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Topography of Cyclodextrin Inclusion Complexes. 8. Crystal and Molecular Structure of the α-Cyclodextrin–Methanol–Pentahydrate Complex. Disorder in a Hydrophobic Cage[1]

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Abstract: α-Cyclodextrin (α-CD, cyclohexaamylose) is a cyclic molecule consisting of six glucoses. Owing to its 5 Å wide annular aperture it is able to form inclusion complexes with small molecules even in aqueous solution. Complex formation was recently attributed to a strained, high-energy "tense" conformation of "empty" α-CD which transforms into an unstrained low-energy, "relaxed" conformation upon inclusion of some substrate molecule. In order to test this mechanism, the structure of the α-CD–methanol complex was of interest to study. The α-CD–methanol–pentahydrate adduct crystallizes in space group $P2_12_12_1$ with $a = 14.339$ Å, $b = 37.365$ Å, $c = 9.465$ Å. A total of 4283 intensities were collected using a diffractometer and corrected for absorption with empirical methods. The structure was solved on the basis of the isomorphous α-CD–propanol-4.8hydrate complex and refined by full-matrix least-squares methods to $R = 4.3\%$ for all the data. All hydrogen atoms except those of disordered hydroxyl groups were located from difference Fourier maps. The α-CD molecule is in an unstrained "relaxed" conformation stabilized through a ring of O(2)···O(3) hydrogen bonds between adjacent glucoses; all C(6)–O(6) bonds point away from the center of the molecule but one is twofold disordered, with 25% occupancy toward the center and in hydrogen bonding contact with the included methanol molecule. The latter assumes two sites at equal population: 50% near the O(6) side of the α-CD molecule and hydrogen bonded to the disordered O(6) group; the other 50% within the cavity of the α-CD and not involved in hydrogen bonding. Both methanol molecules perform excessive thermal motion and are held mainly by van der Waals contacts to C(3)–H and C(5)–H methine protons. This study clearly supports the mechanism of inclusion formation described at the outset.

Cyclodextrins (cycloamyloses) are cyclic molecules consisting of six to nine glucose units linked together through α(1 → 4) glucosidic bonds. The smallest of these molecules, α-cyclodextrin (α-CD), has an annular space 5 Å in diameter and assumes the shape of a truncated cone about 9 Å high, 8 Å at the narrow side, and 13.5 Å at the wide side. The narrow side is lined with the primary O(6) hydroxyl groups while the wide side is lined with secondary O(2) and O(3) hydroxyls. α-CD is therefore mainly hydrophilic in character at the outside of the cavity but at the inside it is hydrophobic, as here the lining consists of hydrogen atoms and of the O(4) atoms which link the glucose units.

α-CD is soluble in water and, owing to its cavity, it is able to form inclusion complexes with other guest (substrate) molecules even in aqueous solution.[2-5] A number of these complexes could be crystallized and were analyzed in detail by x-ray structural studies.[5] It was striking to find that in the water inclusion complex α-CD·2H₂O, which represents the "empty" α-CD molecule occurring in aqueous solution,[6] the α-CD appears unsymmetrical, collapsed to fit its 5 Å wide cavity to the 3.8 Å thick water molecules. In all the other complexes, even with krypton of 4 Å diameter,[7] the α-CD molecule is almost cyclic and the cavity is opened fully to accommodate the substrate molecules. On the basis of these results the following mechanism for the inclusion process was proposed.[5-7] In the "empty", collapsed state with two included water molecules, the α-CD is in a high-energy conformation owing to unfavorable conformational angles and to disruption of the otherwise fully developed ring of six hydrogen bonds between the O(2), O(3) hydroxyls of adjacent glucoses. When inclusion occurs with some substrate molecule, the α-CD assumes a circular, unstrained conformation with the formation of O(2)···O(3) hydrogen bonds. This represents a low-energy state (Figure 1). As there is an analogy between this mechanism and the mechanism proposed for the enzyme–substrate adduct formation,[8] the two states of the α-CD molecule have been termed "tense" and "relaxed".[5,7] The driving force toward inclusion complex formation resides mainly in the α-CD molecule itself while substrate-α-CD interactions are of minor importance. This mechanism also explains why a variety of substrates, ranging from the purely hydrophilic such as salts, methanol, and water to the purely hydrophobic such as halogen, krypton, and paraffins, react with α-CD. The conformational change of α-CD upon complex formation has also been observed by CD spectroscopy in aqueous solution.[9] The x-ray studies support this finding and provide a basis to understand

Table I. Final Atomic Coordinates and Anisotropic Temperature Factors for the α-CD–Methanol–Pentahydrate Complex[a]

Atom	x	y	z	$B(11)$, $\times 10^4$	$B(22)$, $\times 10^5$	$B(33)$, $\times 10^4$	$B(12)$, $\times 10^5$	$B(13)$, $\times 10^4$	$B(23)$, $\times 10^5$
C(1)1	0.7865 (3)	0.2329 (1)	0.0088 (5)	46 (2)	46 (3)	119 (6)	−15 (7)	3 (3)	4 (1)
C(2)1	0.8448 (3)	0.2185 (1)	−0.1131 (5)	39 (2)	58 (3)	96 (6)	−18 (7)	0 (3)	4 (1)
C(3)1	0.9006 (3)	0.1862 (1)	−0.0631 (5)	41 (2)	49 (3)	88 (5)	−18 (7)	10 (3)	0 (1)
C(4)1	0.9550 (3)	0.1951 (1)	0.0707 (5)	40 (2)	39 (3)	100 (5)	−21 (7)	2 (3)	0 (1)
C(5)1	0.8973 (3)	0.2138 (1)	0.1839 (5)	47 (2)	43 (3)	98 (5)	−7 (7)	4 (3)	−1 (1)
C(6)1	0.9560 (4)	0.2299 (1)	0.3002 (5)	67 (3)	68 (4)	113 (7)	−33 (9)	−7 (4)	−6 (1)
O(4)1	0.9853 (2)	0.1614 (1)	0.1264 (3)	31 (1)	44 (2)	105 (4)	−17 (4)	3 (2)	3 (1)
O(5)1	0.8466 (2)	0.2434 (1)	0.1216 (3)	51 (2)	38 (2)	122 (4)	−5 (5)	2 (2)	0 (1)
O(2)1	0.7853 (2)	0.2078 (1)	−0.2269 (3)	51 (2)	94 (3)	101 (4)	−26 (6)	−7 (2)	5 (1)
O(3)1	0.9640 (2)	0.1756 (1)	−0.1724 (3)	46 (2)	71 (2)	99 (4)	−1 (5)	8 (2)	−2 (1)
O(6)1A	1.0422 (4)	0.2454 (1)	0.2595 (7)	48 (3)	60 (4)	147 (9)	−53 (10)	−12 (5)	−2 (2)
O(6)1B	0.8972 (6)	0.2389 (2)	0.4118 (7)	128 (6)	83 (6)	129 (10)	−31 (16)	4 (7)	−8 (2)
C(1)2	0.4548 (3)	0.1887 (1)	0.1747 (5)	36 (2)	42 (3)	123 (6)	18 (7)	2 (3)	6 (1)
C(2)2	0.4738 (3)	0.1874 (1)	0.0167 (5)	43 (2)	53 (3)	97 (6)	−8 (7)	−6 (3)	4 (1)
C(3)2	0.5768 (3)	0.1837 (1)	−0.0092 (4)	46 (2)	50 (3)	76 (5)	10 (7)	0 (3)	2 (1)
C(4)2	0.6283 (3)	0.2134 (1)	0.0672 (5)	35 (2)	46 (3)	97 (5)	8 (7)	1 (3)	2 (1)
C(5)2	0.6026 (3)	0.2147 (1)	0.2238 (5)	40 (2)	53 (3)	98 (6)	1 (7)	5 (3)	0 (1)
C(6)2	0.6424 (4)	0.2472 (1)	0.2993 (6)	64 (3)	79 (4)	132 (7)	−25 (10)	4 (4)	−8 (2)
O(4)2	0.7259 (2)	0.2055 (1)	0.0535 (3)	36 (1)	38 (2)	126 (4)	−1 (4)	8 (2)	3 (1)
O(5)2	0.5027 (2)	0.2175 (1)	0.2379 (3)	43 (2)	50 (2)	115 (4)	7 (5)	10 (2)	0 (1)
O(2)2	0.4215 (2)	0.1591 (1)	−0.0476 (3)	48 (2)	71 (2)	115 (4)	−30 (6)	−18 (2)	6 (1)
O(3)2	0.5925 (2)	0.1858 (1)	−0.1586 (3)	54 (2)	96 (3)	90 (4)	−35 (6)	3 (2)	0 (1)
O(6)2	0.6277 (2)	0.2795 (1)	0.2230 (5)	63 (2)	62 (3)	252 (7)	−31 (6)	12 (4)	−5 (1)
C(1)3	0.4040 (3)	0.0773 (1)	0.5163 (4)	26 (2)	46 (3)	83 (5)	22 (6)	0 (3)	2 (1)
C(2)3	0.3672 (3)	0.0732 (1)	0.3666 (5)	30 (2)	42 (3)	104 (6)	14 (6)	−8 (3)	0 (1)
C(3)3	0.4197 (3)	0.0976 (1)	0.2655 (4)	36 (2)	44 (3)	79 (5)	22 (7)	−4 (3)	0 (1)
C(4)3	0.4195 (3)	0.1359 (1)	0.3205 (4)	32 (2)	43 (3)	72 (5)	15 (6)	3 (3)	2 (1)
C(5)3	0.4513 (3)	0.1376 (1)	0.4735 (4)	42 (2)	45 (3)	84 (5)	3 (7)	0 (3)	0 (1)
C(6)3	0.4413 (4)	0.1746 (1)	0.5409 (5)	86 (4)	53 (3)	107 (6)	−20 (9)	−9 (4)	−5 (1)
O(4)3	0.4826 (2)	0.1553 (1)	0.2326 (3)	36 (1)	45 (2)	106 (4)	21 (5)	6 (2)	4 (1)
O(5)3	0.3973 (2)	0.1134 (1)	0.5593 (3)	42 (2)	48 (2)	79 (3)	29 (5)	8 (2)	1 (1)
O(2)3	0.3777 (2)	0.0360 (1)	0.3288 (3)	53 (2)	38 (2)	138 (4)	0 (5)	−23 (3)	0 (1)
O(3)3	0.3775 (2)	0.0973 (1)	0.1275 (3)	56 (2)	65 (2)	75 (4)	46 (6)	−12 (2)	−2 (1)
O(6)3	0.3483 (3)	0.1883 (1)	0.5301 (4)	103 (3)	52 (2)	137 (5)	117 (7)	21 (3)	0 (1)
C(1)4	0.7074 (2)	0.0152 (1)	0.7219 (4)	26 (2)	38 (3)	68 (4)	10 (6)	3 (3)	3 (1)
C(2)4	0.6451 (2)	−0.0094 (1)	0.6341 (4)	27 (2)	37 (3)	77 (5)	9 (6)	2 (3)	0 (1)
C(3)4	0.5833 (3)	0.0132 (1)	0.5386 (4)	26 (2)	38 (3)	70 (4)	1 (6)	−1 (3)	0 (1)
C(4)4	0.5321 (3)	0.0423 (1)	0.6211 (4)	30 (2)	36 (3)	69 (5)	1 (6)	2 (3)	1 (1)
C(5)4	0.5958 (3)	0.0632 (1)	0.7211 (4)	30 (2)	37 (3)	75 (5)	14 (6)	−6 (3)	0 (1)
C(6)4	0.5438 (3)	0.0858 (1)	0.8279 (5)	45 (2)	48 (3)	92 (5)	25 (7)	2 (3)	−3 (1)
O(4)4	0.4976 (2)	0.0660 (1)	0.5133 (3)	26 (1)	52 (2)	75 (3)	17 (4)	1 (2)	5 (1)
O(5)4	0.6515 (2)	0.0389 (1)	0.8022 (3)	33 (1)	49 (2)	60 (3)	32 (4)	−2 (2)	0 (1)
O(2)4	0.7057 (2)	−0.0321 (1)	0.5557 (3)	31 (1)	41 (2)	125 (4)	14 (4)	0 (2)	−6 (1)
O(3)4	0.5161 (2)	−0.0101 (1)	0.4718 (3)	33 (1)	41 (2)	81 (3)	−9 (4)	−10 (2)	0 (1)
O(6)4	0.4845 (2)	0.0648 (1)	0.9164 (3)	44 (2)	67 (2)	89 (4)	64 (5)	14 (2)	1 (1)
C(1)5	1.0343 (3)	0.0677 (1)	0.5689 (4)	29 (2)	61 (3)	65 (5)	−17 (7)	−5 (3)	0 (1)
C(2)5	1.0210 (3)	0.0271 (1)	0.5728 (4)	30 (2)	56 (3)	83 (5)	4 (6)	1 (3)	1 (1)
C(3)5	0.9187 (3)	0.0179 (1)	0.5622 (4)	31 (2)	36 (3)	71 (5)	0 (6)	1 (3)	0 (1)
C(4)5	0.8611 (2)	0.0384 (1)	0.6694 (4)	24 (2)	43 (3)	65 (4)	0 (6)	0 (3)	0 (1)
C(5)5	0.8822 (3)	0.0785 (1)	0.6621 (4)	28 (2)	49 (3)	67 (5)	−20 (6)	0 (3)	−1 (1)
C(6)5	0.8376 (3)	0.0995 (1)	0.7830 (4)	40 (2)	44 (3)	80 (5)	−18 (7)	−1 (3)	0 (1)
O(4)5	0.7656 (2)	0.0337 (1)	0.6291 (3)	24 (1)	41 (2)	65 (3)	−9 (4)	−1 (2)	1 (1)
O(5)5	0.9810 (2)	0.0844 (1)	0.6752 (3)	28 (1)	61 (2)	75 (3)	−30 (4)	2 (2)	−2 (1)
O(2)5	1.0748 (2)	0.0116 (1)	0.4611 (4)	41 (2)	68 (2)	141 (4)	28 (5)	32 (2)	−1 (1)
O(3)5	0.9079 (2)	−0.0201 (1)	0.5873 (3)	35 (1)	37 (2)	99 (4)	7 (4)	2 (2)	0 (1)
O(6)5	0.8735 (2)	0.0891 (1)	0.9179 (3)	44 (2)	56 (2)	66 (3)	−34 (5)	6 (2)	0 (1)
C(1)6	1.0803 (3)	0.1544 (1)	0.1356 (4)	35 (2)	58 (3)	84 (5)	−35 (7)	0 (3)	1 (1)
C(2)6	1.0955 (3)	0.1149 (1)	0.0945 (4)	31 (2)	57 (3)	65 (5)	−18 (7)	0 (3)	0 (1)
C(3)6	1.0461 (3)	0.0907 (1)	0.1964 (4)	32 (2)	42 (3)	80 (5)	−13 (6)	0 (3)	−3 (1)
C(4)6	1.0710 (2)	0.0992 (1)	0.3484 (4)	27 (2)	49 (3)	75 (5)	−35 (6)	0 (3)	0 (1)
C(5)6	1.0623 (3)	0.1393 (1)	0.3803 (4)	44 (2)	50 (3)	81 (5)	−34 (7)	3 (3)	0 (1)
C(6)6	1.1030 (4)	0.1504 (1)	0.5224 (5)	68 (3)	65 (4)	91 (6)	−40 (9)	−6 (4)	−2 (1)
O(4)6	1.0062 (2)	0.0793 (1)	0.4320 (3)	29 (1)	61 (2)	65 (3)	−36 (5)	0 (2)	2 (1)
O(5)6	1.1139 (2)	0.1596 (1)	0.2760 (3)	42 (2)	59 (2)	77 (3)	−54 (5)	1 (2)	−1 (1)
O(2)6	1.0589 (2)	0.1096 (1)	−0.0444 (3)	41 (2)	86 (3)	62 (3)	−19 (5)	0 (2)	−2 (1)
O(3)6	1.0726 (2)	0.0536 (1)	0.1731 (3)	42 (2)	48 (2)	92 (3)	7 (5)	−6 (2)	−3 (1)
O(6)6A	1.1989 (3)	0.1379 (1)	0.5330 (5)	38 (2)	119 (4)	156 (7)	−28 (8)	−23 (3)	−5 (2)
O(6)6B	1.0641 (13)	0.1861 (3)	0.5477 (14)	200 (17)	39 (9)	123 (18)	−116 (33)	−89 (16)	0 (3)
C(A)	0.7806 (24)	0.1686 (9)	0.5060 (24)	531 (51)	558 (6)	186 (31)	1377 (96)	35 (39)	37 (11)
O(A)	0.8519 (6)	0.1709 (2)	0.5303 (9)	107 (6)	79 (6)	124 (10)	51 (17)	24 (7)	3 (2)
1(B)	0.7062 (9)	0.1268 (4)	0.4031 (22)	53 (7)	198 (18)	475 (43)	67 (30)	−21 (16)	−13 (8)

Table I *(Continued)*

Atom	x	y	z	$B(11)$ $\times 10^4$	$B(22)$, $\times 10^5$	$B(33)$, $\times 10^4$	$B(12)$, $\times 10^5$	$B(13)$, $\times 10^4$	$B(23)$, $\times 10^5$
2(B)	0.7309 (10)	0.1086 (4)	0.2804 (16)	169 (12)	297 (19)	431 (29)	345 (40)	0 (17)	−23 (6)
W1	0.2423 (5)	0.1694 (2)	0.8805 (12)	48 (4)	102 (7)	296 (18)	4 (14)	−1 (8)	0 (3)
W2	0.2930 (2)	0.0394 (1)	0.8495 (4)	59 (2)	110 (3)	209 (6)	52 (7)	−17 (3)	−4 (1)
W3	0.2418 (3)	0.2251 (1)	0.3284 (5)	75 (2)	134 (4)	216 (7)	−101 (8)	0 (4)	12 (1)
W4A	0.2726 (5)	0.1704 (2)	0.7791 (8)	46 (4)	70 (5)	147 (10)	29 (12)	−9 (6)	−3 (2)
W4B	0.2034 (2)	0.1014 (1)	0.7872 (4)	54 (2)	110 (3)	143 (5)	18 (7)	10 (3)	1 (1)
W5	0.2404 (2)	0.0145 (1)	0.1416 (4)	54 (2)	102 (3)	137 (5)	0 (7)	−16 (3)	0 (1)

^{a} Temperature factors are multiplied by 10^4 or 10^5 and are in the form $T = \exp\,[-(b_{11}h^2 + b_{22}k^2 + b_{33}l^3 + 2b_{12}hk + 2b_{13}hl + 2b_{23}kl)]$. Standard deviations obtained from the least-squares correlation matrix are given in parentheses. Occupational parameters for disordered atoms are: O(6)1A, 0.5; O(6)1B, 0.5; O(6)6A, 0.75; O(6)6B, 0.25; O(A), 0.5; C(A), 0.5; 1(B), 0.5; 2(B), 0.5; W1, 0.5; W4A, 0.5 Å.
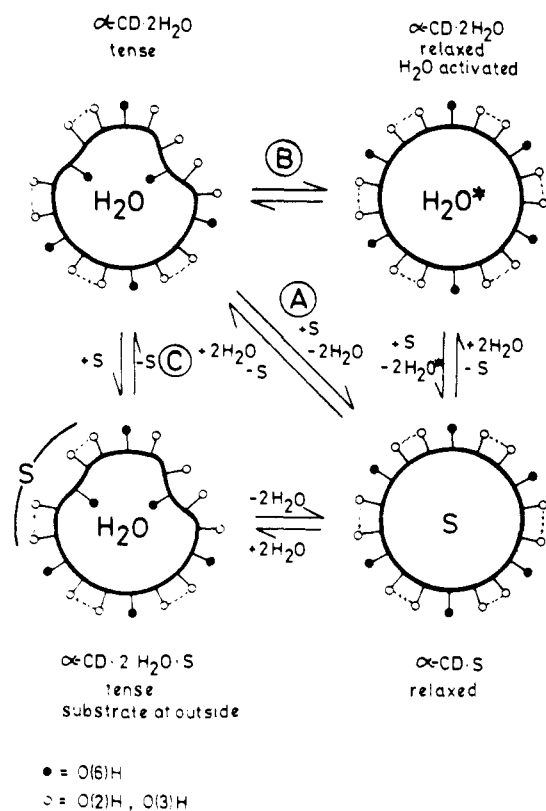

Figure 1. Schematic representation of the α-CD–substrate inclusion process. The "empty" α-CD molecule in the upper left hand corner corresponds to the α-CD·(H$_2$O)$_2$ complex found in the crystalline state.[6] The molecule has a collapsed, distorted conformation with only four O(2)⋯O(3) hydrogen bonds formed and corresponds to a high-energy, "tense" state. Upon inclusion of a substrate molecule via routes A, B, or C it goes into a low-energy, "relaxed" state with unstrained conformation and all six O(2)⋯O(3) hydrogen bonds (indicated by broken lines) formed.[5-7] H$_2$O* represents "activated" water in unstrained, relaxed α-CD.

and to interpret these data. In this context it was of interest to study the α-CD–methanol complex as here a structure similar to the one found for the α-CD·2H$_2$O complex could be expected—H$_2$O and methanol are both hydrophilic and have dimensions smaller than the 5 Å wide α-CD cavity. The question was whether the α-CD molecule would collapse to fit to the methanol molecule dimensions or whether it would assume an unstrained, cyclic structure. In the latter case, this would provide a strong support for the proposed mechanism of inclusion complex formation. A short account of the α-CD–methanol complex structure has been given recently.[10]

Experimental Section

Materials and Methods. α-CD was purchased from Corn Products Development, Englewood Cliffs, N.J., and used after further purifi-

cation by recrystallization once from 1-propanol and twice from water.[2b] Methanol p.a. grade was a product of Merck Co., Darmstadt.

Crystals were grown by slow cooling of a 10^{-2} M aqueous solution of α-CD containing 20% (v/v) of methanol. The space group of the prismatic crystals is $P2_12_12_1$. The cell constants were determined by least-squares methods from 12 diffractometer measured reflections using Ni-filtered Cu Kα radiation and are $a = 14.339$ (3) Å, $b = 37.365$ (10) Å, $c = 9.465$ (3) Å. With four formula units (C$_6$H$_{10}$O$_5$)$_6$·CH$_3$OH·5H$_2$O (1095 Daltons) per unit cell of volume 5071 Å^3, the calculated density is 1.435 g/cm^3. The experimentally obtained density using the flotation method with cyclohexane-methyl iodide is 1.44 g/cm^3.

A total of 4283 intensities were collected up to $2\theta = 125°$ using an automated STOE four-circle diffractometer equipped with Cu tube and Ni filter. The $2\theta/\omega$ scan method was utilized with stationary background counts before and after each scan. The data were corrected for absorption according to an empirical method[11] and further corrected for Lorentz and polarization effects.

As the crystal structure of the α-CD-methanol-adduct is pseudoisomorphous with the previously determined structures of adducts with water,[6] iodine,[12] 1-propanol,[13] and krypton,[7] the coordinates of the α-CD molecule of the 1-propanol structure were used for initial phasing of an electron density distribution. From then on, a series of full-matrix least-squares refinement cycles followed by difference Fourier calculations allowed us to locate all the water of hydration molecules, the methanol molecule, and the hydrogen atoms except those bonded to the disordered methanol molecule and to two O(6) hydroxyl groups.

The final disagreement index $R = \Sigma||F_{obsd}| - |F_{calcd}||/\Sigma|F_{obsd}|$ is 4.3% for all the 4283 data. In the refinement cycles, the carbon and oxygen atoms were refined anisotropically. The hydrogen atoms were assigned the isotropic B's of the atoms to which they were bonded covalently but were not refined. The scattering factors were taken from International Tables.[14] Intensity data showing secondary extinction effects were corrected at the very end of the refinement using a graphical method.[15]

Results and Discussion

Final coordinates and thermal parameters are given in Tables I and II; observed and calculated structure factors are listed in Table III (see paragraph at end of paper regarding supplementary material). In Tables IV–IX geometric data are gathered and Figures 2–7 illustrate the structure of the complex.

Bond Angles and Distances. The present study represents the most accurate α-CD structure yet determined and it is worthwhile to examine the results of the statistical analysis of the bond lengths and angles within the six independent glucoses (Table IV), even though details on glucose geometry have been published previously.[6]

In Table IV bond distances and angles are listed, with standard deviations obtained from the least-squares correlation matrix given in parentheses. The weighted average for each bond and angle type has been evaluated together with the weighted average standard deviation σ_i. It is obvious from the row entries in the table that the same bond or angle in the six
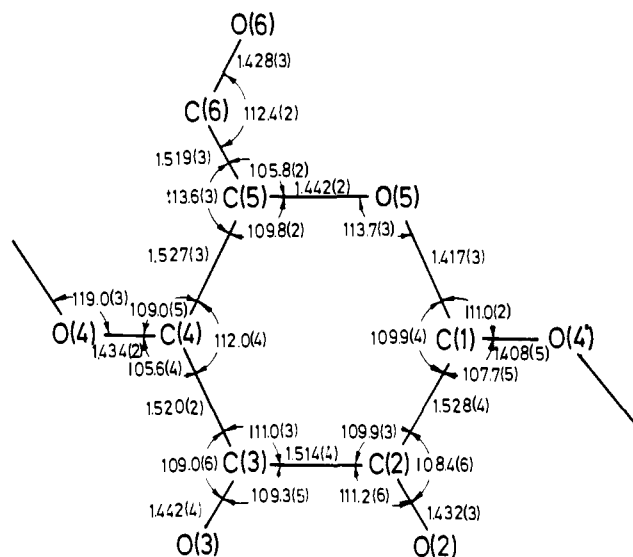
Figure 2. Averaged bond distances and angles for the glucose unit. Standard deviations are given in parentheses.

Table II. Coordinates and Isotropic Temperature Factors for the Hydroxyl Hydrogen Atoms

Name	x	y	z	B
H021	0.767	0.230	0.725	4.44
H031	0.993	0.152	0.855	3.67
H022	0.410	0.140	0.020	3.84
H032	0.660	0.189	0.831	4.19
H062	0.554	0.289	0.203	5.29
H023	0.335	0.030	0.260	3.36
H033	0.416	0.080	0.065	3.45
H063	0.323	0.160	0.528	4.87
H024	0.674	0.949	0.515	2.91
H034	0.489	0.004	0.405	2.47
H064	0.505	0.040	0.962	3.37
H025	1.060	0.021	0.375	3.72
H035	0.843	0.971	0.569	2.68
H065	0.943	0.092	0.931	2.69
H026	1.104	0.102	0.900	3.35
H036	1.033	0.043	0.100	2.87
H1W2	0.360	0.042	0.882	5.82
H2W2	0.280	0.019	0.760	5.82
H1W3	0.174	0.221	0.320	6.38
H2W3	0.250	0.241	0.410	6.38
H1W4B	0.241	0.079	0.833	5.13
H2W4B	0.240	0.122	0.838	5.13
H1W5	0.192	0.029	0.139	4.61
H2W5	0.263	0.018	0.051	4.61

[a] Positions of hydrogen atoms bonded to carbon atoms were computed from the α-CD skeleton and are not given in this table.

glucoses has the same value with >99.5% or >95% probability while the column entries for bonds and angles within one individual glucose differ from one another, the probability that they are the same being <50%.[16] The weighted averages for bond lengths, angles, and standard deviations have been entered in the diagram of Figure 2.

As in other α-CD adduct structures[5] the C(5)–O(5) and C(4)–O(4') bonds are longer than C(1)–O(5) and C(1)–O(4). (Primed atoms belong to the adjacent glucose.) Similarly, the exocyclic angles C(3)–C(4)–O(4), 105.6 (4)°, and C(6)–C(5)–O(5), 105.8 (2)°, are significantly smaller than tetrahedral with C(2)–C(1)–O(4'), 107.7 (5)°, only marginally smaller. It should be noted that each of these relatively small angles is compensated by a larger than tetrahedral angle with the same vertex atom: C(3)–C(4)–C(5), 112.0 (4)°; C(4)–C(5)–C(6), 113.6 (3)°; O(5)–C(1)–O(4'), 111.0 (2)°. The
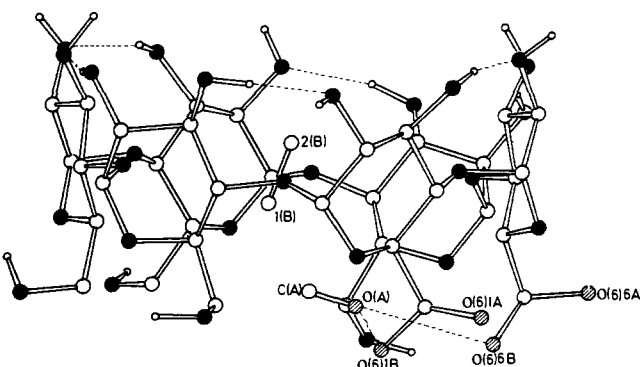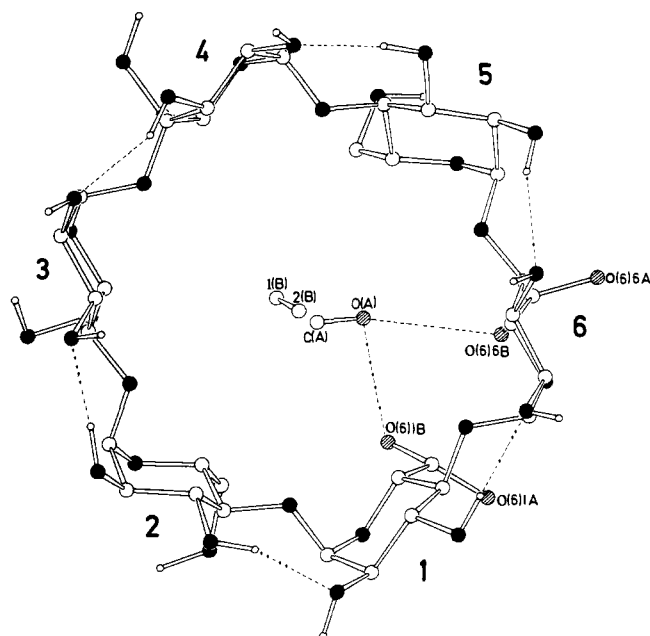

Figure 3. Schematic diagram of the α-CD–methanol complex, water of hydration molecules and hydrogen atoms bonded to carbons omitted: O = C, ● = O, ○ = H, ⊘ = disordered O. Hydrogen bonds are indicated by broken lines. The glucoses are numbered according to the entries in the tables.

ether-like linkage C(4)–O(4)–C(1'), 119.0 (3)°, is wider than the comparable C(5)–O(5)–C(1) angle of 113.7 (3)°, probably owing to ring geometry requirements in the latter case. The relatively free primary hydroxyl group has a C(5)–C(6)–O(6) angle of 112.4 (2)°, a value considerably greater than tetrahedral. On the other hand, the angles around C(2) and C(3) appear more "normal".

Glucose Conformation. The six glucoses are in the C(1) chair conformation with rather similar endocyclic torsional angles (Table V) and similar deviations of the glucose atoms from the least-squares planes through atoms C(2), C(3), C(5), O(5) (Table VI). As mentioned previously[5] the individual glucoses behave as rather rigid units. The exocyclic dihedral angles involving the C(1)–O(4') and C(4)–O(4) bonds vary from glucose to glucose owing to different rotations of glucoses relative to their neighbors. These rotations are better described by the torsional angles ϕ, ψ (Table VII). The variation in these angles is 14.3° for ϕ and 35.8° for ψ, while in the α-CD·2H$_2$O adduct,[6] variations are 13.7° for ϕ and 50.2° for ψ owing to the collapsed α-CD ring structure. If the ϕ, ψ angles found for the α-CD–methanol adduct are plotted in potential energy contour diagrams calculated for disaccharides,[17,18] all values are close to the computed local minimum—in contrast to the data for the α-CD·2H$_2$O adduct where one ϕ, ψ value falls well outside the energy minimum.[6]

The α-Cyclodextrin Macrocycle. The α-CD macrocycle in

Table IV

Bond Distances (Å) in the α-CD–Methanol Adduct[a]

Atom	Glucose unit 1	2	3	4	5	6	Mean y_i	
C(1)-C(2)	1.522 (6)	1.521 (7)	1.520 (6)	1.526 (5)	1.530 (5)	1.543 (5)	1.528 (4)	S_b = 0.000834
C(2)-C(3)	1.525 (6)	1.503 (6)	1.520 (6)	1.522 (5)	1.509 (6)	1.500 (6)	1.514 (4)	S_w = 0.001410
C(3)-C(4)	1.524 (7)	1.517 (6)	1.522 (5)	1.527 (6)	1.517 (5)	1.516 (5)	1.520 (2)	F = 3.697
C(4)-C(5)	1.523 (6)	1.528 (7)	1.519 (5)	1.530 (6)	1.529 (5)	1.535 (5)	1.527 (3)	Prob >95%
C(5)-C(6)	1.511 (7)	1.520 (6)	1.520 (6)	1.512 (6)	1.527 (6)	1.524 (6)	1.519 (3)	
Mean G_i	1.521 (3)	1.517 (4)	1.520 (3)	1.523 (3)	1.523 (4)	1.525 (7)	1.521	
		S_b = 0.000225		S_w = 0.002137		F = 0.505	Prob <50%	
C(5)-O(5)	1.450 (5)	1.442 (5)	1.442 (5)	1.433 (5)	1.440 (5)	1.447 (5)	1.442 (2)	
O(5)-C(1)	1.427 (5)	1.408 (5)	1.411 (5)	1.417 (5)	1.410 (5)	1.426 (5)	1.417 (3)	S_b = 0.005742
C(1)-O(4')[b]	1.406 (5)	1.420 (5)	1.408 (5)	1.397 (5)	1.426 (5)	1.390 (5)	1.408 (5)	S_w = 0.002238
C(2)-O(2)	1.431 (5)	1.432 (5)	1.445 (5)	1.423 (5)	1.431 (5)	1.429 (5)	1.432 (3)	F = 14.11
C(3)-O(3)	1.433 (5)	1.434 (5)	1.434 (5)	1.446 (5)	1.448 (5)	1.454 (5)	1.442 (4)	Prob >99.5%
C(4)-O(4)	1.432 (5), 1.419 (8)[c]	1.436 (5)	1.436 (5)	1.439 (5)	1.433 (4)	1.429 (5), 1.456 (7)[d]	1.434 (2)	
C(6)-O(6)	1.392 (9)[e]	1.422 (6)	1.433 (7)	1.427 (5)	1.431 (5)	1.466 (13)[f]	1.428 (3)	
Mean G_i	1.430 (8)	1.428 (6)	1.430 (5)	1.426 (7)	1.431 (4)	1.429 (8)		
		S_b = 0.00016		S_w = 0.007955		F = 0.137	Prob <50%	

Bond Distances in Methanol Molecule

O(A)-C(A)	1.05 (4)[g]
1(B)-2(B)	1.39 (2)

Bond Angles in the α-CD Molecule

Angle	Glucose unit 1	2	3	4	5	6	Mean y_i	
C(1)-C(2)-C(3)	109.3 (4)	109.8 (3)	110.8 (3)	109.3 (3)	110.2 (3)	110.4 (3)	109.9 (3)	S_b = 44.46
C(2)-C(3)-C(4)	110.7 (4)	109.5 (3)	110.2 (3)	111.8 (3)	111.7 (3)	111.9 (3)	111.0 (3)	S_w = 14.56
C(3)-C(4)-C(5)	114.0 (4)	111.6 (3)	111.5 (3)	113.1 (3)	111.0 (3)	111.8 (3)	112.0 (4)	F = 20.36
C(4)-C(5)-C(6)	113.2 (4)	113.0 (4)	114.1 (3)	113.8 (3)	112.8 (3)	114.1 (3)	113.6 (3)	Prob >99.5%
Mean (G_i)	111.8 (11)	110.7 (8)	111.7 (9)	112.0 (8)	111.4 (6)	112.1 (6)	111.6	
		S_b = 5.24		S_w = 57.33		F = 0.329	Prob <50%	
C(4)-O(4)-C(1)[h,m]	118.8 (3)	119.7 (3)	119.9 (3)	117.7 (3)	118.5 (3)	119.2 (3)	119.0 (3)	
C(1)-O(5)-C(5)[m]	113.4 (3)	113.0 (3)	113.6 (3)	115.1 (3)	113.9 (3)	113.1 (3)	113.7 (3)	
O(5)-C(1)-O(4)[h,m]	110.4 (3)	111.7 (3)	110.9 (3)	111.4 (3)	110.1 (3)	111.3 (3)	111.0 (2)	
C(2)-C(1)-O(5)	109.5 (3)	110.8 (3)	110.0 (3)	109.8 (3)	110.8 (3)	108.5 (3)	109.9 (4)	
C(2)-C(1)-O(4)[h]	108.1 (3)	107.5 (3)	106.4 (3)	109.8 (3)	106.8 (3)	107.7 (3)	107.7 (5)	
C(1)-C(2)-O(2)	110.0 (3)	110.4 (3)	106.9 (3)	106.6 (3)	108.4 (3)	108.2 (3)	108.4 (6)	S_b = 225.30
C(3)-C(2)-O(2)	109.0 (3)	112.2 (3)	111.7 (3)	112.1 (3)	112.5 (3)	109.6 (3)	111.2 (6)	S_w = 71.46
C(2)-C(3)-O(3)	109.1 (3)	108.1 (3)	111.0 (3)	108.2 (3)	108.4 (3)	110.7 (3)	109.3 (5)	F = 16.71
C(4)-C(3)-O(3)	109.6 (3)	110.7 (3)	108.4 (3)	109.4 (3)	109.2 (3)	106.4 (3)	109.0 (6)	Prob >99.5%
C(3)-C(4)-O(4)	105.6 (3)	106.3 (3)	106.1 (3)	104.0 (3)	106.3 (3)	105.3 (3)	105.6 (4)	
C(5)-C(4)-O(4)	107.9 (3)	109.3 (3)	110.1 (3)	109.2 (3)	107.3 (3)	110.2 (3)	109.0 (5)	
C(4)-C(5)-O(5)	109.7 (3)	109.4 (3)	110.4 (3)	109.9 (3)	109.9 (3)	109.6 (3)	109.8 (2)	
C(6)-C(5)-O(5)	105.8 (3)	105.8 (4)	106.4 (3)	105.7 (3)	105.6 (3)	105.3 (3)	105.8 (2)	
C(5)-C(6)-O(6)	116.7 (4)[i] 108.2 (5)[k] 108.4 (6)	112.6 (4) 109.4 (6)	112.3 (4) 108.9 (7)	112.4 (3) 108.8 (8)	112.2 (3) 108.9 (7)	109.6 (4)[j] 104.2 (7)[l] 108.2 (6)	112.4 (2) 108.8	
		S_b = 9.38		S_w = 284.01		F = 0.383	Prob <50%	

[a] Standard deviations are given in parentheses. Observations: y_{ij}, $i = l,n$; $j = l,m$; n = number of classes; m = number of observations in each class; $S_w = \Sigma\Sigma_{ij}(y_{ij} - \hat{y}_i)^2$; $S_b = m\Sigma_i(\hat{y}_i - \hat{y})^2$; $F = (S_b|(n - 1))|(S_w|(mn - n))$; G_i = weighted average standard deviations. [b] See footnote c, Table V. [c] A site, 50% occupancy. [d] A site, 75% occupancy. [e] B site, 50% occupancy. [f] B site, 25% occupancy. [g] C(A) ill defined with high elongated temperature factor. [h] See footnote c in Table V. [i] A site, 50% occupancy. [j] A site, 75% occupancy. [k] B site, 50% occupancy. [l] B site, 25% occupancy. [m] These lines and partially occupied sites not included in averages.

the α-CD–methanol adduct is conical in shape with the hexagon formed by the six O(4) atoms being rather regular (Table VIII). The O(4)···O(4) diagonal distances are at 8.45 ± 0.21 Å, the sides of the hexagon are at 4.23 ± 0.07 Å, and the O(4)···O(4)···O(4) angles are at 119.8 ± 2.7°. As in the other α-CD structures it is surprising to find that the O(4) atoms for a macrocycle of such size are fairly coplanar with maximum deviation of only 0.174 Å from the common least-squares plane (Table VIII). The distances of the C(1) and C(4) atoms from this plane vary more owing to the slight rotations of the individual glucoses. While the diagonal distances have a greater variability in the methanol adduct [0.21 Å in Table VIII (b)] compared to the 1-propanol adduct (0.1 Å), which indicates more strain, the conformation of the α-CD molecule adduct is clearly more similar to the open, circular conformation rather than to the collapsed conformation of the water adduct structure.

The macrocycle conformation is stabilized through a ring

Table V. Dihedral Angles (deg) in Glucose Units[a]

	Glucose unit					
	1	2	3	4	5	6
C(1)-C(2)-C(3)-C(4)	−52.0 (5)	−54.2 (4)	−52.4 (4)	−51.3 (4)	−51.3 (4)	−51.9 (4)
C(2)-C(3)-C(4)-C(5)	47.9 (5)	53.5 (4)	50.8 (4)	47.4 (4)	51.2 (4)	49.2 (4)
C(3)-C(4)-C(5)-O(5)	−49.1 (5)	−54.5 (4)	−53.1 (4)	−47.9 (4)	−53.4 (4)	−51.7 (4)
C(4)-C(5)-O(5)-C(1)	58.0 (4)	59.0 (4)	59.6 (4)	57.4 (4)	59.8 (4)	61.1 (4)
C(5)-O(5)-C(1)-C(2)	−64.8 (4)	−61.6 (4)	−61.4 (4)	−63.5 (4)	−60.8 (4)	−64.1 (4)
O(5)-C(1)-C(2)-C(3)	60.3 (4)	58.5 (4)	57.1 (4)	58.1 (4)	55.2 (4)	58.2 (4)
O(5)-C(5)-C(6)-O(6)	−82.9 (5), [73.3 (5)][b]	−72.6 (5)	−67.3 (4)	−61.0 (4)	−56.6 (4)	−66.9 (4), [75.4 (7)][b]
C(4)-C(5)-C(6)-O(6)	37.2 (6), [−166.7 (5)][b]	47.0 (5)	54.7 (5)	59.7 (5)	63.4 (4)	53.3 (5), [−164.4 (7)][b]
C(2)-C(1)-O(4')-C(4')[c]	−129.1 (4)	−129.0 (4)	−134.0 (4)	−138.9 (3)	−124.2 (4)	−140.6 (3)
C(1)-O(4')-C(4')-C(3')[c]	131.2 (4)	131.9 (4)	132.0 (4)	115.4 (3)	150.8 (3)	117.0 (4)
C(2)-C(1)-O(4')-C(4')[c]	−129.1 (4)	−129.0 (4)	−134.0 (4)	−138.9 (3)	−124.2 (4)	−140.6 (3)
O(5)-C(1)-O(4')-C(4')[c]	111.1 (4)	109.3 (4)	106.5 (4)	100.6 (4)	114.9 (4)	100.6 (4)
C(1)-O(4')-C(4')-C(5')[c]	−108.2 (4)	−107.4 (4)	−107.1 (4)	−125.8 (3)	−88.4 (4)	−120.7 (4)
O(2)-C(2)-C(3)-O(3)	67.0 (4)	62.0 (4)	68.4 (4)	70.2 (4)	67.3 (4)	70.6 (4)
C(3)-C(4)-C(5)-C(6)	−166.8 (4)	−172.1 (4)	−172.9 (3)	−166.2 (3)	−170.9 (4)	−169.5 (3)

[a] The angles A-B-C-D are defined as zero when the bonds A-B and C-D are cis-planar. They are counted positive when looking along the central bond; the far bond is rotated clockwise with respect to the near bond. [b] Value in brackets for B site, without brackets for A site. [c] Primed atoms belong to glucose of next higher number on cyclic permutation.
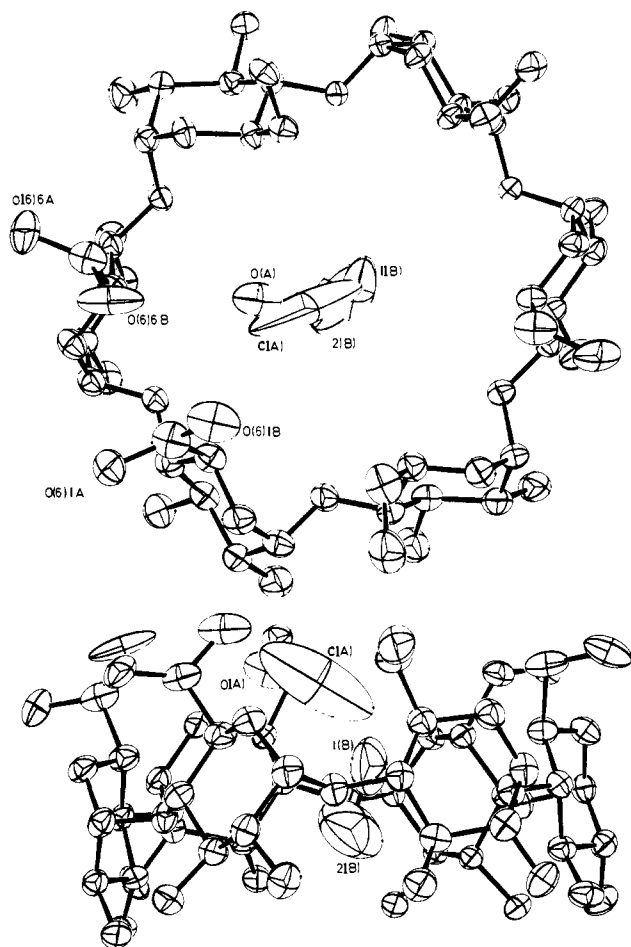

Figure 4. Thermal ellipsoids plot of the α-CD–methanol complex to show the excessive thermal motion of the two disordered methanol molecules A and B. Ellipsoids represent 50% probability distribution. Hydrogen atoms are omitted for clarity.
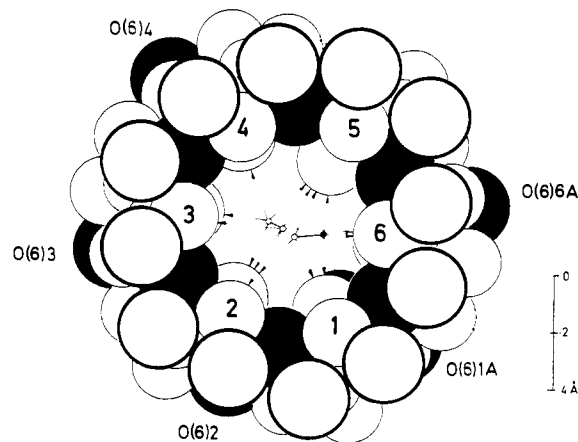

Figure 5. van der Waals plot of the α-CD molecule projected on the O(4) mean plane. Hydroxyl hydrogen atoms are omitted, atomic radii are H = 1.2 Å, O = 1.4 Å. O(4) and O(6) atoms are shown as solid circles, O(2) and O(3) atoms designated by thicker lines, and hydrogen atoms by thin lines. Closest contacts between included methanol and α-CD atoms are indicated by arrows and hydrogen bonds O(A)···O(6)6B and O(A)···O(6)1B by broken lines: O(A) to 1(B), 2.92 Å; to HC(5)1, 3.03 Å; to HC(6)1, 2.91 Å; to HC(5)5, 3.10 Å; to HC(6)5, 2.82 Å; to HC(5)6, 2.67 Å. C(A) to HC(5)1, 3.02 Å; to HC(6)5, 3.12 Å; to HC(5)2, 3.24 Å; to HC(5)5, 3.25 Å. 1(B) to HC(5)2, 2.95 Å; to HC(5)3, 2.78 Å; to HC(5)4, 3.15 Å; to HC(5)5, 3.05 Å. 2(B) to HC(5)5, 3.37 Å; to HC(5)2, 3.44 Å; to HC(3)3, 3.59 Å; to HC(3)2, 3.60 Å.

of hydrogen bonds between hydroxyl groups O(2)···O(3) (Figure 3 and Table IX). As all the hydrogen atoms were located from difference Fourier syntheses, the assignment of hydrogen bonds is certain; five of the O(2)···O(3) distances are

in the normally accepted range of 2.8–3.0 Å but one distance, O(2)5···O(3)6, is significantly longer at 3.145 Å. The latter is due to the increased rotation of glucose 5 relative to glucose 6 (Figure 4 and Table VII). It is of interest to note that not all of the six O(2)···O(3) hydrogen bonds are in the same direction, i.e., not all six O(2) hydroxyl groups are donor or acceptor but they alternate. As shown in Figure 4 the hydrogen bonding scheme is O(3)1 → O(2)6, O(2)2 → O(3)3, O(3)4 → O(2)3, O(2)5 → O(3)6, O(3)2 → O(2)1, O(3)5 → O(2)4, with three O(2) hydroxyl groups acting as hydrogen donors and the three other O(2) atoms acting as acceptors. It may be assumed that in aqueous solutions of the α-CD molecules these intramolecular hydrogen bonds break down and form continuously—one could speak of a ring current—and that in the α-CD-methanol-5H$_2$O crystal structure the particular distribution

Table VI. Deviations of Atoms (Å) from Individual Glucose Least-Squares Planes Defined by Atoms C(2), C(3), C(5), and O(5)

	Glucose unit					
	1	2	3	4	5	6
C(1)	−0.701	−0.669	−0.666	−0.681	−0.652	−0.702
C(2)	−0.009	−0.006	−0.012	−0.008	−0.017	−0.020
C(3)	0.009	0.005	0.012	0.007	0.017	0.019
C(4)	0.583	0.653	0.632	0.582	0.637	0.617
C(5)	−0.009	−0.006	−0.012	−0.008	−0.018	−0.020
C(6)	0.777	0.737	0.677	0.766	0.716	0.705
O(2)	−0.715	−0.660	−0.771	−0.758	−0.753	−0.776
O(3)	0.808	0.743	0.780	0.814	0.796	0.852
O(4)	0.253	0.471	0.411	0.209	0.347	0.348
O(5)	0.010	0.006	0.013	0.008	0.018	0.021
O(6)	2.189[a]	2.140	2.075	2.118	2.047	2.115,[a]
	0.002[b]					−0.255[b]
O(4′)	−2.016	−2.024	−1.999	−2.009	−2.017	−2.012

[a] A site. [b] B site.

Table VII. Dihedral Angles O(4)n···C(1)n–O(4)(n + 1)–C(4)(n + 1) (ϕ) and C(1)n–O(4)(n + 1)–C(4)(n + 1)···O(4)(n + 2) (ψ) to Describe Relative Orientations of Two Adjacent Glucose Units about the Common Glucosidic Linkage[a]

	ϕ
O(4)1···C(1)1–O(4)2–C(4)2	169.2 (3)
O(4)2···C(1)2–O(4)3–C(4)3	169.0 (3)
O(4)3···C(1)3–O(4)4–C(4)4	164.7 (3)
O(4)4···C(1)4–O(4)5–C(4)5	159.1 (3)
O(4)5···C(1)5–O(4)6–C(4)6	173.3 (3)
O(4)6···C(1)6–O(4)1–C(4)1	159.0 (3)
	ψ
C(1)1–O(4)2–C(4)2···O(4)3	−168.1 (3)
C(1)2–O(4)3–C(4)3···O(4)4	−167.1 (3)
C(1)3–O(4)4–C(4)4···O(4)5	−167.6 (3)
C(1)4–O(4)5–C(4)5···O(4)6	−183.8 (2)
C(1)5–O(4)6–C(4)6···O(4)1	−148.0 (3)
C(1)6–O(4)1–C(4)1···O(4)2	−177.9 (3)

[a] For definition of dihedral angles, see Table V.

of O(2)···O(3) hydrogen bonds is a result of packing requirements.

The Methanol Inclusion. Intermolecular Interactions. In total, one methanol molecule is enclosed within the α-CD cavity but distributed over two sites with equal (50%) population (Table I). One site, A, is close to the O(6) side of the α-CD cavity and the methanol C–O bond is almost perpendicular to the axis of the α-CD toroid. This methanol molecule is hydrogen bonded to two of the O(6) hydroxyl groups which

Table VIII

Geometric Data for the Hexagon Described by the O(4) Atoms

(a) O(4)···O(4) Distances in the Six Glucose Units, Å

1	O(4)6···O(4)1	4.228 ± 0.005
2	O(4)1···O(4)2	4.127 ± 0.004
3	O(4)2···O(4)3	4.310 ± 0.004
4	O(4)3···O(4)4	4.269 ± 0.005
5	O(4)4···O(4)5	4.173 ± 0.004
6	O(4)5···O(4)6	4.276 ± 0.004
		Mean = 4.23 ± 0.07

(b) Diagonal O(4)···O(4) Distances, Å

O(4)1···O(4)4	8.662 ± 0.004
O(4)2···O(4)5	8.439 ± 0.005
O(4)3···O(4)6	8.246 ± 0.004
	Mean = 8.45 ± 0.21

(c) Angles, deg

O(4)6···O(4)1···O(4)2	117.9 ± 0.1
O(4)1···O(4)2···O(4)3	119.3 ± 0.1
O(4)2···O(4)3···O(4)4	123.0 ± 0.1
O(4)3···O(4)4···O(4)5	115.8 ± 0.1
O(4)4···O(4)5···O(4)6	120.9 ± 0.1
O(4)5···O(4)6···O(4)1	122.0 ± 0.1
	Mean = 119.8 ± 2.7

Deviations of Atoms (Å) from the Least-Squares Plane Defined by the Six O(4) Atoms: $0.0598x + 0.6514y + 0.7564Z - 5.8537 = 0$

	Glucose unit					
	1	2	3	4	5	6
O(4)	−0.174	0.154	0.005	−0.144	0.128	0.032
C(1)	0.552	0.380	0.071	0.290	0.753	−0.198
C(4)	0.220	0.360	0.107	0.079	0.612	−0.027
C(6)	2.711	2.857	2.647	2.627	2.892	2.493
O(2)	−1.747	−1.960	−2.300	−2.051	−1.348	−2.596
O(3)	−1.987	−1.958	−2.248	−2.280	−1.360	−2.391

by themselves are disordered, O(6)1B at 25% and O(6)6B at 50% population. It is further in hydrogen bonding contact with the O(2)1 hydroxyl group of a symmetry-related α-CD molecule (Table IX). Figure 4 shows that this methanol molecule performs excessive thermal motion with the "loose" CH_3 group vibrating considerably more than the OH group which is fixed by the hydrogen bonds. The other (B) site is within the center of the hydrophobic α-CD cavity (Figures 3 and 4). This methanol molecule is oriented almost along the α-CD molecular axis and since it is not in hydrogen bonding contact with any hydroxyl group, its CH_3 and OH groups could not be distinguished on the basis of Fourier syntheses. It might well be that in this site the methanol molecule takes on two positions with CH_3 and OH groups interchanged.
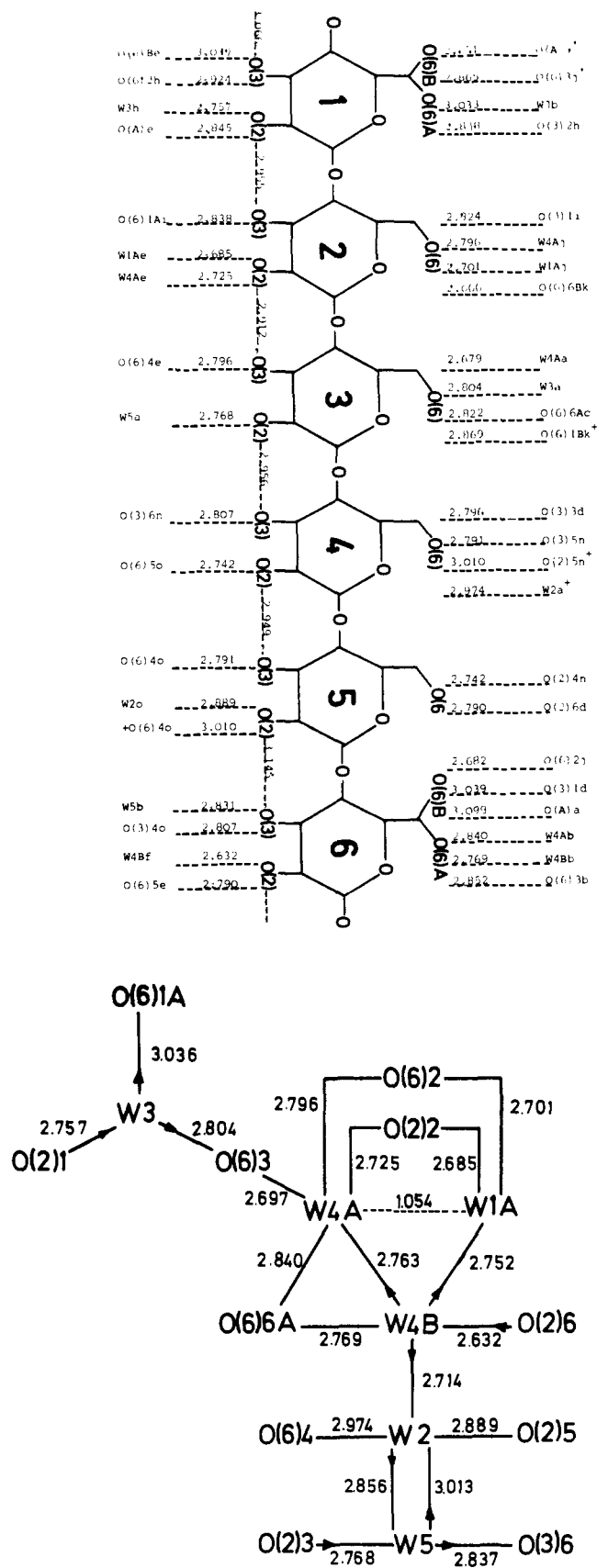

Figure 6. Stereoview of the α-CD molecule in the methanol–pentahydrate complex with all O···O distances less than 3.0 Å indicated. Small, medium, and large size circles represent C, O, and H_2O atoms, respectively.

Table IX. Hydrogen Bonds of α-CD-Methanol[a]

Donor	Acceptor[b]	O–O distance, Å	O–H–O angle, deg
O(2)1	W3 h	2.757	168
O(3)1	O(2)6 a	3.066	167
O(2)2	O(3)3 a	2.912	170
O(3)2	O(2)1 a	2.955	163
O(6)2	O(3)1 i	2.924	153
O(2)3	W5 a	2.768	171
O(3)3	O(6)4 e	2.796	158
O(6)3	O(6)6A c	2.852	134
O(2)4	O(6)5 o	2.742	172
O(3)4	O(2)3 a	2.807	152
O(6)4	O(2)5 n	3.010	127
	O(3)5 n	2.791	142
O(2)5	O(3)6 a	3.145	160
O(3)5	O(2)4 a	2.949	163
O(6)5	O(2)6 d	2.790	165
O(2)6	W4B f	2.632	162
O(3)6	O(3)4 o	2.807	161
W2	O(6)4 a	2.974	159
W2'[c]	W5 1	2.856	174
W3	O(6)1A c	3.036	144
W3'	O(6)3 a	2.804	87
W4B	W2 a	2.714	161
W4B'	W1A a	2.752	146
	W4A a	2.763	132
W5	O(3)6 c	2.837	165
W5'	W2 d	3.013	164

[a] Hydrogens from disordered atoms O(A), O(B), O(6)1, O(6)6, W1A, and W4A are not included. [b] Equivalent points are in Figure 7. [c] Second hydrogen atoms denoted by a prime.
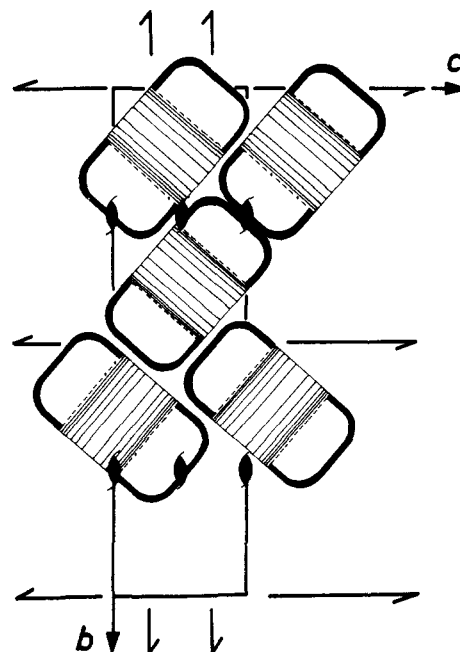

Figure 8. Schematic representation of the packing of α-CD molecules within the crystal lattice.

Figure 7. A schematic representation of Figure 6 indicating O···O distances (Å) and, in the letters after atomic designations, symmetry transformations. These transformations are a, x,y,z; b, $1 + x,y,z$; c, $-1 + x,y,z$; d, $x,y,1 + z$; e, $x,y,-1 + z$; f, $1 + x,y,-1 + z$; g, $-1 + x,y,1 + z$; h, $\frac{1}{2} + x, \frac{1}{2} - y,-z$; i, $-\frac{1}{2} + x, \frac{1}{2} - y,-z$; j, $\frac{1}{2} + x, \frac{1}{2} - y,1 - z$; k, $-\frac{1}{2} + x, \frac{1}{2} - y,1 - z$; l, $\frac{1}{2} - x,-y,\frac{1}{2} + z$; m, $\frac{1}{2} - x,-y,-\frac{1}{2} + z$; n, $1\frac{1}{2} - x,-y,\frac{1}{2} + z$; o, $1\frac{1}{2} - x,-y,-\frac{1}{2} + z$. Bonds marked + were not observed in the α-CD propanol adduct.

The intermolecular interactions between the α-CD ring and the methanol molecules in sites A and B can be understood from inspection of the van der Waals plot shown in Figure 5. Methanol molecule A is hydrogen bonded while its methyl group of 4.0 Å diameter is in van der Waals contact with three C(5)-H hydrogen atoms. The two methyl or hydroxyl groups of the methanol molecule in site B are in van der Waals contact with either four C(3)-H hydrogen atoms for the group nearer to the O(2), O(3) side of α-CD cavity or with four C(5)-H

hydrogen atoms for the group nearer to the center of the cavity. As discussed previously,[5] the O(4) oxygen atoms are hidden behind the C(3)–H and C(5)–H hydrogen bonds and cannot interact with substrate molecules.

Although the hexagon formed by the six O(4) atoms is rather regular, Figure 5 clearly indicates that the α-CD cavity is elliptical in shape; viz. at the O(6) side of the cavity, the shortest C(5)–H$\cdots$C(5)–H distance is about 3.4 Å and the longest is 4.5 Å; at the O(2), O(3) side the shortest C(3)–H$\cdots$C(3)–H distance is about 4.6 Å and the longest is 5.5 Å. The α-CD molecule has adapted its cavity somewhat to the dimensions of the enclosed methanol molecules.

Hydrogen Bonding and Packing Scheme. The hydrogen bonding scheme within the crystal structure is explained by Table IX and Figure 7 and shown in the stereoplot of Figure 6. As all the hydroxyl hydrogen atoms except those attached to disordered oxygen atoms were located, the assignment of hydrogen bonds is certain even in cases where rather long O$\cdots$O distances are observed. Table IX shows that hydrogen bond lengths vary from 2.632 to 3.145 Å and O–H$\cdots$O angles vary from 87 to 174°.

The packing of the α-CD molecules is described schematically in Figure 8. Since the void of an individual α-CD is blocked on both ends by adjacent, symmetry related α-CD molecules, this structure belongs to the cage type previously described in greater detail.[6,12,19] Channel type structures with the α-CD molecules stacked like coins in a roll have been observed in the adducts with salts like potassium acetate[20] and polyiodide[21] and with long, molecular guest molecules.[19]

Confirmation of Mechanism of α-CD Inclusion Formation. As mentioned at the outset, this x-ray structural study was undertaken in order to find out whether the α-CD molecule in the α-CD–methanol adduct would assume a strained, collapsed conformation as in the "empty" water adduct or an unstrained, open, cyclic conformation common to all the other thus far investigated adducts. From the above it is clear that the latter structure exists here. The α-CD macrocycle is rather cyclic and regular and all of the six O(2)$\cdots$O(3) intramolecular hydrogen bonds have formed, in agreement with the proposed inclusion formation mechanism.

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Malformin C, a New Metabolite of *Aspergillus niger*

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Abstract: A strain of *Aspergillus niger* collected from mold damaged rice produces malformin C, a new, highly toxic metabolite. It was established to be the disulfide of *cyclo*-D-cysteinyl-D-cysteinyl-L-valyl-D-leucyl-L-leucyl. Amino acid sequencing was accomplished using gas chromatographic mass spectrometry. A 100-m capillary gas chromatographic column allowed the separation of two diastereomeric N-trifluoroacetyl dipeptide methyl esters and the chirality of a critical L-valyl-D-leucyl dipeptide could be determined with the aid of this method.

As part of a continuing search for food borne mycotoxins we had occasion to investigate a highly toxic methylene chloride extract of an *Aspergillus niger* strain AN-1 that originally had been collected from mold-damaged rice. The physiologically active principle was separated from inactive metabolites by chromatographic techniques and obtained in the form of an amorphous powder, mp >300° dec. A high-resolution mass spectrum indicated a composition of $C_{23}H_{39}N_5O_5S_2$ and in-

frared absorptions at 3280 and 1630 cm^{-1} were attributed to NH and amide functions, respectively. A proton NMR spectrum revealed inter alia six methyl groups bound to carbon atoms, and deuterium exchange caused the disappearance of five NH signals. The toxin thus appeared to be a pentapeptide and the spectral data were in general agreement with those of the malformins, a family of cyclic pentapeptides discovered by Curtis[3] and found to produce malformations of bean plants