should be viewed in the light of these limitations and taken at best as semiquantitative. The CD data point out that this tripeptide is not completely ordered in TFE solution but exists as a mixture of the β-turn and disordered conformation. From NMR data, the extent of the hydrogen-bonded conformation is found to be about 40% in MeOH or Me_2SO-d_6. It is interesting to compare this value with that obtained for the analogous *N*-acetyl-Pro-Gly-$NHCH_3$, viz., about 68% in Me_2SO-d_6.[19] The lower value for the Phe-tripeptide indicates that the Phe side chain tends to destabilize the β-turn conformation formed by the backbone in solution. In the solid state, however, this effect appears to be offset by intermolecular hydrogen bonding (Figure 2). In globular proteins, the interaction of the Phe side chain with other aromatic side chains may stabilize this conformation. In these proteins, Phe is found to have relatively high preference for the fourth position of the β turn in the R_1-Pro_2-R_3-R_4 sequence comparable to Leu.[2] The results presented here are also of relevance to the conformational requirement of prolyl hydroxylase which hydroxylates selected Pro residues in the Pro-Gly-X segments of nascent procollagen. Two of the authors have recently shown[3] that the β turn is a conformational requirement in these segments for enzymic proline hydroxylation. It is interesting to note that all the seven segments that contain the Pro-Gly-Phe sequence in procollagen are hydroxylated.[6] It is also worth noting that out of the three Pro residues in bradykinin, that in the -Pro-Gly-Phe-segment gets hydroxylated.[31]

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Supplementary Material Available: Listings of the observed and calculated structure factors (Table A) and anisotropic thermal parameters (Table B) (8 pages). Ordering information is given on any current masthead page.

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Topography of Cyclodextrin Inclusion Complexes. 15.[1] Crystal and Molecular Structure of the Cyclohexaamylose–7.57 Water Complex, Form III. Four- and Six-Membered Circular Hydrogen Bonds

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Abstract: Cyclohexaamylose, α-cyclodextrin (α-CD), is a doughnut-shaped molecule composed of six $\alpha(1\rightarrow4)$ linked glucoses. Owing to an annular aperture of 5.0 Å, it is able to form inclusion complexes with a variety of substrate molecules. Two crystal modifications with water as included guest have already been described. A third crystal modification of α-CD with water included was obtained while crystallizing α-CD from 1.2 M $BaCl_2$. The space group in all three hydrate modifications is orthorhombic, $P2_12_12_1$. The cell dimensions of the present crystals are a = 14.356 (5), b = 37.538 (12), and c = 9.400 (4) Å, with four formula units α-CD·7.57H_2O per cell. Of the 7.57 hydration water molecules/asymmetric unit, 5 are located outside the cyclodextrin cavity with an extensive hydrogen bonded network between themselves as well as with the hydroxyl oxygen atoms of α-CD. The remaining 2.57 water molecules are enclosed within the cavity and disordered with four alternative sites of approximately 0.64 occupancy each. There are three "circular" hydrogen bonds observed for this structure involving three of the external water molecules and O–H groups of α-CD. Two of the circles, one six membered and one four membered, are *antidromic*, and one is four-membered *homodromic*. The macrocyclic conformation of α-CD is nearly symmetrical with all the possible O(2)···O(3) intramolecular hydrogen bonds formed. In terms of "induced fit" type complex formation of this model enzyme, the α-CD molecule exists in a relaxed state with "activated" water inside the cavity. In contrast, α-CD in the other two hydrate modifications is observed in a tense state with only four or five of the six O(2)···O(3) hydrogen bonds formed and one glucose rotated to fix the included waters in fully occupied positions by hydrogen bonding to O(6) hydroxyls.

Cyclodextrins are doughnut-shaped, cyclic oligosaccharides obtained by the action of glucanotransferase on the helical starch molecule. They consist of six or more $\alpha(1\rightarrow4)$-linked glucopyranose rings. The hexasaccharide α-cyclodextrin (α-CD) has an annular aperture of 5.0 Å, and hence it is able to form inclusion complexes with a variety of guest molecules small enough to fit inside its cavity. A number of nonisomorphous crystalline modifications of several α-CD inclusion complexes with different guest molecules are known.[1-3] Two hexahydrate modifications of the "empty" α-CD, i.e., the species occurring in aqueous solution without added guest molecule, have already been described.[4,5] In one of these, two water molecules are located inside the cavity.[4] In the second modification,[5] only one water molecule and the primary O(6) hydroxyl of an adjacent α-CD molecule are in the center of the cavity with five of the remaining water molecules located outside. The above hexahydrate modifications have only four[4] and five[5] of the possible intramolecular O(2)···O(3) hydrogen bonds between adjacent glucoses. Here we report of a third crystal modification of α-CD with five water molecules located outside

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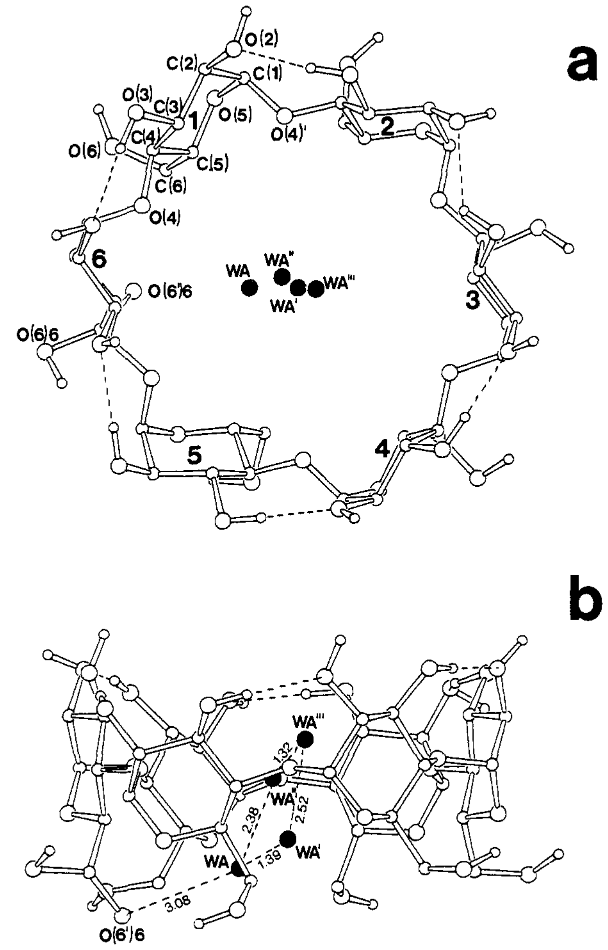

Figure 1. Top (a) and side (b) view of α-CD form III indicating the atomic numbering scheme and the O(2)···O(3) hydrogen bonds (dotted lines). The disordered water molecules (WA, WA′, WA″, and WA‴) in the annular cavity are drawn hatched and distances between them are indicated (Å).

the molecular annular cavity while 2.57 water molecules are found inside as disordered water, split up into four sites of approximately 0.64 occupancy (Figure 1).

Experimental Section

This α-CD-hydrate inclusion complex was obtained when α-CD was crystallized from 1.2 M aqueous $BaCl_2$ in the hope of obtaining a Ba^{2+} complex of α-CD. Crystals have orthorhombic space group $P2_12_12_1$ with cell dimensions $a = 14.356$ (5), $b = 37.538$ (12), and $c = 9.400$ (4) Å. On the basis of a composition of $C_{36}H_{60}O_{30}\cdot 7.57H_2O$ per asymmetric unit and a cell volume of 5065.6 Å^3, the calculated density of the crystals is 1.455 g/cm^3. Three-dimensional X-ray intensities were measured on a Stoe automatic diffractometer with Cu Kα radiation ($\lambda = 1.5418$ Å) up to a limiting 2θ value of 120°. The θ–2θ scan mode was employed, and background measurements were made both at the beginning and end of each scan. A total of 4255 reflections were measured, of which 201 reflections had intensities less than 3σ above background, as estimated from counting statistics.[6]

The structure determination was based on the assumption that it would be nearly isomorphous with the I_2 inclusion complex[3] which has previously been reported so that coordinates of the latter could be applied as starting model. The O(6) oxygens were excluded from the initial starting set of coordinates as these could possibly have large deviations from expected positions (for atom numbering scheme, see Figure 1). Almost the entire structure could thus be obtained by a combination of least-squares refinement and Fourier methods which also indicated the absence of the Ba^{2+} ion. The structure could be isotropically refined to an R value of 0.15. A difference Fourier map computed at this stage showed four weak peaks approximately 1.4 Å from each other. They were located within the α-CD cavity and could be accounted for as disordered water molecules. The positional and occupancy factors of these were refined. Further, one of the water oxygens (W(5)) outside the cavity and the O(6)6 hydroxyl oxygen showed disordered low occupancy sites.

The positions of C–H hydrogen atoms were calculated and the hydroxyl and water hydrogen atoms (except those involving disorder) could be positioned from a difference Fourier map. They were included in the structure factor calculations with isotropic temperature factors of the bonded oxygen atoms. Hydrogen atom parameters were not refined. Two of the reflections (200 and 040), which showed a large extinction effect, were removed from the data for final cycles of refinement. The nonhydrogen atoms were treated anisotropically, and the structure was refined by full-matrix least squares[7] to a final R value of 0.059 for all the 4253 data with weights $1/\sigma^2$ obtained from counting statistics. Scattering factors were taken from the "International Tables for X-ray Crystallography".[8] The final coordinates and thermal parameters are given in Tables I and II.

Results and Discussion

Glucopyranose Conformation: Bond Lengths and Angles. The α-CD molecule may be considered to represent six independent observations of glucopyranose rings in the C(1) chair conformation. The mean bond lengths and angles are given in Tables III and IV. As in the other cyclodextrin structures the C–C and C–O bond lengths are specifically dependent upon the chemical nature of the atoms involved. In particular the C(5)–O(5) and C(4)–O(4) mean bond lengths of 1.443 (8) and 1.441 (11) Å, respectively, are larger than the overall mean C–O distance of 1.433 Å. The mean C(1)–O(5) and C(1)–O(4) bonds are each approximately 0.027 Å shorter than the above mean value. These differences are similar to those found in other diffraction studies involving glucopyranose rings.[9]

The angles within the glucopyranose unit given in Table IV are comparable to those observed for other cyclodextrin structures. For instance the average C–C–C bond angles are significantly larger than tetrahedral with an overall mean value of 111.6 while the mean C–C–O bond angle is close to tetrahedral and has a value of 108.6°.

Macrocyclic Ring Conformation. The macrocyclic conformation of the cyclodextrin ring is defined in terms of the C(1′)–O(4)–C(4) linkages between the six glucopyranose rings, the primed atom C(1′) belonging to the adjacent glucose. The parameters which characterize these linkages are the two C–O bonds, the C–O–C bond angle, and the torsion angles about the C–O bonds. The latter are found to be highly specific with regard to the various partially isomorphous modifications of α-CD. It is interesting to compare this new hydrate modification (form III) with the other two water inclusion complexes (forms I and II). Table V gives the mean values of the various parameters and also the variation of these parameters in each of the three forms. The variations of the C–O bonds in form III are in the same range as those of the C–O bonds in forms I and II, and no specific differences between the three forms are observed. The C–O–C bond angles have mean values of 117.9, 118.3, and 118.4°, respectively, for forms I, II, and III. The variation of this bond angle is observed to be a minimum for form III, indicating that this form is more symmetric in nature compared to the other two forms. Table V also gives the O(4)···O(4) distances and the O(4)···O(4)···O(4) angles between adjacent glucosidic bonds. The mean O(4)···O(4) distances show a gradual decrease in value in going from form I to III, and the variation is minimum for form III. The mean O(4)···O(4)···O(4) angle is close to 120° for all the forms, with minimum variation for form III and larger variations for forms I and II.

The relative orientation of $\alpha(1\rightarrow4)$ linked glucoses is described by torsion angles ϕ and ψ, which involve the "virtual" O(4)–C(1) bonds.[10] The ϕ and ψ values of this new modification are given

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Table I. Final Atomic Coordinates and Anisotropic Temperature Factors of α-Cyclodextrin–7.57 Water Complex[a]

atom	x	y	z	10^4B_{11}	10^5B_{22}	10^4B_{33}	10^5B_{12}	10^4B_{13}	10^4B_{23}
C(1)1	0.7917 (5)	0.2322 (2)	0.0110 (8)	43 (4)	44 (5)	90 (9)	−14 (12)	3 (5)	2 (2)
C(2)1	0.8495 (5)	0.2161 (2)	−0.1100 (7)	41 (4)	51 (5)	74 (9)	−4 (12)	3 (5)	2 (2)
O(2)1	0.7897 (3)	0.2047 (1)	−0.2246 (5)	49 (3)	65 (4)	84 (6)	0 (9)	−11 (4)	2 (1)
C(3)1	0.9034 (5)	0.1847 (2)	−0.0540 (7)	37 (4)	41 (5)	77 (8)	−19 (11)	2 (6)	0 (2)
O(3)1	0.9671 (3)	0.1730 (1)	−0.1635 (5)	43 (3)	64 (4)	76 (6)	12 (9)	12 (4)	−3 (1)
C(4)1	0.9589 (5)	0.1942 (2)	0.0783 (7)	37 (4)	37 (5)	86 (8)	−15 (11)	−1 (5)	0 (2)
O(4)1	0.9874 (3)	0.1606 (1)	0.1394 (5)	33 (3)	42 (3)	90 (6)	−19 (8)	−2 (3)	3 (1)
C(5)1	0.8995 (5)	0.2138 (2)	0.1915 (7)	43 (4)	39 (5)	78 (8)	0 (12)	0 (5)	−1 (2)
O(5)1	0.8521 (3)	0.2429 (1)	0.1223 (5)	48 (3)	34 (3)	101 (6)	−13 (8)	1 (4)	−1 (1)
C(6)1	0.9558 (5)	0.2286 (2)	0.3100 (8)	52 (4)	59 (6)	106 (10)	−44 (13)	−3 (6)	−4 (2)
O(6)1	1.0419 (4)	0.2449 (1)	0.2642 (6)	62 (4)	75 (5)	182 (10)	−45 (11)	−17 (5)	−1 (2)
C(1)2	0.4553 (5)	0.1905 (2)	0.1796 (7)	35 (4)	39 (5)	103 (9)	19 (11)	−1 (5)	4 (2)
C(2)2	0.4760 (5)	0.1885 (2)	0.0201 (7)	35 (4)	45 (5)	97 (9)	2 (12)	−7 (5)	4 (2)
O(2)2	0.4242 (3)	0.1596 (1)	−0.0430 (5)	41 (3)	66 (4)	105 (7)	−7 (9)	−14 (4)	0 (1)
C(3)2	0.5784 (5)	0.1846 (2)	−0.0051 (7)	38 (4)	45 (5)	67 (8)	−8 (12)	−1 (5)	4 (2)
O(3)2	0.5962 (3)	0.1858 (1)	−0.1555 (5)	51 (3)	69 (4)	75 (6)	−16 (10)	3 (4)	0 (1)
C(4)2	0.6309 (5)	0.2140 (2)	0.0699 (7)	33 (4)	43 (5)	86 (9)	16 (11)	0 (5)	0 (2)
O(4)2	0.7281 (3)	0.2057 (1)	0.0594 (5)	33 (3)	39 (3)	102 (7)	−5 (7)	12 (3)	2 (1)
C(5)2	0.6045 (5)	0.2163 (2)	0.2262 (8)	39 (4)	52 (5)	85 (9)	1 (12)	7 (5)	0 (2)
O(5)2	0.5042 (3)	0.2193 (1)	0.2391 (5)	39 (3)	46 (3)	99.(6)	4 (8)	11 (4)	0 (1)
C(6)2	0.6439 (6)	0.2493 (2)	0.2998 (9)	58 (5)	96 (8)	112 (11)	−17 (17)	3 (7)	−16 (3)
O(6)2	0.6286 (4)	0.2813 (1)	0.2193 (7)	67 (4)	54 (4)	219 (11)	−15 (11)	16 (6)	−5 (2)
C(1)3	0.4042 (4)	0.0794 (2)	0.5228 (7)	24 (3)	34 (4)	84 (8)	22 (10)	1 (4)	0 (2)
C(2)3	0.3683 (4)	0.0756 (2)	0.3727 (7)	30 (3)	39 (5)	85 (8)	15 (11)	−9 (5)	0 (2)
O(2)3	0.3808 (3)	0.0386 (1)	0.3347 (5)	52 (3)	37 (3)	123 (7)	−2 (8)	−24 (4)	0 (1)
C(3)3	0.4213 (4)	0.0992 (2)	0.2719 (7)	34 (4)	36 (5)	71 (8)	2 (11)	0 (5)	1 (2)
O(3)3	0.3789 (3)	0.0985 (1)	0.1330 (5)	53 (3)	60 (4)	74 (6)	28 (9)	−15 (4)	0 (1)
C(4)3	0.4176 (4)	0.1378 (2)	0.3248 (7)	29 (3)	40 (5)	71 (8)	1 (11)	0 (5)	0 (2)
O(4)3	0.4837 (3)	0.1574 (1)	0.2397 (5)	35 (3)	45 (3)	91 (6)	26 (8)	7 (3)	6 (1)
C(5)3	0.4471 (5)	0.1407 (2)	0.4813 (7)	41 (4)	31 (5)	72 (8)	4 (11)	1 (5)	−1 (2)
O(5)3	0.3952 (3)	0.1159 (1)	0.5662 (4)	40 (3)	42 (3)	67 (5)	26 (8)	5 (3)	1 (1)
C(6)3	0.4302 (6)	0.1773 (2)	0.5439 (8)	66 (5)	43 (5)	91 (9)	−3 (14)	−1 (1)	−6 (2)
O(6)3	0.3359 (4)	0.1886 (1)	0.5272 (6)	67 (3)	44 (4)	139 (8)	68 (10)	17 (5)	1 (1)
C(1)4	0.7063 (4)	0.0160 (2)	0.7320 (7)	26 (3)	35 (5)	58 (7)	5 (10)	3 (4)	0 (2)
C(2)4	0.6421 (4)	−0.0079 (2)	0.6419 (7)	27 (3)	36 (5)	67 (7)	11 (10)	6 (5)	0 (2)
O(2)4	0.7022 (3)	−0.0305 (1)	0.5622 (5)	32 (3)	34 (3)	98 (6)	15 (7)	−2 (3)	−5 (1)
C(3)4	0.5809 (4)	0.0150 (2)	0.5467 (7)	28 (3)	38 (5)	58 (7)	−12 (10)	0 (4)	0 (2)
O(3)4	0.5130 (3)	−0.0076 (1)	0.4802 (2)	32 (3)	40 (3)	83 (6)	−10 (7)	−12 (3)	−2 (1)
C(4)4	0.5312 (4)	0.0445 (2)	0.6312 (6)	29 (3)	35 (5)	57 (7)	13 (10)	0 (4)	0 (2)
O(4)4	0.4986 (3)	0.0694 (1)	0.5234 (4)	24 (2)	43 (3)	69 (5)	23 (7)	2 (3)	4 (1)
C(5)4	0.5970 (4)	0.0646 (1)	0.7303 (6)	30 (3)	39 (5)	65 (7)	18 (11)	−3 (4)	0 (2)
O(5)4	0.6510 (3)	0.0398 (1)	0.8138 (4)	30 (2)	45 (3)	51 (5)	33 (7)	0 (3)	−1 (1)
C(6)4	0.5459 (5)	0.0873 (2)	0.8412 (7)	43 (4)	47 (5)	87 (9)	48 (12)	6 (5)	−5 (2)
O(6)4	0.4875 (3)	0.0661 (1)	0.9301 (5)	46 (3)	73 (4)	74 (6)	54 (9)	17 (4)	1 (1)
C(1)5	1.0383 (4)	0.0651 (2)	0.5812 (7)	26 (3)	56 (5)	61 (7)	−8 (11)	−2 (4)	0 (2)
C(2)5	1.0217 (4)	0.0247 (2)	0.5832 (7)	28 (3)	56 (5)	75 (8)	8 (11)	5 (5)	1 (2)
O(2)5	1.0724 (3)	0.0096 (1)	0.4679 (5)	46 (3)	58 (4)	131 (7)	39 (9)	39 (4)	0 (1)
C(3)5	0.9191 (4)	0.0164 (1)	0.5730 (7)	31 (3)	29 (4)	64 (7)	−13 (10)	0 (4)	0 (2)
O(3)5	0.9066 (3)	−0.0211 (1)	0.5973 (5)	36 (2)	32 (3)	84 (6)	−5 (7)	1 (3)	0 (1)
C(4)5	0.8631 (4)	0.0370 (1)	0.6802 (6)	22 (3)	36 (4)	59 (7)	−10 (10)	0 (4)	0 (2)
O(4)5	0.7665 (3)	0.0341 (1)	0.6394 (4)	24 (2)	37 (3)	62 (5)	−17 (6)	−1 (3)	1 (1)
C(5)5	0.8867 (4)	0.0771 (2)	0.6767 (7)	28 (3)	41 (5)	60 (7)	−23 (10)	0 (4)	0 (2)
O(5)5	0.9858 (3)	0.0816 (1)	0.6904 (4)	27 (2)	54 (4)	57 (5)	−44 (8)	3 (3)	−1 (1)
C(6)5	0.8433 (5)	0.0980 (2)	0.7981 (7)	42 (4)	33 (5)	81 (9)	−9 (11)	−1 (5)	−4 (2)
O(6)5	0.8788 (3)	0.0873 (1)	0.9343 (4)	46 (3)	45 (3)	57 (5)	−30 (8)	3 (3)	0 (1)
C(1)6	1.0833 (5)	0.1536 (2)	0.1512 (7)	34 (4)	53 (5)	69 (8)	−32 (12)	−1 (5)	3 (2)
C(2)6	1.0992 (5)	0.1144 (2)	0.1064 (6)	31 (4)	59 (5)	51 (7)	−16 (12)	0 (4)	1 (2)
O(2)6	1.0626 (3)	0.1095 (1)	−0.0334 (5)	38 (3)	78 (4)	64 (5)	−8 (9)	−2 (3)	0 (1)
C(3)6	1.0474 (4)	0.0897 (2)	0.2083 (7)	31 (3)	37 (5)	67 (8)	−24 (11)	0 (5)	0 (2)
O(3)6	1.0738 (3)	0.0532 (1)	0.1816 (5)	46 (3)	41 (3)	84 (6)	−2 (8)	−2 (4)	−3 (1)
C(4)6	1.0723 (4)	0.0980 (2)	0.3625 (7)	28 (3)	39 (5)	64 (7)	−28 (11)	4 (4)	1 (2)
O(4)6	1.0079 (3)	0.0779 (1)	0.4450 (4)	28 (2)	52 (3)	56 (5)	−22 (8)	−1 (3)	3 (1)
C(5)6	1.0615 (5)	0.1378 (2)	0.3955 (7)	41 (4)	45 (5)	62 (8)	−40 (11)	5 (5)	1 (2)
O(5)6	1.1151 (3)	0.1583 (1)	0.2918 (5)	41 (3)	48 (3)	69 (5)	−52 (8)	−1 (3)	0 (1)
C(6)6	1.0996 (6)	0.1483 (2)	0.5399 (7)	64 (5)	53 (6)	66 (9)	−28 (14)	−7 (6)	−1 (2)
O(6)6	1.1975 (5)	0.1372 (2)	0.5516 (7)	54 (4)	101 (6)	112 (9)	−58 (13)	−13 (5)	−2 (2)
W1	0.2427 (4)	0.0151 (1)	0.1519 (6)	58 (3)	105 (5)	131 (8)	−10 (11)	−9 (4)	−2 (2)
W2	0.2929 (4)	0.0393 (2)	0.8569 (7)	63 (4)	128 (6)	215 (11)	68 (14)	−19 (6)	−5 (2)
W3	0.7386 (4)	0.2701 (2)	0.6714 (8)	77 (4)	121 (6)	249 (12)	0 (14)	−11 (7)	29 (2)
W4	0.2081 (4)	0.1012 (1)	0.8018 (6)	65 (4)	133 (6)	134 (8)	11 (12)	14 (5)	2 (2)
W5	0.2426 (7)	0.1686 (3)	0.8928 (13)	58 (6)	103 (9)	249 (21)	−6 (19)	−12 (10)	5 (4)
W5′	0.2700 (11)	0.1713 (4)	0.7885 (16)	45 (9)	98 (15)	108 (21)	11 (29)	−5 (12)	7 (5)
WA	0.8367 (6)	0.1634 (3)	0.5155 (10)	68 (6)	142 (11)	144 (13)	−60 (12)	14 (8)	−8 (3)
WA'	0.7504 (9)	0.1493 (3)	0.4774 (11)	111 (9)	139 (11)	156 (16)	45 (27)	−12 (11)	9 (4)
WA"	0.7666 (11)	0.1281 (3)	0.3344 (16)	225 (17)	151 (14)	262 (26)	−243 (41)	−28 (19)	−1 (5)
WA"'	0.7056 (12)	0.1041 (4)	0.2917 (16)	222 (17)	206 (18)	480 (44)	−106 (46)	32 (26)	−17 (7)
O(6′)6	1.0405 (20)	0.1843 (7)	0.5723 (31)						

[a] Temperature factors are of the form $\exp[-(B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + 2B_{12}hk + 2B_{13}hl + 2B_{23}kl)]$, O(6′)6 was treated with isotropic temperature factor and has $B = 4.46$ (2) Å². The occupancy factors of the disordered O(6)6 positions and of the disordered water molecules are as follows: O(6)6, 0.82; O(6′)6, 0.18; W5, 0.64; W5′, 0.36; WA, 0.64; WA′, 0.62; WA″, 0.65; WA‴, 0.66. The average esd's in occupancy are 0.01. Standard deviations given in parentheses refer to the last digit and were obtained from the least-squares correlation matrix.

Table II. Coordinates and Isotropic Temperature Factors (10^2B, Å^2) of the Hydrogen Atoms

atom	x	y	z	B	atom	x	y	z	B
HC11 1	0.7491	0.2549	−0.0259	303	HC65 1	0.7672	0.0936	0.8018	250
HC21 1	0.8989	0.2352	−0.1521	262	HC16 1	1.1193	0.1714	0.0777	289
HC31 1	0.8542	0.1628	−0.0320	256	HC26 1	1.1752	0.1082	0.1087	266
HC41 1	1.0210	0.2092	0.0535	245	HC36 1	0.9715	0.0944	0.1892	241
HC51 1	0.8473	0.1946	0.2322	249	HC46 1	1.1445	0.0896	0.3851	229
HC61 2	0.9122	0.2485	0.3675	386	HC56 1	0.9856	0.1450	0.3885	240
HC61 1	0.9708	0.2072	0.3890	286	HC66 2	1.0964	0.1778	0.5510	345
HC12 1	0.3805	0.1938	0.1934	234	HC66 1	1.0555	0.1371	0.6258	345
HC22 1	0.4524	0.2134	−0.0270	266	HO31 1	0.9986	0.1510	−0.1344	334
HC32 1	0.6027	0.1580	0.0373	250	HO32 1	0.6618	0.1913	−0.1763	357
HC42 1	0.6142	0.2377	0.0204	288	HO33 1	0.4304	0.1144	0.1031	346
HC52 1	0.6303	0.1920	0.2815	281	HO34 1	0.4679	0.0077	0.4320	252
HC62 2	0.7187	0.2452	0.3237	447	HO35 1	0.8390	−0.0249	0.5852	257
HC62 1	0.6088	0.2512	0.4079	447	HO36 1	1.0425	0.0370	0.1088	275
HC13 1	0.3633	0.0625	0.5967	238	HO21 1	0.7609	0.2242	−0.2783	364
HC23 1	0.2941	0.0830	0.3695	217	HO22 1	0.3683	0.1716	−0.0053	358
HC33 1	0.4951	0.0906	0.2650	214	HO23 1	0.3327	0.0306	0.2710	332
HC43 1	0.3480	0.1483	0.3111	216	HO24 1	0.6722	−0.0515	0.5146	252
HC53 1	0.5219	0.1344	0.4898	252	HO25 1	1.0720	0.0227	0.3751	384
HC63 2	0.4751	0.1972	0.4981	358	HO26 1	1.1228	0.0987	−0.0580	333
HC63 1	0.4470	0.1760	0.6623	358	HO61 1	1.0609	0.2696	0.2245	520
HC14 1	0.7483	−0.0007	0.8037	189	HO62 1	0.5727	0.2971	0.2000	481
HC24 1	0.5984	−0.0244	0.7139	221	HO63 1	0.2854	0.1687	0.5356	409
HC34 1	0.6247	0.0276	0.4660	211	HO64 1	0.4291	0.0673	0.8754	334
HC44 1	0.4715	0.0333	0.6898	206	HO65 1	0.9456	0.0951	0.9450	263
HC54 1	0.6442	0.0816	0.6667	248	HO66 1	1.1728	0.1133	0.5773	500
HC64 2	0.5043	0.1085	0.7889	253	H1W1	0.2699	0.0172	0.0565	488
HC64 1	0.5970	0.1013	0.9110	253	H2W1	0.1879	0.0293	0.1743	488
HC15 1	1.1125	0.0716	0.5995	216	H1W2	0.2810	0.0201	0.7819	667
HC25 1	1.0502	0.0139	0.6838	236	H2W2	0.3670	0.0300	0.8670	667
HC35 1	0.8939	0.0241	0.4665	233	H1W3	0.7727	0.2853	0.6018	634
HC45 1	0.8748	0.0263	0.7864	195	H2W3	0.6714	0.2665	0.6664	634
HC55 1	0.8627	0.0886	0.5726	220	H1W4	0.2560	0.1170	0.8333	574
HC65 2	0.8549	0.1267	0.7855	250	H2W4	0.2395	0.0783	0.8216	574

Table III. Mean Bond Lengths (Å) in α-CD·7.57H_2O, Averaged Over the Six Independent Glucoses[a]

bonds	mean length	bonds	mean length
C(1)–O(5)	1.417 (11)	C(1)–C(2)	1.532 (13)
C(1)–O(4′)	1.416 (13)	C(2)–C(3)	1.510 (11)
C(2)–O(2)	1.434 (10)	C(3)–C(4)	1.522 (13)
C(3)–O(3)	1.440 (4)	C(4)–C(5)	1.534 (10)
C(4)–O(4)	1.441 (11)	C(5)–C(6)	1.514 (16)
C(5)–O(5)	1.443 (8)		
C(6)–O(6)	1.440 (16)		

[a] Standard deviations given in parentheses. See paragraph concerning supplementary material.

Table IV. Mean Bond Angles (Deg) in α-CD·7.57H_2O[a]

bonds	mean length	bonds	mean length
C(2)–C(1)–O(5)	109.3 (4)	C(1)–C(2)–C(3)	110.2 (6)
C(2)–C(1)–O(4′)	107.6 (5)	C(2)–C(3)–C(4)	111.0 (10)
C(1)–C(2)–O(2)	108.2 (1.6)	C(3)–C(4)–C(5)	112.0 (5)
C(3)–C(2)–O(2)	110.6 (1.9)	C(4)–C(5)–C(6)	113.3 (2)
C(2)–C(3)–O(3)	109.1 (9)	C(1)–O(5)–C(5)	114.0 (5)
C(4)–C(3)–O(3)	108.7 (1.3)	O(5)–C(1)–O(4′)	110.9 (9)
C(3)–C(4)–O(4)	105.9 (1.1)	C(5)6–C(6)6–O(6′)6	101 (1)
C(5)–C(4)–O(4)	108.1 (1.3)		
C(4)–C(5)–O(5)	109.3 (8)		
C(6)–C(5)–O(5)	106.1 (1.3)		
C(5)–C(6)–O(6)	112.1 (1.3)		

[a] See paragraph concerning supplementary material.

Table V. Comparison of the Macrocyclic Geometries between the Three Hydrate Inclusion Complexes

parameter[a]	α-CD· 6H_2O, form I[4]	α-CD· 6H_2O, form II[5]	α-CD· 7.57H_2O, form III[b]
mean C(1′)–O(4) bond length	1.412	1.411	1.416
variation	0.034	0.013	0.033
mean C(4)–O(4) bond length	1.436	1.439	1.441
variation	0.025	0.013	0.032
mean C(1′)–O(4)–C(4) angle	117.9	118.3	118.4
variation	3.2	3.8	1.9
mean O(4)···O(4) dist	4.307	4.246	4.234
variation	0.332	0.273	0.141
mean O(4)···O(4)···O(4) angle	120.3	119.7	119.9
variation	21.7	19.2	5.4
mean torsion angle ϕ	159.3	165.2	167.2
variation	23.7	17.9	12.2
mean torsion angle ψ	−165.6	−169.1	−170.0
variation	50.2	53.0	15.7
mean O(2)···O(3) dist	3.271	3.062	2.982
variation	1.570	1.227	0.250

[a] All bond lengths in A; all angles in degrees. Variation here means the difference between the maximum and minimum value.
[b] Present study results.

in Table VI. The mean values of ϕ and ψ are compared in Table V, which shows that the variation of these angles is minimum for form III while much larger variations are observed for forms I and II. The mean ϕ and ψ angles, interestingly, show a gradual increase in magnitude in going from forms I to III, corresponding to a cone with steeper walls in form III than in forms I and III.

The mean O(2)···O(3) distance between the neighboring glucose units is another parameter that characterizes these three water inclusion forms of α-CD. The mean values are 3.271, 3.062, and 2.982 Å for forms I, II, and III, respectively, and the mean value and variation of this parameter has minimum values for form III while it has maximum value for form I. This is because in form III all the six O(2)···O(3) type intramolecular hydrogen bonds between adjacent glucose units are formed while form I has four and form II has five intramolecular hydrogen bonds. The above comparison between various parameters of the water inclusion complexes of α-CD shows that this new modification (form III) is more symmetric in shape compared to the other forms, with

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(10) V. S. R. Rao, P. R. Sundarajan, C. Ramakrishnan, and G. N. Ramachandran, "*Conform. Biopolym., Pap. Int. Symp.*, **2** p 721–737 (1967).

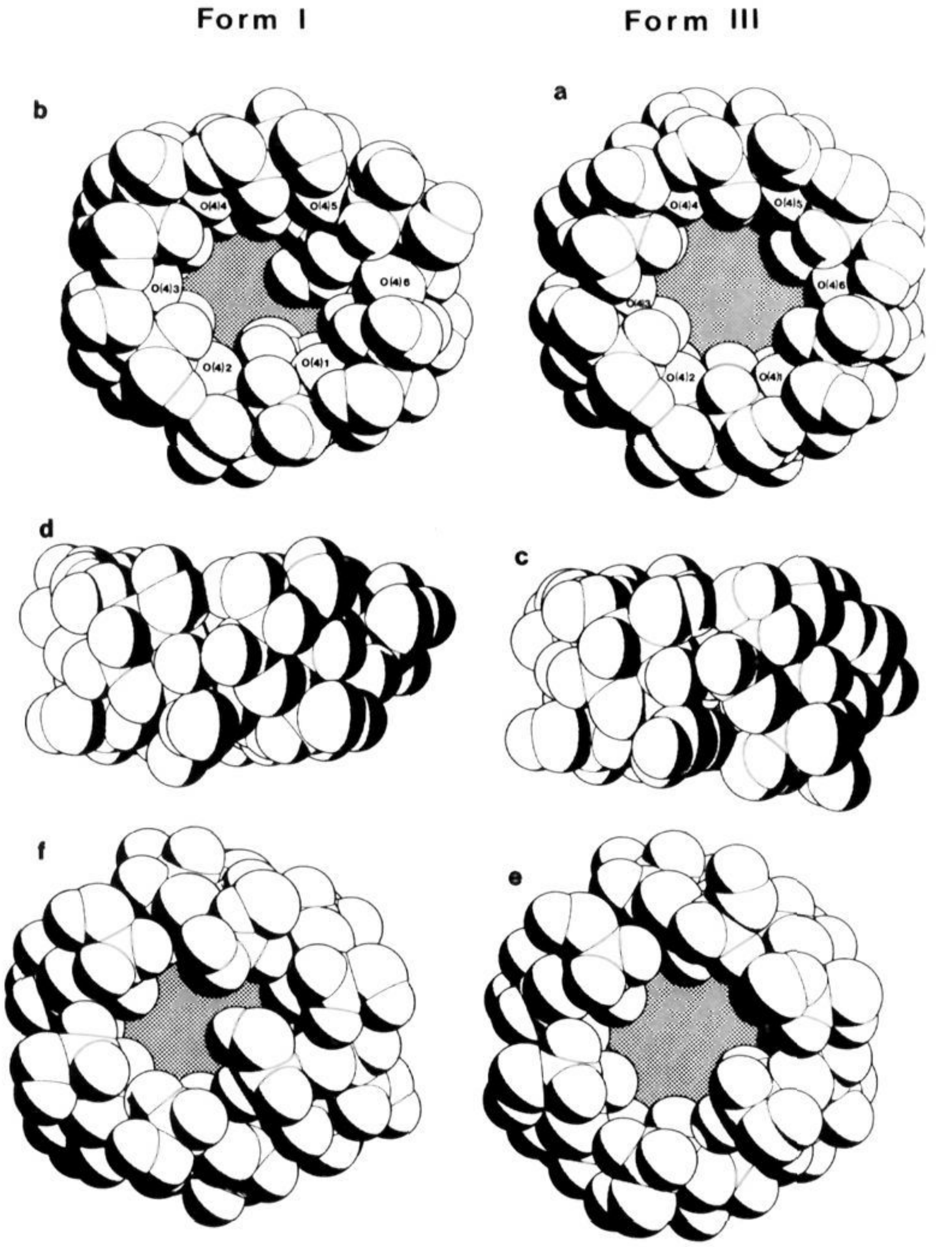

Figure 2. Computer-drawn space filling plots[18] of α-CD form I (b left) and α-CD form III (a) viewed perpendicular to the O(4) hexagon of the molecule facing the O(2)···O(3) side (top), from the side (c, d), and from the back (e, f). Note "round" shape of α-CD in form III but distortions in form I especially in the vicinity of glucoses 1 and 6 (marked by oxygens O(4)1, O(4)6) where O(2)···O(3) hydrogen bonds are broken in form I. Further, in form I, two O(6) hydroxyls point toward the cavity but not in form III.

Table VI. Conformation about the Glucosidic Bonds (Torsion Angles, Deg) in All Three α-CD·H_2O Determined Thus Far[a]

	this study	ref 4	ref 5
	ϕ		
O(4)2···C(1)2–O(4)3–C(4)3	171.6 (4)	162.6 (6)	172.2 (3)
O(4)3···C(1)3–O(4)4–C(4)4	167.9 (4)	165.9 (6)	167.8 (3)
O(4)4···C(1)4–O(4)5–C(4)5	160.2 (4)	147.6 (7)	163.0 (3)
O(4)5···C(1)5–O(4)6–C(4)6	172.4 (4)	147.4 (6)	154.4 (3)
O(4)6···C(1)6–O(4)1–C(4)1	161.2 (4)	160.9 (7)	165.2 (3)
O(4)1···C(1)1–O(4)2–C(4)2	170.1 (5)	171.1 (7)	168.6 (3)
	ψ		
C(1)2–O(4)3–C(4)3···O(4)4	−167.0 (4)	−169.9 (6)	−167.8 (3)
C(1)3–O(4)4–C(4)4···O(4)5	−171.5 (4)	−172.9 (7)	−178.7 (3)
C(1)4–O(4)5–C(4)5···O(4)6	−182.7 (4)	−181.4 (6)	−186.9 (3)
C(1)5–O(4)6–C(4)6···O(4)1	−150.1 (4)	−131.2 (7)	−134.7 (3)
C(1)6–O(4)1–C(4)1···O(4)2	−180.0 (4)	−175.8 (7)	−187.7 (3)
C(1)1–O(4)2–C(4)2···O(4)3	−168.9 (4)	−162.6 (6)	−158.8 (3)

[a] Note that variations in ϕ are 12.2 (in this study) and 23.7,[4] and 17.8°.[5] Variation in ψ is more pronounced, with variations of 32.6 (in this study), 50.2,[4] and 53°,[5] indicating relatively large flexibility in the latter torsion angle.

form I showing maximum asymmetry.

Figure 2 shows computer plots representing space filling model of α-CD form III (Figure 2a) and α-CD form I (Figure 2b) viewed perpendicular to the O(4) hexagon of the molecule facing the O(2)···O(3) side. Figures 2e,f show the back-view (O(6))side and Figures 2c,d show the side view of α-CD forms III and I. The more distorted nature of α-CD form I is clearly seen in comparison with the more symmetric "round" shape of form III.

Table VII

Glucopyranose Torsion Angles[a]

bonds	angle (deg)
C(1)–C(2)–C(3)–C(4)	−52.5 (1.8)
C(2)–C(3)–C(4)–C(5)	50.3 (1.8)
C(3)–C(4)–C(5)–O(5)	−51.9 (1.7)
C(4)–C(5)–O(5)–C(1)	59.9 (1.5)
C(5)–O(5)–C(1)–C(2)	−63.8 (2.1)
O(5)–C(1)–C(2)–C(3)	57.9 (1.5)

Atom O(6) Relative to O(5) and C(4)

glucose	O(5)–C(5)–C(6)–O(6)	C(4)–C(5)–C(6)–O(6)
1	−78.3 (7)	41.2 (7)
2	−72.0 (7)	47.5 (8)
3	−66.9 (7)	54.4 (7)
4	−59.8 (6)	59.9 (7)
5	−55.4 (6)	64.5 (7)
6	−63.8 (6)	55.4 (7)
	84.5 (1.1)[b]	−156.1 (1.1)[b]

[a] Average angles with standard deviations σ are given where $\sigma = [\Sigma_i(y_i - \overline{y})/5]^{1/2}$, where $\overline{y}$ is the mean value and y_i is the individual observation. A full list of these data is included with the supplementary material. [b] Refers to the disordered O(6′)6 position.

The individual glucopyranose torsion angles are presented in Table VII, which also gives the conformations about the C(5)–C(6) bonds. As Table VII indicates, the conformation about the C(5)–C(6) bonds defined by the torsion angles O(5)–C(5)–C(6)–O(6) and C(4)–C(5)–C(6)–O(6) for all the individual glucoses is the preferred[1] gauche–gauche. One of the primary hydroxyls,

Table VIII. Hydrogen Bond Distances (Å) and Angles (Deg)

donor	acceptor	symmetry[b]	O–H	$O\cdots O$	$O–H\cdots O$	$H\cdots O$
O(2)1	W3	c	0.98	2.741	157	1.81
O(3)1	O(2)6	a	0.98	3.011	168	2.04
O(6)1	O(3)2	j	1.04	2.903	179	1.87
O(2)2	W5	c	0.99	2.697	122	2.05
O(2)2	W5′	c	0.99	2.758	101	2.40
O(3)2	O(2)1	a	0.98	2.941	176	1.96
O(6)2	O(3)1	l	1.01	2.930	180	1.92
O(2)3	W1	a	0.96	2.768	179	1.81
O(3)3	O(2)2	a	0.99	2.900	128	2.18
O(6)3	O(6)6	d	1.05	2.778	177	1.74
O(2)4	O(6)5	i	1.00	2.710	180	1.71
O(3)4	O(2)3	a	0.98	2.913	179	1.94
O(6)4	W2	a	0.98	3.048	141	2.23
O(2)5	O(3)6	a	1.00	3.150	177	2.15
O(3)5	O(2)4	a	0.99	2.974	178	1.99
O(6)5	O(2)6	e	1.00	2.783	179	1.78
O(2)6	W4	f	0.98	2.619	138	1.80
O(3)6	O(3)4	i	1.02	2.841	179	1.82
O(6)6	W4	b	0.99	2.717	110	2.22
W1	O(3)6	d	0.97	2.829	168	1.87
W1	W2	c	0.98	3.005	157	2.08
W2	W1	g	1.02	2.854	178	1.83
W2	O(2)5	h	1.12	2.862	134	1.97
W3	O(6)3	k	1.00	2.800	178	1.80
W3	O(6)1	m	0.97	2.942	158	2.02
W4	W2	a	0.99	2.676	179	1.69
W4	W5	a	0.95	2.716	128	2.03
W4	W5′			2.777	128	2.09
W5	O(6)2	m		2.705		
W5′	O(6)2	m		2.700		
W5′	O(6)3	a		2.711		
W5′	O(6)6	d		2.771		
WA	O(2)1	e		2.971		
WA	O(6′)6	a		3.076		

[a] Average standard deviation for $O\cdots O$ distances is 0.007 Å.

[b] Symmetry code: (a) x, y, z; (b) $1 + x, y, z$; (c) $x, y, z - 1$; (d) $x - 1, y, z$; (e) $x, y, z + 1$; (f) $1 + x, y, z - 1$; (g) $\frac{1}{2} - x, -y, \frac{1}{2} + z$; (h) $\frac{1}{2} - x + 1, -y, \frac{1}{2} + z$; (i) $\frac{1}{2} - x + 1, -y, \frac{1}{2} + z - 1$; (j) $\frac{1}{2} + x, \frac{1}{2} - y, -z$; (k) $\frac{1}{2} + x, \frac{1}{2} - y, -z + 1$; (l) $\frac{1}{2} + x - 1, \frac{1}{2} - y, -z$; (m) $\frac{1}{2} + x - 1, \frac{1}{2} - y, -z + 1$; (n) $\frac{1}{2} - x, -y, \frac{1}{2} + z - 1$; (o) $x - 1, y, z + 1$.

O(6)6, is disordered with a low occupancy site (0.18 for O(6′)6), and only with respect to this position, the conformation about the C(5)–C(6) bond is gauche–trans.

Hydrogen Bonding. All the O–H hydrogens in the crystal structure except those associated with the disordered water molecules could be assigned when locations of hydrogen atoms estimated from the difference Fourier synthesis were taken into consideration. The hydrogen bonding scheme is given in Table VIII.

The cyclodextrin secondary hydroxyl groups are involved in intra- and intermolecular hydrogen bonding and also in hydrogen bonding to water oxygens. In this crystal structure, all six O(2)$\cdots$O(3) intramolecular hydrogen bonds exist. Figure 1a,b gives these hydrogen bonds viewed in two perpendicular directions with respect to the molecule. Depicted also are the four disordered water oxygens (WA, WA′, WA″, and WA‴) located at the annular cavity of the torus-shaped α-CD molecule. The included water WA which is near the opening of the cavity has contacts with O(6′)6 and also with a symmetry related O(2)1 with distances of 3.08 and 2.97 Å, respectively. The possibility of hydrogen bonds between the disordered water sites are not ruled out as WA to WA″ is 2.38 Å and WA′ to WA‴ is 2.52 Å. Figure 1b gives the distances between the disordered water sites of the included water molecules.

There are in total five waters of hydration outside the cyclodextrin cavity, and these form an extensive hydrogen-bonded network with each other and also with the cyclodextrin hydroxyl oxygens. There are three "circular" hydrogen bonds[11,12] involving the water molecules W1, W2, and W3 and the hydroxyl oxygens of α-CD, two of them being four-membered hydrogen-bonded circles; the third one is six-membered. One of the four-membered circles is nearly square shaped and is *homodromic* involving O(2)1, O(3)2 of α-CD with symmetry related W3, and O(6)1 atoms (Figure 3a) while the second four-membered circle is *antidromic* involving W1 and symmetry related W2, O(2)5, and O(3)6. The six-membered circle is also *antidromic* involving W1, O(2)3, and O(3)4 of one α-CD with symmetry related W1, W2, and O(3)6 atoms of neighboring α-CD. The latter four- and the six-membered circles have one side in common (Figure 3b) involving W1 and W2 atoms. Another frequently observed hydrogen-bonded configuration is the parallelogram (Figure 3c) formed by antiparallel oriented hydroxyls.

One of the water molecules (W5) located outside α-CD is disordered, having a major position (W5′ of occupancy 0.64) and a minor position (W5′ of occupancy 0.36). The coordination of the water molecules is given in Table IX. As the table indicates, water molecules W1 and W4 have distorted tetrahedral coordination with angles in the range between 86–151° and 80–132°. W2 has fivefold coordination, donating two hydrogen bonds and at the same time accepting three hydrogen bonds. Water W3, however, has only threefold coordination with near planar geometry and donates two hydrogen bonds while it acts as acceptor

Table IX. Coordination of Water Molecules (Distance below 3.2 Å)[a]

atoms		angle, deg
W1	O(3)6–W1–W2	98
	O(3)6–W1–O(2)3	113
	O(3)6–W1–W2(n)	98
	W(2)(c)–W1–O(2)3	108
	W(2)(c)–W1–W2(n)	151
	O(2)3–W1–W2(n)	86
W2	W1(g)–W2–O(2)5 (h)	85
	W1(g)–W2–W4	114
	W1–W2–O(6)4	124
	W1–W2–W1(e)	111
	O(2)5–W2–W4	159
	O(2)5–W2–O(6)4	61
	O(2)5–W2–W1(e)	68
	W4–W2–O(6)4	100
	W4–W2–W1(e)	109
	O(6)4–W2–W1(e)	96
W3	O(6)3(k)–W3–O(6)1(m)	136
	O(6)3(k)–W3–O(2)1(e)	127
	O(6)1(m)–W3–O(2)1(e)	91
W4	W2–W4–W5	132
	W2–W4–O(2)6(o)	111
	W2–W4–O(6)6(d)	129
	W5–W4–O(2)6(o)	81
	W5–W4–O(6)6(d)	80
	O(2)6–W4–O(6)6(d)	114
W5	O(2)2(e)–W5–W4	97
	O(2)2(e)–W5–O(6)2	139
	W4–W5–O(6)2	114
W5′	O(6)3–W5′–O(6)2(m)	95
	O(6)3–W5′–O(6)6(d)	61
	O(6)3–W5′–O(2)2(e)	106
	O(6)3–W5′–W4	112
	O(6)2(m)–W5′–O(6)6(d)	90
	O(6)2(m)–W5′–O(2)2(e)	136
	O(6)2(m)–W5′–W4	112
	O(6)6(d)–W5′–O(2)2(e)	134
	O(6)6(d)–W5′–W4	59
	O(2)2(e)–W5′–W4	95
WA	O(2)1(e)–WA–O(6′)6	87

[a] Average standard deviations for angles are 0.5°; distances given in Table VIII. Letters in parentheses refer to symmetry operations of Table VIII.

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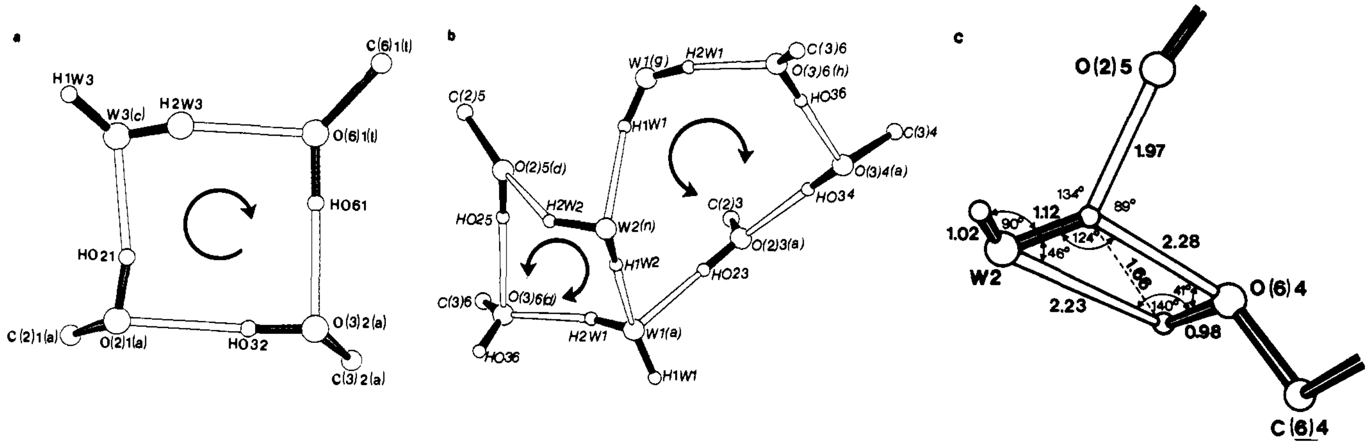

Figure 3. Views of the four-membered *homodromic* circular hydrogen bond (a) and of the *antidromic* four- and six-membered circles (b). Symmetry operations given in parentheses are defined in Table VIII. Circular arrows pointing in one (a) and in two (b) directions indicate dromicity of circles. In (c), the parallelogram-like hydrogen-bonding interactions are displayed. Note short H···H distance, which is considerably less than van der Waals contact.

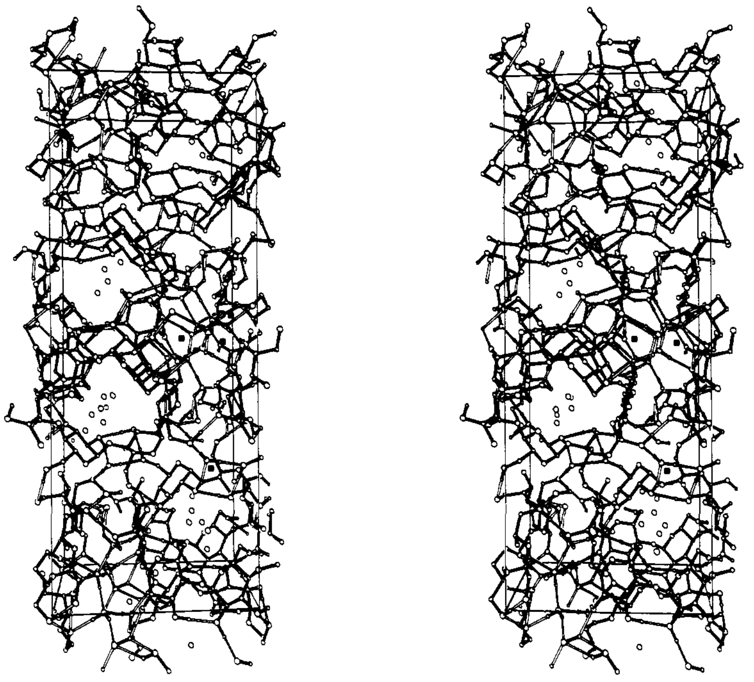

Figure 4. Stereoview of molecular packing and hydrogen bonding in the unit cell: covalent bonds drawn black; hydrogen bonds with open lines; o, hydrogen; ○, oxygen, carbon; ■, circular hydrogen bonds and parallelogram-like hydrogen-bonding interactions.

for only one hydrogen bond. The disordered sites W5 and W5′ are separated by 1.06 Å from each other. The major site W5 has threefold coordination, while the minor site W5′ has fivefold coordination. The hydrogens of these disordered sites could not be located. However, it is clear that W5 acts as an acceptor of two hydrogen bonds from O(2)2 and W4 atoms, and it serves as a donor of only one hydrogen bond to O(6)2. Similarly, the closely located W5′ serves as acceptor of hydrogen bonds from O(2)2 and W4 and donates one hydrogen bond to O(6)2. There are two additional contacts for W5′ with symmetry related O(6)3 and O(6)6 atoms. These may be possible acceptors of hydrogen bonds from W5′. A stereoview[13] showing the packing of α-CD in the unit cell is given in Figure 4 viewed along the *c* axis.

Mechanism of Adduct Formation. An induced-fit type mechanism of adduct formation of α-CD inclusion complexes has been proposed.[2] The "*empty*" α-CD molecule in the earlier hexahydrate crystal structure[4] represents the "empty" state prior to complex formation. It is not "round" but distorted and occurs in a "tense" state because one glucose is rotated inward and gives rise to unfavorable φ and ψ angles; further the ring of O(2)···O(3) hydrogen bonds is disrupted at that glucose. The two included water molecules are in fixed positions due to hydrogen bonding to O(6) of the rotated glucose, with the O(5)–C(5)–C(6)–O(6) torsion angle in the less preferred (+)gauche form. A similar conformation for α-CD was observed in another crystal modification.[5] It had been predicted that this particular "tense" α-CD molecule could undergo complex formation with a substrate either directly or via an intermediate, "round" hydrated α-CD with the ring of O(2)···O(3) hydrogen bonds fully established, all O(6) hydroxyls turned "outside" in preferred (−)gauche form and the water rattling in disordered position, analogous to krypton in the α-CD krypton complex.[14] This structure is now actually observed in this α-CD–7.57 water, which did not crystallize from pure water as the other two modifications with distorted α-CD but from 1.2 M $BaCl_2$. Obviously, the addition of salt induced a conformational change of α-CD, leading to a structure which was considered as transition state for complex formation.[2]

In this respect, the distorted cyclodextrin form with the disrupted ring of O(2)···O(3) hydrogen bonds is only observed for

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α-CD$\cdot$H$_2$O while the higher homologues β-CD and γ-CD both occur, as "empty" hydrate complexes, in the "round", relaxed form with included water molecules displaying extensive statistical disorder.[15,16] As pointed out recently,[17] the main reason for these structural differences might reside in the average O(2)···O(3) distances which in α-CD are approximately 3.0 Å but are shortened to about 2.83 Å in both β-CD and γ-CD. These distances allow only relatively weak hydrogen bonds in α-CD but strong hydrogen bonds in β-CD and δ-CD and therefore contribute significantly to the stabilization of the "round" structure of the macrocycle in β-CD and γ-CD.

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Supplementary Material Available: Tables of bond lengths (Table IIIS), bond angles (Table IVS), torsion angles (Table VIIS), and observed and calculated structure factor amplitudes (Table XS) (27 pages). Ordering information is given on any current masthead page.

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Crystal Structure and Solution Studies of the Molecular Conformation of the Cyclic Hexapeptide *cyclo*-(Gly-L-His-Gly-L-Ala-L-Tyr-Gly)

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Abstract: The crystal structure of *cyclo*-(Gly-L-His-Gly-L-Ala-L-Tyr-Gly)$\cdot$3H$_2$O has been determined by single-crystal X-ray diffraction and refined by block-diagonal least squares to an R value of 0.053. The crystals are monoclinic, $P2_1$, with cell constants of a = 13.163 (1) Å, b = 15.632 (1) Å, c = 7.469 (1) Å, and β = 106.83 (1)°. The molecular conformation in the crystal includes a type I β turn at L-Ala-L-Tyr and a type II′ β turn at Gly-L-His, with 3.10- and 3.06-Å (4→1) hydrogen bonds, respectively. The conformation is very similar to that reported for crystalline *cyclo*-(Gly-L-Ala-Gly-L-Ala-L-Ala-Gly). The results of proton NMR studies of the peptide in solution suggest that the crystal conformation, if present in solution, is in rapid exchange with other conformations. β-turn conformations found in crystalline cyclic hexapeptides are reviewed.

Introduction

In 1958 Schwyzer proposed that cyclic hexapeptides adopt as a stable backbone conformation in antiparallel β structure, in which two chain reversals stabilized by ten-membered hydrogen-bonded rings (β turns) are connected by two extended residues.[2] Since then, evidence has been accumulating that two β-turn structures, where possible, are very much favored by cyclic hexapeptides in the crystal and in solution, although the transannular hydrogen bonds are not consistently present. Because this regularly appearing framework provides the possibility of generating well-defined structures that may be useful in the design of physiologically active peptides, it is of interest to establish what rules operate to position a sequence of six amino acid residues on that backbone. To that end it is still necessary to examine crystal and solution structures of additional cyclic hexapeptides.

We report here the crystal structure of *cyclo*-(Gly-L-His-Gly-L-Ala-L-Tyr-Gly) (*c*-GHGAYG), which provides another example of the two-β-turn backbone. Because the sample from which the crystals were grown was mislabeled as *cyclo*-(Gly-L-His-Gly-L-Tyr-L-Ala-Gly) (*c*-GHGYAG), we reinvestigated[3] the nuclear magnetic resonance spectra of the substance as well. We discuss the likely solution conformations of *c*-GHGAYG and the rules so far evident for placing the hexapeptide sequence within the Schwyzer backbone.

Experimental Section

cyclo-(Gly-L-His-Gly-L-Ala-L-Tyr-Gly)$\cdot$HBr from a bottle labeled *cyclo*-(Gly-L-His-Gly-L-Tyr-L-Ala-Gly) was dissolved in methanol and the solvent was allowed to evaporate slowly. Thick, platelike crystals were obtained. The crystal used for data collection measured 0.3 × 0.2 × 0.2 mm. Examination of the reciprocal lattice showed systematic extinctions characteristic of space group $P2_1$. ($P2_1/m$ is not possible.) Cell constants, obtained by least-squares refinement of $\pm 2\theta$ values of 20 reflections using Cu Kα radiation, are a = 13.163 (1) Å, b = 15.632 (1) Å, c = 7.469 (1) Å, and β = 106.83 (1)°. The measured density of the crystal, by flotation in chloroform–cyclohexane, was 1.35 g/mL, and the calculated density is 1.374, assuming one peptide molecule and three water molecules in the asymmetric unit.

Three-dimensional intensity data were collected using nickel-filtered Cu Kα radiation to a 2θ maximum of 125°. A θ–2θ scan rate of 2° min^{-1}, with a variable scan width and 10-s background measurements at both extremities of the scan, was used to measure 2442 independent reflections. Throughout the data collection three standard reflections were remeasured every 50 reflections to monitor the decay and alignment of the crystal. A regular, periodic fluctuation of about 20%, arising probably from an instability of the X-ray source, was observed. The observed reflection intensities were therefore corrected as a function of time according to the fluctuation observed in standard reflections. The structure amplitudes and their estimated errors were calculated from the expressions $F_o = (QI_n)^{0.5}$ and $\sigma^2(F_o) = (Q/4I_n)[I_s + (t_s/t_b)^2 I_b + (0.02 I_n)^2]$, where Q contains corrections for Lorentz polarization, ab-

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