Cooperative O–H···O Hydrogen Bonds in β-Cyclodextrin–Ethanol–Octahydrate at 15 K: A Neutron Diffraction Study[†]

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Abstract: A single crystal neutron crystallography study of β-cyclodextrin–ethanol–octahydrate was carried out at $T = 15$ K. The composition is $(C_6H_7O_5D_3)_7 \cdot C_2D_5OD \cdot 8D_2O$ with space group $P2_1$ and cell constants $a = 20.460$ (1) Å, $b = 10.003$ (1) Å, $c = 15.227$ (1) Å, $\beta = 109.023$ (4)°, $\lambda = 1.3167$ Å, 4264 unique neutron data, and nominal resolution 0.93 Å ($2\theta = 90°$). All H and D atoms are located and the structure is refined to $R = 4.1\%$. All hydroxyl groups, the ethanol, and six water molecules are well ordered, two water molecules are disordered—in contrast to the room temperature structure, where orientational disorder of hydroxyl groups and extensive disorder of the ethanol and several water molecules is observed and gives rise to flip-flop hydrogen bonds. This ordering upon cooling indicates that the disorder at room temperature is of dynamic and not of static nature. At 15 K all hydrogen bonds in the structure are interconnected to form an infinite ordered network extending through the crystal. Water molecules (except W6 and W8 which are located in the β-cyclodextrin cavity) accept two hydrogen bonds and the hydroxyl groups accept one except for O(2)H of glucoses 3, 5, and 6 which accept two hydrogen bonds and O(3)4 which acts only as donor. Homodromic arrangements of hydrogen bonds dominate and show the strong influence of the cooperative effect. The general observations concerning hydrogen bond patterns are similar to those in β-cyclodextrin undecahydrate, indicating that these characteristics are not unique but are an intrinsic feature of β-cyclodextrin complexes. There is systematic three-center hydrogen bonding with the minor components intramolecular, O(6)H···O(5) in five glucoses and O(2)H···O(4′) or O(3)H···O(4) in all seven glucoses, with the major component intramolecular interresidue O(2)H···O(3) or O(3)H···O(2), with a distribution of 4 to 3. The included ethanol and three water molecules form hydrogen bonds between themselves and the adjacent β-cyclodextrin molecules but are not in hydrogen-bonding contact with the host cavity. This contrasts β-cyclodextrin·11H$_2$O where the included cluster of eight water molecules forms two hydrogen bonds to O(6) hydroxyls.

Introduction

The ring-shaped cyclodextrins are a family of cyclic oligosaccharides consisting of six (α-CD), seven (β-CD), or eight (γ-CD) D-glucoses connected by α(1–4) linkages. In aqueous solution, they form inclusion complexes with guest molecules small enough to fit into their cavities; the complexes readily crystallize and can be studied by diffraction techniques.[1,2] As each of the fused glucoses has three free hydroxyl groups, the crystal structures of CDs and their complexes, which always contain several water molecules, exhibit complicated networks of interconnected O—H···O hydrogen bonds. Because the crystals grow readily to the size required for neutron diffraction work, they permit the study of hydrogen bonding in great detail and accuracy.[3]

In the crystal structure of α-CD·6H$_2$O, a well-ordered system of hydrogen bonding cycles and chains is observed where the O—H···O—H···O—H etc. hydrogen bonds all point in the same direction, which is called homodromic. When a water molecule donates two hydrogen bonds in a cycle or chain so that the hydrogen-bonding directions are opposite, it is called antidromic. There are rare cases where there is no defined direction of hydrogen bonding, which is described as heterodromic.[4,5] The situation is more complex with β-CD·11D$_2$O where at room temperature ($T = 295$ K) the 11 water molecules per asymmetric unit are disordered over 16 positions of which only three are fully occupied.[6,7] In addition, systems of orientationally disordered hydrogen bonds are observed, where the hydrogen atom positions are only half occupied ("flip-flop hydrogen bonds"):
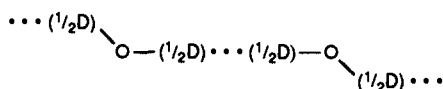
A calorimetric study of the nondeuterated compound indicated an exothermic phase transition at 227 K.[8] A neutron diffraction study carried out well below this temperature, at 120 K,[9] showed that these hydrogen bonds order upon cooling, while the packing of the β-CD molecules remains unchanged. As it is unlikely that static disorder transforms to order upon cooling, the disorder is of the dynamic type, where the hydroxyl groups and water molecules perform rotational jumps. This was supported by a quasielastic neutron scattering experiment that showed local proton diffusion on a time scale of $10^{10}–10^{11}$ per s.[10,11] Therefore the crystallographic observation of these hydrogen bonds has to be regarded as the space and time average over the two states
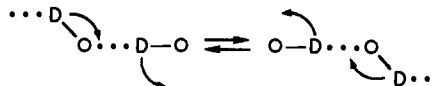
In β-CD·11D$_2$O at room temperature, intramolecular interresidue flip-flop hydrogen bonds are systematically formed between O(2) and O(3) hydroxyl groups. In order to study whether this

[†] Part 25 of the series Topography of Cyclodextrin Inclusion Complexes. Part 24: Steiner, Th.; Hinrichs, W.; Saenger, W.; Hoyer, G. A. *Carbohydr. Res.* 1989, *192*, 43–49. Part 23: Zabel, V.; Saenger, W.; Mason, S. A. *J. Am. Chem. Soc.* 1986, *108*, 3664–3673.
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(1) Saenger, W. *Angew. Chem., Int. Ed. Engl.* 1980, *19*, 344–362.
(2) Huber, O.; Szejtli, J. *Proceedings of the IV International Symposium on Cyclodextrins*; München, 1988; Kluwer Academic Publishers: Dordrecht.
(3) Jeffrey, G. A.; Saenger, W. *Hydrogen Bonding in Biological Structures*; Springer-Verlag, in press.
(4) Saenger, W. *Nature (London)* 1979, *279*, 343–344.
(5) Klar, B.; Hingerty, B. E.; Saenger, W. *Acta Crystallogr. Sect. B* 1980, *B36*, 1154–1165.
(6) Saenger, W.; Betzel, Ch.; Hingerty, B. E.; Brown, G. M. *Nature (London)* 1982, *296*, 581–583.
(7) Betzel, Ch.; Saenger, W.; Hingerty, B. E.; Brown, G. M. *J. Am. Chem. Soc.* 1984, *106*, 7545–7557.
(8) Fujiwara, T.; Yamazaki, M.; Tomizu, Y.; Tokuoka, R.; Tomita, K.-I.; Saenger, W. *J. Chem. Soc. Jpn.* 1983, *2*, 181–187.
(9) Zabel, V.; Saenger, W.; Mason, S. A. *J. Am. Chem. Soc.* 1986, *108*, 3664–3673.
(10) Steiner, Th.; Saenger, W.; Kearley, G.; Lechner, R. E. *Physica B* 1989, *156 & 157*, 336–338.
(11) Steiner, Th.; Saenger, W.; Lechner, R. E. In preparation.

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

	a, Å	b, Å	c, Å	$β$, deg	V, Å³
X-ray[b]	21.115	10.190	15.214	111.4	3048
neutron[c]					
T = 295 K initial	21.125 (2)	10.212 (1)	15.215 (2)	111.47 (1)	3054
T = 15 K	20.460 (1)	10.003 (1)	15.227 (1)	109.023 (4)	2946
T = 295 K rewarmed	21.15 (1)	10.221 (5)	15.23 (1)	111.45 (4)	3063

[a] Estimated standard deviations in parentheses. [b] Nondeuterated.[12]
[c] Partially deuterated, this work.

is accidental or whether these orientationally disordered hydrogen bonds are a structural characteristic of β-CD, we have performed the present neutron diffraction analysis of an inclusion complex, β-CD·EtOD·8D₂O. Its structure has been determined previously by X-ray methods, but the positions of the hydrogen atoms could not be located for technical reasons.[12] The room temperature neutron diffraction data of this complex show unequivocally that the intramolecular flip-flop hydrogen bonds are indeed formed, suggesting that they are an intrinsic property of β-CD (to be published). The ethanol and several water molecules are badly disordered. A calorimetric study (DTA and DSC) has shown an exothermic phase transition at 236 K[8] in the nondeuterated compound. In order to see whether we would observe ordering upon cooling as in β-CD·11H₂O, we proceeded with a low-temperature study at 15 K. In the present contribution we describe the crystal structure of this β-CD·EtOD·8D₂O complex at 15 K and give an analysis of the hydrogen-bonding network.

Experimental Section

β-CD (Serva, Heidelberg) was dissolved in hot ($T \sim 70$ °C) D₂O. After the mixture was cooled, the solvent was removed in a rotary evaporator. This process was repeated five times in order to exchange the hydroxyl H atoms by D and hence to reduce the incoherent neutron scattering contribution of protons. Crystals were grown from a hot, saturated solution of β-CD in a one-to-one mixture of D₂O and C₂D₅OD, which was slowly cooled in a Dewar flask filled with hot water.

A 6-mm³ crystal was mounted with some mother liquor in a quartz capillary and mounted on the D19 diffractometer equipped with an area-detector (with 4° × 64° aperture) at the high-flux reactor of the Institut Laue-Langevin, Grenoble. After collection of a room temperature data set, the crystal was kept in the capillary for three months and then remounted for a low-temperature measurement employing a cryo-refrigerator on the same instrument. For this purpose, the mother liquor surrounding the sample had to be removed as completely as possible. The crystal was cooled slowly (~5 h) to T = 15 K. The unit cell at 15 K differed substantially from that at room temperature. Apart from the (expected) shrinkage in unit cell dimensions, there was a significant change in the angle $β$ (Table I), which we associate with the phase transition observed in the calorimetric study at 236 K.[8]

Neutron diffraction data of some 6500 reflections were measured at 15 K in equatorial and normal-beam geometry with a wavelength of 1.3167 Å. Symmetry-equivalent reflections were averaged to yield a data set consisting of 4264 unique reflections of which only 57 have values of $F^2 < σ(F^2)$; 131 have values of $F^2 < 2σ(F^2)$. The merging R factors on F^2 are 3.7% on repeated measurements and 3.83% on equivalent reflections. Extinction corrections were not applied. The data are essentially complete to a nominal resolution of 0.93 Å ($2θ$ = 90°), with some 320 additional reflections to $2θ$ = 97°. When the crystal was warmed to room temperature after the measurement, the unit cell constants were remeasured and gave only small changes relative to the initial values (Table I).

Structure Determination and Refinement. The atom positions of the β-CD molecule in the 11D₂O crystal structure[7] were used to initiate full-matrix least-squares refinement[13] carried out on blocks of about 500 variables, where the occupation factors of those atoms that are disordered at room temperature were allowed to vary. The crystallographic calculations were based on F_{hkl} of all reflections measured, and the neutron scattering lengths of C, O, H, and D were taken from ref 14. The
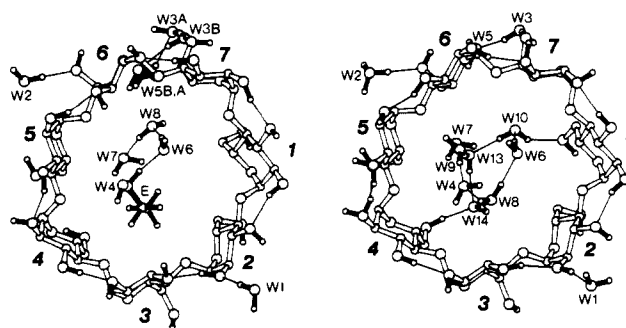
(12) Tokuoka, R.; Abe, M.; Fujiwara, T.; Tomita, K.-I.; Saenger, W. *Chem. Lett. (Jpn.)* **1980**, 491–494.

(13) Sheldrick, G. M., SHELX76. Department of Chemistry, University of Cambridge, UK, 1976.

(14) Sears, V. F. *Thermal-Neutron Scattering Lengths and Cross Sections for Condensed-Matter Research*; AECL-8490, Chalk River, 1984.

Figure 1. The structures of the β-CD inclusion complexes in β-CD·EtOD·8D₂O at 15 K (left) and in β-CD·11D₂O at 120 K (right). O–D bonds are drawn solid, and hydrogen bonds are indicated by thin lines. Spheres with increasing radii indicate D, C, and O atoms; H atoms are omitted for the sake of clarity. Glucose numbers are indicated in italics. Note the orientation of the hydrogen bonds.

function minimized was $\sum w(|F_o| - |F_c|)^2$ with w = 1.0 for all reflections. The atom labeling used in this report is the same as in the previous publications,[7,9] with O(2)3 meaning oxygen atom O(2) of glucose number 3 in the β-CD molecule.

Several cycles of consecutive isotropic least-squares refinement and difference Fourier maps revealed atomic positions of one ethanol and eight water molecules. The β-CD, ethanol, and six water molecules are well ordered with occupation factors of 1.0 for each atom, but two water molecules W3 and W5 that are adjacent to each other in the crystal structure are disordered. The disorder of hydroxyl and C(6)–O(6) groups of the β-CD molecule, which was observed at room temperature, had completely disappeared at 15 K.

After the isotropic refinement had converged, the thermal parameters of all atoms were varied anisotropically, except the C(1) to C(5) and O(2) to O(5) atoms of the glucose residues which exhibit the smallest thermal parameters. This procedure was necessitated by the relatively limited number of measured reflections.

Refinement and interpretation of the sites of the two disordered water molecules W3 and W5 was complicated as there are several partially occupied atomic positions with distances closer than the limit of resolution, 0.93 Å. As the simultaneous refinement of occupation and aniso-tropic thermal parameters was impeded because they are strongly coupled, all positions of disordered atoms were refined isotropically. Refinement converged with two different sites for each of the water molecules W3 and W5 with atom occupation factors summing up in the range of 0.77 to 1.07; the occupation factors were not constrained as it was uncertain whether there would be other (spurious) atomic positions. In a final difference Fourier map, several minor nuclear density peaks were still present in the vicinity of the disordered water atoms which, however, could not be refined or interpreted in terms of stereochemistry. This indicates that the disordered water molecules occupy two major sites for each molecule with minor sites occupied so weakly that they cannot be assigned unambiguously.

During final refinement cycles, six reflections with abnormally large $F_o - F_c$ were excluded from the data set. Refinement converged at R = 4.1% for all the remaining 4258 unique data.

Results and Discussion

In the following, no distinction is made between H and D, if not required in the discussion. The supplementary material contains Tables II–IX (atomic coordinates, anisotropic temperature factors, occupation factors for disordered atoms, bond angles and distances, torsion angles, Cremer and Pople puckering parameters[15] of the β-CD molecule), Table XIII (coordination geometry of the water molecules), and Table XV (structure factor amplitudes).

(a) General Considerations and Structure of the β-CD Macrocycle. The packing of the β-CD molecules in the crystal unit cell is as described in the X-ray structure[12] and in the isomorphous β-CD·11D₂O.[7,9] In contrast to the room temperature X-ray structure, where the included ethanol molecule and one of the three included water molecules are 2-fold disordered, the molecules included in the present β-CD at 15 K are all well-ordered (see Figure 1). The other five water molecules are located outside the cavity, and two of them are disordered, W3 and W5.

(15) Cremer, D.; Pople, J. A. *J. Am. Chem. Soc.* **1975**, *97*, 1354–1358.

Table X. Hydrogen Bond Parameters[a]

bond	O—D	D···O	O···O	O—D···O	symm (acceptor)	code[b]
O(2)1—D(2)1···O(3)2	0.968 (7)	2.123 (7)	3.043 (6)	158.2 (6)	X, Y, Z	(+)
O(3)1—D(3)1···OW4	0.976 (8)	1.800 (8)	2.755 (8)	165.4 (5)	$1 - X, Y - 0.5, -Z$	(−)
O(6)1—D(6)1···OW4	0.973 (9)	1.890 (9)	2.823 (8)	159.8 (7)	$X, Y - 1, Z$	(+)
O(2)2—D(2)2···O(3)3	0.982 (7)	1.872 (7)	2.814 (7)	161.0 (5)	X, Y, Z	(−)
O(3)2—D(3)2···O(2)6	0.952 (8)	1.988 (8)	2.934 (7)	172.0 (6)	$1 - X, Y - 0.5, -Z$	(0)
O(6)2—D(6)2···O(2)3	0.974 (9)	2.021 (7)	2.973 (7)	165.1 (6)	$X, Y - 1, Z$	(+)
O(2)3—D(2)3···OW3A	0.973 (8)	1.63 (1)	2.59 (1)	170.4 (7)	$X, Y + 1, Z - 1$	(+)
O(2)3—D(2)3···OW3B	0.973 (8)	1.70 (3)	2.64 (3)	160 (1)	$X, Y + 1, Z - 1$	(+)
O(3)3—D(3)3···O(2)7	0.986 (7)	1.726 (6)	2.692 (6)	165.7 (6)	$1 - X, Y + 0.5, -Z$	(−)
O(6)3—D(6)3···OW5B	0.90 (1)	2.01 (2)	2.74 (2)	138 (1)	$X, Y, Z - 1$	(+)
O(2)4—D(2)4···OW2	0.983 (7)	1.738 (9)	2.718 (9)	173.9 (5)	$2 - X, Y + 0.5, -Z$	(+, −)
O(3)4—D(3)4···O(2)3	0.961 (7)	1.829 (7)	2.786 (7)	173.9 (6)	X, Y, Z	(+)
O(6)4—D(6)4···OW5A	1.036 (9)	1.54 (3)	2.50 (3)	151 (1)	$2 - X, Y + 0.5, -Z$	(0)
O(6)4—D(6)4···OW5B	1.036 (9)	1.79 (1)	2.82 (1)	175.7 (7)	$2 - X, Y + 0.5, -Z$	(0)
O(2)5—D(2)5···O(3)6	0.971 (7)	1.861 (6)	2.801 (6)	162.0 (6)	X, Y, Z	(−)
O(3)5—D(3)5···O(2)4	0.986 (7)	1.838 (6)	2.768 (6)	156.1 (5)	X, Y, Z	(+, −)
O(6)5—D(6)5···OW7	0.983 (9)	1.73 (1)	2.707 (9)	172.2 (6)	$2 - X, Y + 0.5, -Z$	(+)
O(2)6—D(2)6···OW1	0.981 (7)	1.696 (7)	2.675 (7)	175.0 (6)	$1 - X, Y + 0.5, -Z$	(−)
O(3)6—D(3)6···O(6)1	0.987 (9)	1.786 (9)	2.740 (9)	161.6 (6)	$X, Y + 1, Z$	(0)
O(6)6—D(6)6···O(5)3	0.953 (9)	2.009 (9)	2.862 (8)	148.0 (7)	$X, Y, Z + 1$	(0)
O(2)7—D(2)7···O(3)1	0.986 (7)	1.892 (7)	2.865 (7)	168.8 (5)	X, Y, Z	(−)
O(3)7—D(3)7···O(2)6	0.988 (7)	1.848 (7)	2.831 (7)	173.4 (5)	X, Y, Z	(−)
O(6)7—D(6)7···OW1	0.978 (8)	1.927 (7)	2.855 (7)	157.4 (5)	$1 - X, Y - 0.5, -Z$	(0)
OE—DOE···OW6	1.000 (8)	1.733 (9)	2.725 (8)	170.9 (8)	X, Y, Z	(+)
OW1—D1W1···O(3)7	0.975 (8)	1.781 (7)	2.753 (7)	174.4 (5)	$X, Y, Z - 1$	(−)
OW1—D2W1···O(2)2	0.970 (9)	1.861 (8)	2.804 (8)	163.3 (6)	X, Y, Z	(−)
OW2—D1W2···O(6)6	0.977 (8)	1.818 (8)	2.786 (8)	170.2 (7)	X, Y, Z	(+)
OW2—D2W2···O(6)4	0.982 (9)	1.773 (8)	2.751 (8)	173.3 (7)	$2 - X, Y + 0.5, -Z$	(0)
OW3A—D1W3A···O(6)7	0.97 (2)	1.73 (2)	2.69 (1)	169 (2)	X, Y, Z	(−)
OW3A—D2W3A···O(6)3	0.99 (2)	2.06 (1)	3.04 (1)	168 (1)	$X, Y, Z + 1$	(0)
OW3B—D1W3B···O(6)7	0.98 (5)	1.75 (4)	2.72 (3)	170 (4)	X, Y, Z	(−)
OW3B—D2W3B···OW5B	0.95 (3)	2.03 (3)	2.97 (2)	168 (3)	X, Y, Z	(+)
OW4—D1W4···O(6)2	0.98 (1)	1.88 (1)	2.847 (9)	170.5 (7)	$X, Y + 1, Z$	(+)
OW4—D2W4···OE	0.971 (8)	1.758 (9)	2.711 (9)	166.1 (7)	X, Y, Z	(−)
OW5A—D1W5A···O(6)5	0.99 (7)	1.94 (5)	2.81 (2)	146 (4)	$2 - X, Y - 0.5, -Z$	(+)
OW5A—D2W5A···OW3A	1.03 (2)	2.04 (2)	2.91 (2)	140 (2)	X, Y, Z	(−)
OW5B—D1W5B···O(6)5	1.01 (3)	1.67 (2)	2.66 (1)	167 (2)	$2 - X, Y - 0.5, -Z$	(+)
OW5B—D2W5B···O(2)5	1.00 (3)	2.35 (3)	3.25 (1)	149 (2)	$X, Y - 1, Z$	(0)
OW6—D1W6···O(2)1	0.958 (9)	2.063 (9)	2.935 (8)	150.5 (7)	$1 - X, Y + 0.5, -Z$	(+)
OW6—D2W6···OW8	0.95 (1)	1.90 (1)	2.80 (1)	155.4 (8)	X, Y, Z	(+)
OW7—D1W7···OW2	0.947 (8)	1.980 (9)	2.872 (7)	156.1 (7)	$2 - X, Y - 0.5, -Z$	(+, −)
OW7—D2W7···O(3)5	0.982 (9)	1.742 (8)	2.723 (8)	176.4 (6)	$X, Y - 1, Z$	(+, −)
OW8—D1W8···O(2)5	0.98 (1)	1.96 (1)	2.912 (8)	171.9 (7)	$X, Y - 1, Z$	(−)
OW8—D2W8···OW7	0.959 (8)	2.069 (8)	2.951 (8)	152.1 (7)	X, Y, Z	(0)

[a] Distances in Å, angles in deg, estimated standard deviations given in parentheses. [b] (+) H bond present in the same orientation in β-CD·11H$_2$O (120 K);[9] (−) H bond present in opposite orientation in β-CD·11H$_2$O (120 K); (+, −) because of orientational disorder H bond present in both orientation in β-CD·11H$_2$O (120 K); (0) no equivalent H bond in β-CD·11H$_2$O (120 K).
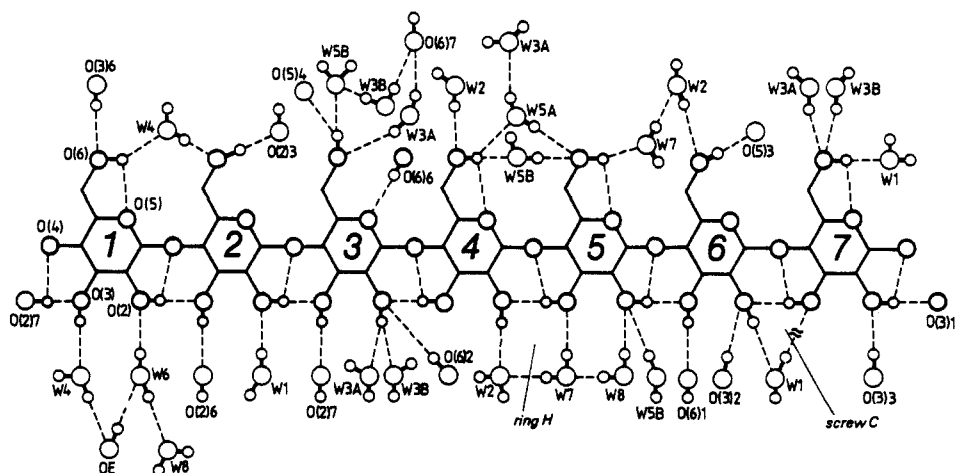

Figure 2. Schematic representation of the hydrogen-bonding arrangement around the β-CD molecule. Large spheres indicate O atoms and small spheres D atoms.

The glucose units of the β-CD are in the usual chair conformation. The torsion angles O(5)–C(5)–C(6)–O(6) are in the (−) gauche range, as usually observed, except for glucose 4 where this torsion angle is (+) gauche (see Figure 1), so that the O(6)4 hydroxyl can accept a hydrogen bond from water W2 and donate a four-center bond to the two sites of the disordered water molecule W5 and to O(5)4 (see Figure 2 and Tables X and XI). The other torsional parameters describing the relative orientations of the glucoses in the macrocycle as well as bond distances and angles occurring in this structure are to be found in the deposited material.

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Table XI. Parameters of Three-Center Hydrogen Bonds (D···A2 shorter than 2.6 Å)[b]

bond	O—D	D···A[b]	O···A[b]	O—D···A	A1···A2	A1···D···A2	sum[c]	symm
O(2)1—D(2)1····O(3)2	0.968 (7)	2.123 (7)	3.043 (6)	158.2 (6)	2.726 (7)	76.1 (2)	343.5	X, Y, Z
···O(4)2		2.295 (7)	2.768 (6)	109.2 (5)				X, Y, Z
O(6)1—D(6)1···OW4	0.973 (9)	1.890 (9)	2.823 (8)	159.8 (7)	2.958 (7)	81.5 (3)	331.3	X, Y - 1, Z
···O(5)1		2.571 (9)	2.749 (8)	90.0 (6)				X, Y, X
O(2)2—D(2)2···O(3)3	0.982 (7)	1.872 (7)	2.814 (7)	161.0 (5)	2.774 (7)	83.8 (3)	354.1	X, Y, Z
···O(4)3		2.262 (7)	2.748 (7)	109.3 (5)				X, Y, Z
O(6)3—D(6)3···OW5B	0.90 (1)	2.01 (2)	2.74 (2)	138 (1)	3.05 (1)	86.6 (5)	359.4	X, Y, Z - 1
···O(5)4		2.43 (1)	3.119 (8)	134.4 (9)				2 - X, Y - 0.5, 1 - Z
O(3)4—D(3)4···O(2)3	0.961 (7)	1.829 (7)	2.786 (7)	173.9 (6)	2.781 (7)	75.4 (3)	347.8	X, Y, Z
···O(4)4		2.607 (7)	2.908 (6)	98.5 (5)				X, Y, Z
O(6)4—D(6)4···OW5A	1.036 (9)	1.54 (3)	2.50 (3)	152 (1)	3.35 (3)	108.8	355.1	2 - X, Y + 0.5, -Z
···O(5)4		2.525 (8)	2.809 (7)	94.8				X, Y, Z
O(6)4—D(6)4···OW5B	1.036 (9)	1.79 (1)	2.82 (1)	175.7 (7)	3.05 (1)	88.5	359.0	2 - X, Y + 0.5, -Z
···O(5)4		2.525 (8)	2.809 (7)	94.8				X, Y, Z
O(2)5—D(2)5···O(3)6	0.971 (7)	1.861 (6)	2.801 (6)	162.0 (6)	2.813 (6)	84.0 (3)	354.5	X, Y, Z
···O(4)6		2.312 (7)	2.777 (7)	108.5 (5)				X, Y, Z
O(3)5—D(3)5···O(2)4	0.986 (7)	1.838 (6)	2.768 (6)	156.1 (5)	2.774 (7)	81.7 (3)	346.4	X, Y, Z
···O(4)5		2.357 (6)	2.831 (6)	108.6 (5)				X, Y, Z
O(6)5—D(6)5···OW7	0.983 (9)	1.73 (1)	2.707 (9)	172.2 (6)	3.181 (8)	91.7	359.9	2 - X, Y + 0.5, -Z
···O(5)5		2.618 (6)	2.891 (6)	96.0 (4)				X, Y, Z
O(2)7—D(2)7 O(3)1	0.986 (7)	1.892 (7)	2.865 (7)	168.8 (5)	2.766 (7)	80.0 (3)	354.0	X, Y, Z
···O(4)1		2.373 (6)	2.798 (5)	105.2 (4)				X, Y, Z
O(3)7—D(3)7···O(2)6	0.988 (7)	1.848 (7)	2.831 (7)	173.4 (5)	2.736 (6)	78.1 (2)	357.4	X, Y, Z
···O(4)7		2.435 (6)	2.868 (6)	105.9 (4)				X, Y, Z
O(6)7—D(6)7···OW1	0.978 (8)	1.927 (7)	2.855 (7)	157.4 (5)	3.129 (7)	95.1 (3)	359.5	1 - X, Y - 0.5, -Z
···O(5)7		2.302 (8)	2.738 (7)	106.1 (5)				X, Y, Z

[a] Distances in Å, angles in deg, estimated standard deviations given in parentheses. [b] A = acceptor oxygens. [c] Sum of the angles at D.

(b) Two Disordered Water Molecules. The two water molecules W3 and W5 are adjacent in this crystal structure and disordered over several sites, of which two for each water molecule show major occupations, OW3A (0.63), OW3B (0.25), OW5A (0.34), OW5B (0.73) (see footnotes to Table II (deposited)). The occupation factors of the attached D atoms and of oxygen OW3, which were determined with an accuracy of ±0.03, sum up to somewhat below 1.0 for the atom sites of W3, indicating that there must be some additional weakly occupied site(s) for this water molecule which could not be unambiguously located from the difference Fourier maps.

The covalent and hydrogen-bonding geometries of and around these water molecules are not unusual except for the two sites of water W5, where the O—D distances are somewhat long and the D—O—D angles, 95 and 91°, are significantly smaller than the expected 105° (Table IX, deposited). Also, for water site W5B, the occupation of D atom D2W5B, 0.32, is less than half of the occupation of the oxygen atom, 0.73, i.e. there should be at least one additional minor D atom site in appropriate bonding geometry. However, such a position could not be found in difference Fourier maps.

For geometrical reasons the alternative positions of water molecules W3 and W5 cannot all be occupied independently. If W3 is in position A, occupation 0.63, W5 can be both in sites W5A and W5B. If W3 is placed in position W3B with occupation 0.25, short D···D contacts exclude sites W5A and D2W5B.

(c) General Remarks about Hydrogen-Bonding Donors and Acceptors. All hydroxyl and water hydrogen atoms take part in hydrogen-bonding interactions with geometrical parameters listed in Table X. The hydrogen-bonding potentials are almost fully satisfied. All water molecules accept two hydrogen bonds except W6 and W8, which are enclosed in the β-CD cavity and consequently have partially apolar surroundings. Most of the hydroxyl groups including that of the ethanol molecule accept one hydrogen bond; O(2)3, O(2)5, and O(2)6 accept two hydrogen bonds and O(3)4 only donates and does not accept a hydrogen bond (see Figure 2).

Intramolecular, interresidue hydrogen bonds are formed between the O(2) and O(3) hydroxyl groups of all seven glucose units (Figures 1 and 2). They are the major component of unsymmetrical three-center (bifurcated) hydrogen bonds with D···O(4) the minor component, Table XI (see next paragraph). The ring of O(2)···O(3) hydrogen bonds, which stabilizes the macrocyclic conformation of the β-CD molecule, has been observed

Table XII. Distances for Short Non-H Bonding O···O Contacts of Hydroxyl and Water Oxygens, where an H Bond Would Be Stereochemically Possible (d Shorter than 3.5 Å)

contact	d, Å	symm
O(2)1-O(6)1	3.21	1 - X, Y + 0.5, -Z
O(2)1-OW4	3.46	1 - X, Y - 0.5, -Z
O(6)1-O(3)2	3.32	1 - X, Y - 0.5, -Z
O(6)2-O(2)7	3.03	1 - X, Y - 0.5, -Z
O(6)3-O(6)6	3.47	X, Y, Z - 1
O(6)3-OW5A	3.38	X, Y, Z - 1
O(2)5-OW5A	3.16	X, Y + 1, Z
O(3)6-OW3B	3.42	X, Y + 1, Z
OW2-OW5A	3.48	X, Y + 1, Z

in all crystal structures of β-CD molecules published so far. The distribution of O(2)—D···O(3) to O(2)···D—O(3) interresidue hydrogen bonds is four to three (Figure 2 and Table X), indicating that they are about equally probable. This might be one of the reasons why they form the disordered flip-flop hydrogen bonds at room temperature, a feature not yet observed in the smaller α-CD molecule.

In crystal structures where for technical reasons hydrogen atoms were not located, hydrogen bonds are often interpreted on the basis of short O···O contacts. In Table XII we have listed such contacts which are definitely not involved in hydrogen bonds but represent only van der Waals contacts. They are all greater than the 2.8 Å expected from the oxygen van der Waals radius of 1.4 Å,[16] but they still suggest that one has to be careful in the interpretation of hydrogen bonds from O···O distances if the hydrogen atoms are not located.

(d) Three-Center Hydrogen Bonds. Three-center (bifurcated) hydrogen bonds can be either symmetrical, with both H···O distances comparable, or unsymmetrical, with the shorter distance called the major component and the longer distance the minor component. In this analysis, we have included minor D···O distances which are shorter than the van der Waals distance of 2.6 Å.[14] Of the 44 symmetry-independent hydrogen bonds in this crystal structure, 12 can be defined as three-center, with parameters listed in Table XI.

All 12 three-center hydrogen bonds are largely asymmetric. They involve the seven intramolecular, interresidue hydrogen bonds

(16) Weast, R. C., Ed. Handbook of Chemistry and Physics; CRC Press: Cleveland. 1976; p D-178.

Table XIV. Structure Elements of the Hydrogen Bond Network[a]

A	chain along *b* (homodromic)
	W6 → W8 → O(2)5 → O(3)6 → O(6)1 → W4 → OE → W6' etc.
B	chain along *c* (homodromic)
	W5B → O(2)5 → O(3)6 → O(6)1 → W4 → O(6)2 → O(2)3 → W3A → O(6)3 → W5B' etc.
C	screw along *b* (homodromic)
	W2 → O(6)4 → W5 → O(6)5 → W7 → W2' etc.
D	screw along *b* (homodromic)
	O(2)6 → W1 → O(3)7 → O(2)6' etc.
E	screw along *b* (homodromic)
	W3 → O(6)7 → W1 → O(2)2 → O(3)3 → O(2)7 → O(3)1 → W4 → O(6)2 → O(2)3 → W3' etc.
F	screw along *b* (homodromic)
	OE → W6 → O(2)1 → O(3)2 → O(2)6 → W1 → O(2)2 → O(3)3 → O(2)7 → O(3)1 → W4 → OE' etc.
G	ring (heterodromic)
	W7 ← O(6)5 ← W5B → O(2)5 ← W8 → W7
H	ring (antidromic)
	W7 → O(3)5 → O(2)4 → W2 ← W7
I	finite chain (homodromic)
	W2 → O(6)6 → O(5)3
K	finite chain
	O(3)4 → O(2)3

[a] Arrows point from the donor to the acceptor and hence give the orientation of the H bond.

with the D⋯O(4) interaction being the minor component. The other five three-center bonds are donated by O(6) hydroxyl groups. In four of them the ring oxygen O(5) of the same glucose residue is the minor (intramolecular) acceptor, and in one, donated by O(6)3-D, it is the O(5)4 oxygen of a neighboring β-CD molecule.

(e) **Coordination of the Water Molecules.** The coordination of the ten water sites is described in Table XIII (deposited). The five water sites W1, W2, W3A, W4, and W7 are tetrahedrally coordinated, as expected for the two-donor and two-acceptor functions. The nonbonded O⋯O distances vary from 3.339 to 5.578 Å, and these distances are correlated with the extremes in the O⋯W⋯O angles, 69.2° and 146.6°. The data indicate that the geometry of the coordination tetrahedron around a water molecule displays a certain flexibility, as expected from the relative "softness" of the hydrogen bonds.

Four water sites are only 3-fold coordinated, W3B, W5A, W6, and W8. The sums of O⋯W⋯O angles are between 332.6° and 346.2°, i.e. closer to tetrahedral (3 × 109.5 = 328.5°) than to planar trigonal, 360°. The disordered water molecule W5B is 5-fold coordinated with W⋯O distances from 3.253 to 3.665 Å, O⋯W⋯O angles from 77.0 to 154.4°, and nonbonded O⋯O distances in the range 3.704–5.482 Å.

(f) **Description of the Hydrogen-Bonding Network.** All the O—D⋯O hydrogen bonds of this crystal structure are interconnected to form an infinite spatial network (see the overall view in Figure 3). Because of its complexity, we will describe this network in terms of infinite chains, cycles, and finite chains which are listed in Table XIV and drawn in Figure 3. These elements are joined by hydroxyl groups and water molecules with more than two acceptor and/or donor functions, i.e. O(2)3, O(2)5, O(2)6, and all eight water molecules.

We have defined the infinite chains as "chains" when the next symmetry-equivalent atoms are only related by translation and as "screw" when the screw operation of space group $P2_1$ applies. According to Table XIV, there are two chains, one (A) along the crystallographic *b* axis and the other (B) along *c*. These chains and the four screws C, D, E, F, which wind in the crystallographic *b* direction, are homodromic and indicate the strong influence of the cooperative effect on the directionality of O—D⋯O hydrogen bonds. Cycle G is heterodromic, which means that the hydrogen bonds do not adopt a preferred direction. In cycle H, water molecule W7 donates two hydrogen bonds to give rise to an antidromic arrangement with the oxygen of water W2 as double acceptor. There are only two finite chains, one (J) terminating at O(5)3 that can act only as a hydrogen bond acceptor and the other (K) initiated by O(3)4 that acts only as a hydrogen bond donor.

(g) **Comparison with β-CD·11D₂O (T = 120 K).** The crystal structures of β-CD·EtOD·8D₂O (**1**) and β-CD·11D₂O (**2**) are isomorphous. They have been studied by neutron diffraction at low temperatures (15 K for **1** and 120 K for **2**) to comparable

accuracy and differ only in the substitution of three water molecules in **2** by ethanol in **1**. Therefore a comparison of the hydrogen-bonding patterns is appropriate.

In the two crystal structures, the coordinates of the β-CD C, H, O atoms are virtually identical except for O(6)1, which is oriented (−) gauche in **1** but (+) gauche in **2**. The β-CD D atoms can be in different positions, depending on their hydrogen-bonding interactions (see the first column in Table X). Likewise water oxygen atoms W1 to W7 (identical numbering) are in similar positions, while W8 in **1** is roughly in the same place as W10 in **2**. The equivalent position of the ethanol molecule in **1** is occupied in **2** by water molecules W8, W9, W13, W14, with W8 in **2** substituting the ethanol OD group in **1**. In **1** all water molecules except W3 and W5 are well ordered, occupancy 1.0, and in **2** this holds for all water molecules except W8, which is only 64% occupied.

The differences in atomic positions are correlated with changes in hydrogen-bonding patterns. They are indicated in the last column in Table X.

(a) If the hydrogen bonds are counted with each flip-flop in **2** considered as one bond and the two minor sites W3B and W5A in **1** omitted, there are a total of 38 hydrogen bonds in **1** and 45 in **2**, clearly reflecting the substitution of three water molecules for the ethanol.

(b) Considering the spatially close atom pairs W8 in **1**, W10 in **2** and OE in **1**, W8 in **2** as equivalent, of the 38 hydrogen bonds in **1**, 14 are in the same orientation in **2** (symbol (+) in Table X) and 12 are in the opposite direction (i.e. the donor in **1** is acceptor in **2** and vice versa; symbol (−) in Table X), 4 hydrogen bonds display flip-flop disorder (in **2**; symbol (+ −)), and 8 hydrogen bonds in **1** have no correspondence in **2**.

(c) Figure 1 discloses that the β-CD molecule in **1** has no direct hydrogen-bonding contact with the enclosed ethanol and water whereas in **2**, the enclosed water molecules are bonded to O(6)1 and O(6)4 hydroxyls, which are turned "inward" with torsion angles O(5)–C(5)–C(6)–O(6) in (+) gauche range.

The hydrogen-bonding OD oxygen atoms in the central section of the unit cell around $a = \frac{1}{2}$, represented by the two screws D and F (see Figure 4), are similar in **1** and **2**; however, the directions of the O—D⋯O bonds differ. They are opposite in screw D, O(2)6 → W1 → O(3)7 → O(2)6' in **1** and O(2)6 ← W1 ← O(3)7 ← O(2)6' in **2**. Screw F is homodromic in **1** and antidromic in **2**, where the OD of the ethanol is substituted by the double donor W8; O(3)7, which is not part of this screw in **1**, is inserted in F **2** as a double acceptor. Another difference for screw F concerns O(3)2, which donates a hydrogen bond to O(2)6 in **1** and to O(3)7 in **2**.

The hydrogen-bonding scheme in the section around $a = 0$ is less comparable in the two crystal structures as it involves water molecules W8, W13, and W14 in **2** which are substituted by the ethanol molecule in **1**, and the two hydrogen bonds between β-CD
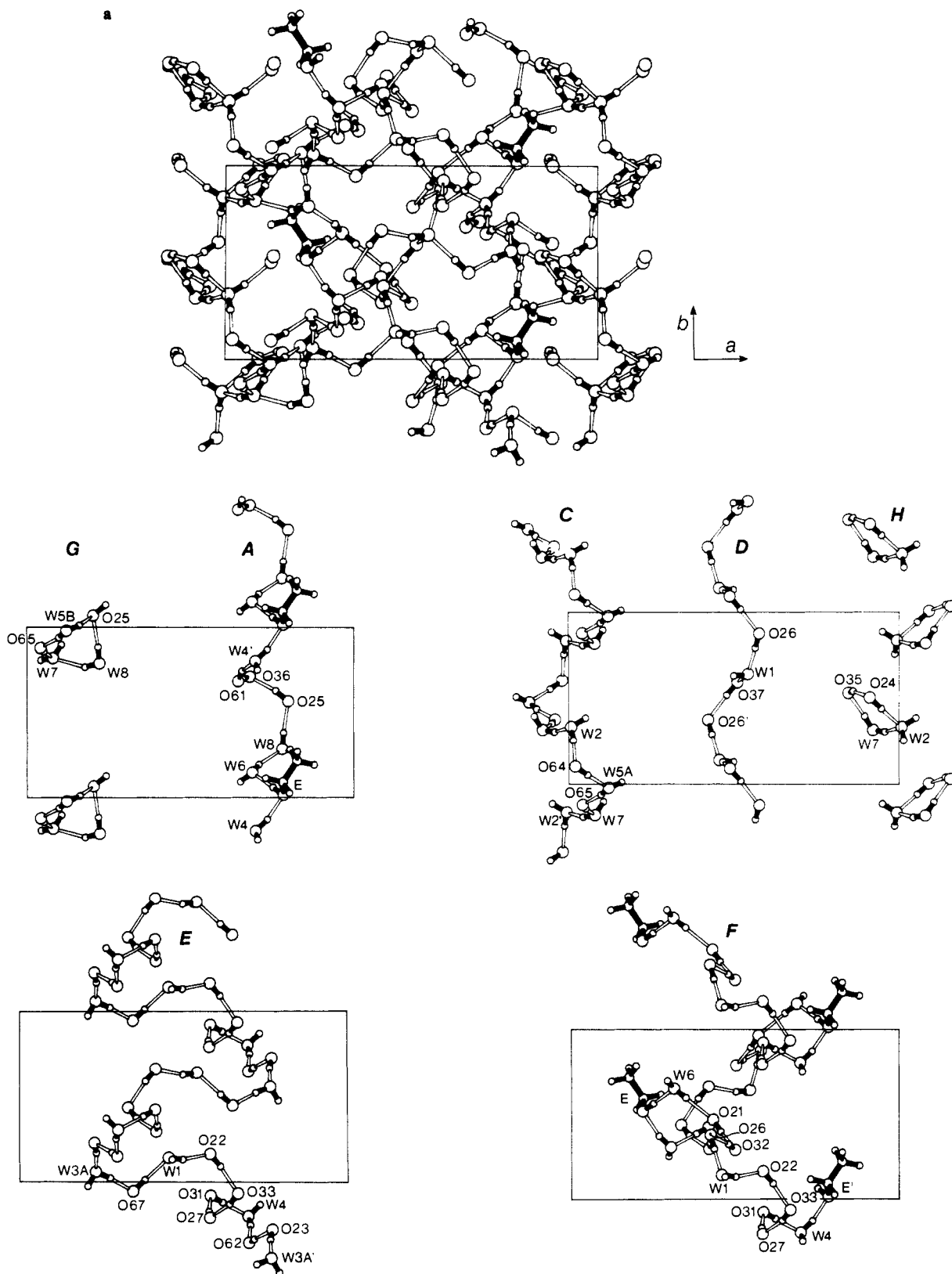
β-Cyclodextrin-Ethanol-Octahydrate at 15 K

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Figure 3. (a) Overall view of the hydrogen-bonding network in β-CD·EtOD·8D$_2$O. Only the ethanol molecule, O–D groups, and water molecules are drawn; projection is along the *c* axis. (b) Chains, screws, and cycles A, C, D, E, F, G, and H described in Table XIV are drawn in side views, projections along the *c* axis. Chain B and finite chains J and K are not drawn.

and enclosed water molecules in **2** are not observed in **1**. However, the four-membered cycle H (Table XIV) in **1** is also observed in **2**, where the four intracyclic hydrogen bonds are orientationally disordered.

Conclusions

This analysis shows that the characteristic hydrogen-bonding patterns observed in β-CD·11D$_2$O are not unique and associated

with this particular crystal structure but are an intrinsic feature of β-CD complexes. Thus the intramolecular, interresidue O-(2)—($^1/_2$D)···($^1/_2$D)—O(3) flip-flop hydrogen bonds that occur in both the β-CD·11D$_2$O and the β-CD·EtOD·8D$_2$O crystal structures at room temperature disappear when the crystals are cooled below the transition temperature around 230 K and become ordered, indicative of dynamic (and not static) disorder. In both crystal structures, the ordering gives rise to extended hydrogen-
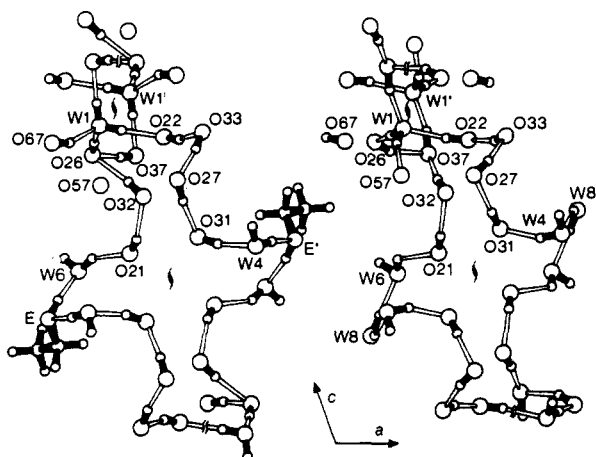
Figure 4. Comparison of hydrogen-bonding structure around $a = \frac{1}{2}$ for (left) β-CD·EtOD·8D$_2$O and (right) β-CD·11D$_2$O.

bonding networks in which the homodromic orientation is the dominating theme due to the cooperative effect that strengthens O—H···O bonds in homodromic chains by ~25% relative to the isolated hydrogen bond.[17,18]

The similarity of the hydrogen-bonding patterns in β-CD·11D$_2$O and β-CD·EtOD·8D$_2$O and the dominance of the homodromic arrangement suggest that the latter has a decisive influence on the crystallisation of these complexes. The fact that the O—D···O directions can be reversed although the positions of the O atoms are nearly equivalent indicates that the reversal can occur easily. It may be promoted by disorder in the β-CD cavity, which is initiated above a transition temperature (203 K in β-CD·11D$_2$O[9]) and propagates by the formation of flip-flop disordered hydrogen bonds.

Supplementary Material Available: Listing of atomic coordinates and anisotropic temperature factors, individual bond distances, bond angles, and torsion angles for β-CD, ethanol, and water molecules, Cremer and Pople puckering parameters, and coordination geometry for the water molecules (16 pages); tables of structure factor amplitudes (27 pages). Ordering information is given on any current masthead page.

(17) Lesyng, B.; Saenger, W. *Biochem. Biophys. Acta* **1981,** *678,* 408-413.
(18) Koehler, J. E. H.; Saenger, W.; Lesyng, B. *J. Comput. Chem.* **1987,** *8,* 1090-1098.

Structure and Dynamic Behavior of Solvated Neopentyllithium Monomers, Dimers, and Tetramers: ^{1}H, ^{13}C, and ^{6}Li NMR

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Abstract: NMR studies of neopentyllithium-^{6}*Li*, Np^{6}Li, in the presence of a variety of solvents and potential ligands reveal four species of unknown aggregation in methylcyclohexane-d_{14}, dimers and tetramers in toluene-d_8-diethyl-d_{10} ether, dimers in diethyl-d_{10} ether, and monomers and dimers in THF-d_8. The thermodynamic parameters for the latter equilibrium are $\Delta H = -1.4$ kcal and $\Delta S = -11.4$ eu toward the monomer. States of aggregation are inferred from the multiplicity of the ^{13}C resonance for carbon bound to lithium-6. In bulk THF Np^{6}Li does not complex with TMEDA or 1,2-di(*N*-piperidino)ethane, within the limits of NMR detection. However in the presence of the triamines pentamethyldiethylenetriamine (PMDTA) or 1,4,7-trimethyl-1,4,7-triazacyclononane (TMTAN) in diethyl-d_{10} ether or THF-d_8, Np^{6}Li forms tridentate complexed monomers between which interaggregate carbon-lithium bond exchange and lithium–nitrogen coordination exchange are much slower than among the etherate or THF complexes. Carbon-13 NMR of the Np^{6}Li·PMDTA complex in diethyl-d_{10} ether at 150 K shows all but two of the PMDTA carbons to be magnetically nonequivalent, implying that the system exists as one rotamer about the C$_\alpha$–Li bond and that rotation about this bond is slow relative to the NMR time scale at this temperature. In this system we observe ^{13}C line-shape changes above 150 K indicative of faster C–Li bond rotation with $\Delta H_r^* = 7.7$ kcal and $\Delta S_r^* = -8.8$ eu and then, above 180 K, fast inversion at the N(CH$_3$)$_2$ nitrogens with $\Delta H_i^* = 8.7$ kcal and $\Delta S_i^* = -3$ eu. The latter process appears to be concerted with the exchange of lithiums between Np^{6}Li·PMDTA monomer and Np^{6}Li etherate dimer, as determined from the ^{6}Li NMR line shapes. The monomeric complex Np^{6}Li·TMTAN shows two triamine ^{13}CH$_2$ carbon resonances, of equal amplitude, which support the proposed conformation of the TMTAN.

The broad outlines of organolithium aggregation are well-known.[1,2] Unsolvated primary (RLi)$_n$ species are hexamers,[3,4] octamers,[4] and nonamers;[4] for the secondary species[5] $n = 4$ and

6 while the more hindered tertiary reagents are largely tetramers.[3b,5b,6] Organolithiums solvated by monoethers (except THF) and tertiary monoamines are largely tetramers.[7] In THF *n*-butyllithium forms equilibrium mixtures of dimers and tetramers[7] with the dimers favored at low temperature.[8] However, the more

(1) Reviewed: (a) Wardell, J. L. In *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Abel, E. W., Eds.; Pergammon Press: Oxford, 1982; Vol. 1, p 43. (b) Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon Press: Oxford, 1974.
(2) (a) Fraenkel, G.; Hsu, H.-P.; Su, B. M. In *Lithium: Current Applications in Science, Medicine and Technology*; Bach, R. O., Ed.; John Wiley: New York, 1985; p 273. (b) Fraenkel, G. In *Recent Advances in Anionic Polymerization*; Hogen-Esch, T., Smid, J., Eds.; Elsevier: New York, 1987; p 23.
(3) (a) Margerison, D.; Newport, J. P. *Trans. Faraday Soc.* **1963,** *59,* 2058. (b) Brown, T. L. *Acc. Chem. Res.* **1968,** *23,* 1. (c) Beckenbaugh, W.; Fraenkel, G.; Yang, P. P. *J. Am. Chem. Soc.* **1976,** *98,* 6878.
(4) Fraenkel, G.; Henrichs, M.; Hewitt, J. M.; Su, B. M.; Geckle, M. J. *J. Am. Chem. Soc.* **1980,** *102,* 3345-3350. (b) Fraenkel, G.; Fraenkel, A. M.; Geckle, M. J.; Schloss, F. *J. Am. Chem. Soc.* **1979,** *101,* 4745-4747.

(5) (a) Fraenkel, G.; Henrichs, M.; Hewitt, M.; Su, B. M. *J. Am. Chem. Soc.* **1984,** *106,* 255. (b) Thomas, R. D.; Jensen, R. M.; Young, T. C. *Organometallics* **1987,** *6,* 565.
(6) (a) McKeever, L. D.; Waack, R. *Chem. Commun.* **1969,** 751. (b) Thomas, R. D.; Clark, M. T.; Jensen, R. M.; Young, T. C. *Organometallics* **1986,** *5,* 1851. (c) Weiner, M.; Vogel, C.; West, R. *Inorg. Chem.* **1962,** *1,* 654.
(7) (a) Novak, D. P.; Brown, T. L. *J. Am. Chem. Soc.* **1972,** *94,* 3793. (b) McKeever, L. D.; Waack, R.; Doran, M. A.; Baker, E. B. *J. Am. Chem. Soc.* **1969,** *91,* 1057; **1968,** *90,* 3244. (c) West, P.; Waack, R. *J. Am. Chem. Soc.* **1967,** *89,* 4395. (d) Rochonov, A. N.; Shigarin, D. N.; Talaleeva, T. L.; Tsareva, G. V.; Kocheshkov, K. A. *Zh. Fiz. Khim.* **1966,** *40,* 2265.