\bullet$) or clocks[4] with rate constants in excess of 10^8 s^{-1} at the in vivo temperature of 37 °C (Scheme I). The additional requirements were that the rearrangement rate constants could be measured, i.e., that the clocks could be "calibrated", and that hydrogen atom abstraction by the activated cytochrome P-450 ($UH \rightarrow U^\bullet$) should lead to simple product mixtures, preferably via a *single* initial radical species. To meet all these requirements we chose symmetrically alkyl-substituted cyclopropanes for our clock substrates (UH).

Scheme I



Calibration of the unimolecular ring openings of ring-substituted cyclopropylcarbinyl radicals by competition with a bimolecular radical-trapping reagent requires not only an extremely efficient radical trap but also a radical trap that can be used at high concentrations. For instance, Pereyre, Davies, and co-workers[5] have shown that ring openings of both the *trans*- and *cis*-2-methylcyclopropylmethyl radicals[6] (**1b**• and **1c**•) are, unlike **1a**•[8] (see Figure 1), too fast to calibrate by the stannane reduction method[9]—only products from the rearranged radicals being observed. Scission of the internal bond of the bicyclo[2.1.0]pent-2-yl

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[1] Issued as NRCC No. 32835.

[2] NRCC Research Associate, 1988–1990.

[3] Bowry, V. W.; Ingold, K. U., following paper in this issue.

[4] Griller, D.; Ingold, K. U. *Acc. Chem. Res.* **1980**, *13*, 317–323.

[5] (a) Castaing, M.; Pereyre, M.; Ratier, M.; Blum, P. M.; Davies, A. G. *J. Chem. Soc., Perkin Trans. 2* **1979**, 287–292. (b) Ratier, M.; Pereyre, M.; Davies, A. G.; Sutcliffe, R. *J. Chem. Soc., Perkin Trans. 2* **1984**, 1907–1915.

[6] These two radicals rearrange too rapidly to be measured by the "conventional"[7] steady-state EPR method.

[7] Maillard, B.; Forrest, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1978**, *98*, 7024–7026.

[8] Kinney, R. J.; Jones, W. D.; Bergman, R. G. *J. Am. Chem. Soc.* **1978**, *100*, 7902–8015.

[9] However, this method can, apparently, be "pushed" even further, i.e., can be used to calibrate clock radicals which rearrange even more rapidly than **1b**• and **1c**•. See: Lemieux, R. P.; Beak, P. *J. Org. Chem.* **1990**, *55*, 5454–5460.

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