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*Acta Cryst.* (1982). **B38**, 203–210

## Topography of Cyclodextrin Inclusion Complexes.

### XVI.\* Cyclic System of Hydrogen Bonds: Structure of $\alpha$ -Cyclodextrin Hexahydrate, Form (II): Comparison with Form (I)

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(Received 8 October 1980; accepted 19 June 1981)

#### Abstract

The cyclic hexasaccharide  $\alpha$ -cyclodextrin ( $\alpha$ -CD; cyclohexaamylose) crystallizes from water as the hexahydrate in two different forms with the same space group  $P2_12_12_1$  but cell constants  $a = 14.858$  (3),  $b = 34.038$  (7),  $c = 9.529$  (2) Å (form I) and  $a = 13.70$  (1),  $b = 29.35$  (2),  $c = 11.92$  (1) Å (form II). Final  $R$  for form (II) is 3.8% for all the 4860 reflections. Form (I) grows preferentially and has been described previously [Klar, Hingerty & Saenger (1980). *Acta Cryst.* **B36**, 1154–1165]. In form (I), the  $\alpha$ -CD annulus encloses a pair of water molecules and

four water molecules are located 'outside'. The  $\alpha$ -CD molecule is distorted, the O(2)···O(3) hydrogen-bonding ring is disrupted at one glucose moiety which is rotated out of alignment with the other glucose units and associated glucosidic torsion angles  $\varphi$  and  $\psi$  indicate high-energy distortion. The  $\alpha$ -CD in form (II) crystals has an almost identical conformation, with one water molecule and an O(6) hydroxyl of a symmetry-related  $\alpha$ -CD included while five water molecules are located 'outside'. It is concluded that this distorted  $\alpha$ -CD is intrinsically associated with the 'empty' water complex and that upon complexation with guest molecules,  $\alpha$ -CD changes its conformation to a 'round, undistorted' molecule with the ring of O(2)···O(3) hydrogen bonds fully established, a model for the 'induced-fit'-type complex formation.

\* For part XV, see Chacko & Saenger (1980).

## Introduction

Several years ago, the X-ray crystal-structure analysis of the cyclic hexasaccharide  $\alpha$ -cyclodextrin hexahydrate (cyclohexaamylose hexahydrate;  $\alpha$ -CD.6H<sub>2</sub>O) was reported (Manor & Saenger, 1972, 1974). As this investigation did not show all H-atom positions, a more recent neutron diffraction study, combined with new, improved X-ray data, was carried out from which all H atoms could be located (Klar *et al.*, 1980). When batches were set up to grow single crystals big enough for neutron data collection, one of the batches did not show the usual stout, prismatic  $\alpha$ -CD.6H<sub>2</sub>O crystals but rather tabular, flaky specimens. The observation of a second crystal form of  $\alpha$ -CD crystallized from water is not unexpected because Wiedenhof & Lammers (1967) reported the existence of three different crystalline modifications, with solubilities of 8.80, 9.75 and 10.33 g  $\alpha$ -CD/100 g solution. Unfortunately, we cannot correlate our structure with these data because

we had only one small batch of the new crystal form. The crystals obtained were investigated by X-ray methods, yielding the same space group as the earlier crystals but different cell constants. Initial attempts to solve the structure of the new (form II) crystals by 'isomorphous replacement' with atomic coordinates of the earlier (form I) crystals failed because, as was found out later, the packing schemes are quite different.

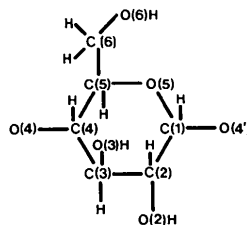


Fig. 1. Atomic-numbering scheme for one glucose: in the  $\alpha$ -CD molecule, glucose units are numbered 1 to 6, and in the text atom C(5)4 refers to C(5) of glucose 4.

Table 1. Fractional atomic coordinates and isotropic temperature factors for the heavy atoms of  $\alpha$ -CD.6H<sub>2</sub>O, form (II), with *e.s.d.*'s in parentheses

$B_{eq}$  values have been derived from the corresponding anisotropic temperature factors via  $B_{eq} = \frac{1}{3}$  (trace of orthogonalized  $\beta_{ij}$  matrix).

	<i>x</i>	<i>y</i>	<i>z</i>	$B_{eq}$ (Å <sup>2</sup> )		<i>x</i>	<i>y</i>	<i>z</i>	$B_{eq}$ (Å <sup>2</sup> )
C(1)1	0.1623 (2)	0.5371 (1)	0.8829 (3)	2.71 (7)	O(2)1	0.2047 (2)	0.4840 (1)	0.7337 (2)	3.70 (6)
C(2)1	0.1622 (2)	0.4872 (1)	0.8427 (3)	2.91 (8)	O(3)1	0.0541 (2)	0.4238 (1)	0.8061 (2)	2.99 (5)
C(3)1	0.0568 (2)	0.4712 (1)	0.8376 (3)	2.55 (7)	O(4)1	-0.0936 (1)	0.4671 (1)	0.9391 (2)	2.50 (5)
C(4)1	0.0088 (2)	0.4779 (1)	0.9509 (3)	2.43 (7)	O(5)1	0.1187 (1)	0.5401 (1)	0.9899 (2)	2.91 (5)
C(5)1	0.0178 (2)	0.5274 (1)	0.9910 (3)	2.69 (7)	O(6)1	-0.0292 (2)	0.5809 (1)	1.1380 (2)	3.73 (6)
C(6)1	-0.0172 (3)	0.5337 (1)	1.1100 (3)	3.46 (8)	O(2)2	0.1085 (2)	0.6460 (1)	0.4623 (2)	4.03 (7)
C(1)2	0.1014 (2)	0.6849 (1)	0.6409 (3)	2.57 (7)	O(3)2	0.1714 (2)	0.5647 (1)	0.5773 (2)	3.56 (6)
C(2)2	0.1441 (2)	0.6451 (1)	0.5744 (3)	2.81 (8)	O(4)2	0.1088 (1)	0.5620 (1)	0.8029 (2)	2.68 (5)
C(3)2	0.1214 (2)	0.6010 (1)	0.6333 (2)	2.50 (7)	O(5)2	0.1359 (2)	0.6844 (1)	0.7519 (2)	2.75 (5)
C(4)2	0.1503 (2)	0.6027 (1)	0.7553 (3)	2.40 (7)	O(6)2	0.2470 (2)	0.6547 (1)	0.9331 (2)	6.04 (10)
C(5)2	0.1084 (2)	0.6442 (1)	0.8134 (3)	2.68 (7)	O(2)3	-0.2803 (2)	0.7147 (1)	0.4159 (2)	3.26 (6)
C(6)2	0.1447 (3)	0.6511 (1)	0.9322 (3)	3.44 (9)	O(3)3	-0.0765 (2)	0.6851 (1)	0.4198 (2)	3.50 (6)
C(1)3	-0.2561 (2)	0.7503 (1)	0.5945 (3)	2.44 (7)	O(4)3	-0.0010 (1)	0.6809 (1)	0.6381 (2)	2.46 (5)
C(2)3	-0.2074 (2)	0.7340 (1)	0.4879 (3)	2.69 (7)	O(5)3	-0.1847 (2)	0.7715 (1)	0.6631 (2)	2.61 (5)
C(3)3	-0.1302 (2)	0.6991 (1)	0.5171 (3)	2.61 (7)	O(6)3	-0.0829 (2)	0.7866 (1)	0.8686 (2)	4.51 (7)
C(4)3	-0.0573 (2)	0.7190 (1)	0.5999 (3)	2.36 (7)	O(2)4	-0.5916 (2)	0.6265 (1)	0.6366 (2)	3.71 (6)
C(5)3	-0.1076 (2)	0.7414 (1)	0.7001 (3)	2.70 (7)	O(3)4	-0.4605 (2)	0.6844 (1)	0.5138 (2)	3.22 (6)
C(6)3	-0.0380 (3)	0.7706 (1)	0.7685 (3)	3.67 (9)	O(4)4	-0.2958 (1)	0.7120 (1)	0.6484 (2)	2.50 (5)
C(1)4	-0.5316 (2)	0.6573 (1)	0.8074 (3)	2.66 (7)	O(5)4	-0.4870 (2)	0.6953 (1)	0.8582 (2)	3.00 (5)
C(2)4	-0.5450 (2)	0.6656 (1)	0.6825 (3)	2.64 (7)	O(6)4	-0.4257 (2)	0.7863 (1)	0.8506 (2)	4.30 (7)
C(3)4	-0.4463 (2)	0.6742 (1)	0.6293 (3)	2.46 (7)	O(2)5	-0.5914 (2)	0.4656 (1)	0.8700 (2)	3.59 (6)
C(4)4	-0.3947 (2)	0.7133 (1)	0.6881 (3)	2.30 (7)	O(3)5	-0.6190 (2)	0.5494 (1)	0.7723 (2)	3.22 (6)
C(5)4	-0.3918 (2)	0.7065 (1)	0.8155 (3)	3.02 (8)	O(4)5	-0.4738 (1)	0.6176 (1)	0.8214 (2)	2.52 (5)
C(6)4	-0.3612 (3)	0.7494 (1)	0.8757 (3)	3.82 (9)	O(5)5	-0.4458 (2)	0.5384 (1)	1.0574 (2)	3.05 (5)
C(1)5	-0.4733 (2)	0.4971 (1)	1.0029 (3)	2.80 (7)	O(6)5	-0.3027 (2)	0.6067 (1)	1.1118 (2)	5.97 (9)
C(2)5	-0.5604 (2)	0.5058 (1)	0.9267 (3)	2.65 (7)	O(2)6	-0.1335 (2)	0.3869 (1)	0.8222 (2)	3.56 (6)
C(3)5	-0.5353 (2)	0.5420 (1)	0.8413 (3)	2.45 (7)	O(3)6	-0.3430 (2)	0.3949 (1)	0.8250 (2)	3.14 (5)
C(4)5	-0.5051 (2)	0.5850 (1)	0.9033 (2)	2.50 (7)	O(4)6	-0.3959 (2)	0.4795 (1)	0.9381 (2)	3.17 (6)
C(5)5	-0.4190 (2)	0.5746 (1)	0.9811 (3)	3.01 (8)	O(5)6	-0.1787 (1)	0.4380 (1)	1.0921 (2)	3.11 (6)
C(6)5	-0.3919 (3)	0.6150 (1)	1.0526 (3)	4.17 (10)	O(6)6	-0.3286 (3)	0.4197 (1)	1.2353 (3)	9.03 (15)
C(1)6	-0.1256 (2)	0.4272 (1)	0.9950 (3)	2.38 (6)	W(1)	-0.8215 (2)	0.3727 (1)	0.6457 (2)	4.85 (8)
C(2)6	-0.1896 (2)	0.3996 (1)	0.9164 (3)	2.42 (6)	W(2)	-0.6312 (2)	0.3697 (1)	0.7293 (2)	4.44 (7)
C(3)6	-0.2807 (2)	0.4259 (1)	0.8853 (2)	2.43 (7)	W(3)	0.1611 (2)	0.3617 (1)	0.9261 (2)	4.45 (7)
C(4)6	-0.3334 (2)	0.4454 (1)	0.9876 (3)	2.71 (7)	W(4)	-0.6017 (2)	0.7801 (1)	0.9654 (3)	5.16 (9)
C(5)6	-0.2649 (2)	0.4655 (1)	1.0766 (3)	3.40 (8)	W(5)	-0.1421 (2)	0.6279 (1)	0.9701 (3)	6.10 (9)
C(6)6	-0.3100 (3)	0.4662 (2)	1.1964 (4)	5.55 (13)	W(6)	-0.2370 (4)	0.7413 (1)	0.2076 (3)	9.95 (16)

## Experimental

A crystal,  $0.2 \times 0.5 \times 0.5$  mm, was sealed with some mother liquor in a quartz capillary and used for all X-ray experiments. Data up to  $2\theta = 120^\circ$  were collected in the  $2\theta/\theta$  scan mode with stationary background counts on each side of the scan using an automated Stoe diffractometer equipped with a Cu tube and Ni filter. The 4860 data were corrected for absorption (North, Phillips & Matthews, 1968) and converted to normalized structure amplitudes,  $E_{hkl}$ . The structure was solved by direct methods (*MULTAN*, Main, Lessinger, Woolfson, Germain & Declercq, 1977) and refined by full-matrix least squares (Busing, Martin & Levy, 1962). Data were given weights according to counting statistics (Stout & Jensen, 1968) with 3% allowance for machine instability, and scattering factors from *International Tables for X-ray Crystallography* (1974) were used throughout. H-atom positions were located from difference Fourier maps and allowed to vary, together with isotropic temperature factors, in the final refinement cycles. Refinement

converged, with average parameter shifts  $<0.3$  e.s.d.'s, at  $R = 3.8\%$  for all the 4860 data.

## Results and discussion

The atomic-numbering scheme for one glucose unit is shown in Fig. 1. Results of the structure analysis are summarized in Tables 1 to 7 and in Figs. 2 to 5.\*

## (a) General considerations

The general molecular shape of  $\alpha$ -CD in this crystal structure corresponds to a toroidal form with O(2) and O(3) hydroxyls at the wide side while the narrow side is

\* Lists of structure factors and anisotropic temperature factors, Table 5 (geometrical data for glucose units describing several dihedral angles defining glucose orientation) and Table 6 [geometry of hexagon formed by six O(4) atoms] have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 36078 (30 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 2. Fractional atomic coordinates and isotropic temperature factors for the H atoms of  $\alpha$ -CD.  $6\text{H}_2\text{O}$ , form (II), with e.s.d.'s in parentheses

	x	y	z	B (Å <sup>2</sup> )		x	y	z	B (Å <sup>2</sup> )
H(C11)1	0.232 (3)	0.5468 (12)	0.887 (3)	1.2 (7)	H(C16)1	-0.071 (3)	0.4087 (12)	1.020 (3)	1.7 (7)
H(C21)1	0.202 (3)	0.4669 (12)	0.897 (3)	1.0 (6)	H(C26)1	-0.207 (3)	0.3713 (12)	0.962 (3)	1.1 (6)
H(C31)1	0.018 (3)	0.4895 (12)	0.778 (3)	1.4 (7)	H(C36)1	-0.257 (3)	0.4541 (11)	0.826 (3)	1.1 (7)
H(C41)1	0.037 (3)	0.4592 (13)	1.010 (3)	1.9 (7)	H(C46)1	-0.375 (3)	0.4207 (11)	1.025 (3)	1.1 (7)
H(C51)1	-0.021 (3)	0.5474 (12)	0.941 (3)	1.8 (7)	H(C56)1	-0.243 (3)	0.4972 (13)	1.053 (3)	1.4 (7)
H(C61)1	0.029 (3)	0.5192 (13)	1.165 (4)	2.4 (8)	H(C66)1	-0.256 (3)	0.4855 (14)	1.249 (4)	3.2 (9)
H(C61)2	-0.089 (3)	0.5221 (14)	1.110 (4)	2.4 (8)	H(C66)2	-0.370 (3)	0.4795 (14)	1.205 (4)	3.1 (9)
H(C12)1	0.124 (3)	0.7160 (12)	0.606 (3)	1.1 (6)	H(O21)1	0.264 (4)	0.4838 (15)	0.741 (4)	4.1 (11)
H(C22)1	0.215 (3)	0.6491 (12)	0.576 (3)	1.6 (7)	H(O31)1	-0.025 (4)	0.4148 (16)	0.807 (5)	5.4 (13)
H(C32)1	0.045 (3)	0.5955 (11)	0.629 (3)	1.0 (6)	H(O61)1	0.030 (4)	0.5957 (18)	1.166 (5)	5.7 (13)
H(C42)1	0.226 (3)	0.6032 (12)	0.765 (3)	1.1 (7)	H(O22)1	0.041 (3)	0.6543 (12)	0.467 (3)	1.8 (7)
H(C52)1	0.036 (3)	0.6388 (13)	0.806 (3)	2.0 (7)	H(O32)1	0.166 (3)	0.5411 (14)	0.630 (4)	3.0 (9)
H(C62)1	0.119 (3)	0.6241 (14)	0.981 (4)	2.3 (8)	H(O62)1	0.271 (4)	0.6459 (16)	0.989 (4)	4.2 (11)
H(C62)2	0.112 (3)	0.6796 (14)	0.958 (4)	2.4 (8)	H(O23)1	-0.265 (3)	0.7176 (13)	0.345 (3)	2.3 (8)
H(C13)1	-0.310 (3)	0.7711 (12)	0.577 (3)	1.2 (7)	H(O33)1	-0.117 (3)	0.6622 (15)	0.377 (4)	3.6 (10)
H(C23)1	-0.181 (3)	0.7620 (14)	0.453 (4)	2.3 (8)	H(O63)1	-0.112 (3)	0.8114 (16)	0.852 (4)	4.1 (11)
H(C33)1	-0.164 (3)	0.6697 (12)	0.550 (3)	1.8 (7)	H(O24)1	-0.602 (4)	0.6372 (15)	0.578 (4)	3.6 (10)
H(C43)1	-0.013 (3)	0.7411 (12)	0.563 (3)	1.4 (7)	H(O34)1	-0.400 (3)	0.6913 (14)	0.486 (4)	3.0 (9)
H(C53)1	-0.140 (3)	0.7162 (13)	0.750 (3)	1.9 (7)	H(O64)1	-0.480 (3)	0.7812 (14)	0.882 (4)	3.3 (9)
H(C63)1	0.020 (3)	0.7534 (13)	0.787 (3)	1.8 (7)	H(O25)1	-0.606 (3)	0.4499 (14)	0.919 (4)	3.1 (9)
H(C63)2	-0.011 (3)	0.7973 (13)	0.726 (4)	2.3 (8)	H(O35)1	-0.598 (3)	0.5705 (13)	0.722 (3)	2.3 (8)
H(C14)1	-0.593 (3)	0.6523 (13)	0.849 (3)	1.8 (7)	H(O65)1	-0.239 (4)	0.6191 (17)	1.066 (5)	5.3 (13)
H(C24)1	-0.577 (3)	0.6928 (13)	0.676 (3)	1.8 (7)	H(O26)1	-0.174 (3)	0.3824 (14)	0.776 (4)	3.3 (10)
H(C34)1	-0.407 (3)	0.6471 (12)	0.637 (3)	1.2 (7)	H(O36)1	-0.379 (3)	0.4097 (14)	0.780 (4)	3.0 (10)
H(C44)1	-0.424 (3)	0.7434 (13)	0.671 (3)	1.9 (7)	H(W1)1	-0.762 (4)	0.3709 (17)	0.679 (5)	4.5 (12)
H(C54)1	-0.336 (3)	0.6828 (12)	0.826 (3)	1.2 (6)	H(W1)2	-0.860 (4)	0.3948 (16)	0.675 (4)	4.5 (12)
H(C64)1	-0.362 (4)	0.7421 (16)	0.964 (4)	3.8 (10)	H(W2)1	-0.628 (3)	0.3693 (14)	0.791 (4)	3.0 (11)
H(C64)2	-0.288 (3)	0.7585 (15)	0.845 (4)	2.9 (9)	H(W2)2	-0.621 (4)	0.3452 (16)	0.706 (4)	4.9 (13)
H(C15)1	-0.491 (3)	0.4758 (12)	1.069 (3)	1.2 (7)	H(W3)1	0.117 (3)	0.3833 (15)	0.882 (4)	3.7 (10)
H(C25)1	-0.613 (3)	0.5158 (12)	0.977 (3)	1.2 (7)	H(W3)2	0.145 (4)	0.3317 (16)	0.900 (4)	5.1 (13)
H(C35)1	-0.473 (3)	0.5320 (11)	0.788 (3)	1.1 (7)	H(W4)1	-0.614 (4)	0.7550 (17)	0.982 (5)	4.8 (14)
H(C45)1	-0.560 (3)	0.5964 (13)	0.942 (3)	1.9 (7)	H(W4)2	-0.618 (4)	0.8072 (16)	0.987 (4)	4.8 (13)
H(C55)1	-0.360 (3)	0.5668 (13)	0.935 (3)	1.9 (7)	H(W5)1	-0.109 (4)	0.6138 (18)	1.027 (5)	6.5 (16)
H(C65)1	-0.446 (3)	0.6236 (12)	1.103 (3)	1.3 (7)	H(W6)1	-0.193 (6)	0.7330 (25)	0.151 (7)	10.2 (22)
H(C65)2	-0.382 (3)	0.6445 (13)	1.008 (3)	2.1 (8)	H(W6)2	-0.248 (6)	0.7687 (25)	0.177 (7)	10.7 (24)

lined by O(6) hydroxyls. The conformation of  $\alpha$ -CD is similarly strained and collapsed as observed in  $\alpha$ -CD.6H<sub>2</sub>O, form (I), i.e. the inclusion of water

molecules leads to a distortion of the  $\alpha$ -CD macrocycle while all other guest molecules allow  $\alpha$ -CD to adopt a 'round, circular' shape (Saenger, 1976).

Table 3. Bond distances (Å) and angles (°) in  $\alpha$ -CD.6H<sub>2</sub>O, form (II)

E.s.d.'s obtained from the least-squares correlation are given in parentheses.

	Glucose unit						Mean	$\sigma$
	1	2	3	4	5	6		
C(1)–C(2)	1.541 (4)	1.527 (4)	1.513 (4)	1.520 (5)	1.521 (4)	1.517 (4)	1.523	0.010
C(2)–C(3)	1.520 (4)	1.505 (4)	1.513 (4)	1.514 (4)	1.512 (4)	1.513 (4)	1.513	0.005
C(3)–C(4)	1.514 (4)	1.507 (4)	1.521 (4)	1.520 (4)	1.520 (4)	1.528 (4)	1.518	0.007
C(4)–C(5)	1.534 (4)	1.514 (4)	1.528 (4)	1.532 (4)	1.531 (4)	1.535 (5)	1.529	0.008
C(5)–C(6)	1.509 (5)	1.514 (5)	1.519 (5)	1.508 (5)	1.507 (5)	1.556 (6)	1.519	0.019
C(1)–O(5)	1.411 (4)	1.405 (4)	1.419 (4)	1.410 (4)	1.424 (4)	1.404 (4)	1.412	0.008
C(1)–O(4)	1.409 (4)	1.408 (4)	1.404 (4)	1.417 (4)	1.410 (4)	1.417 (4)	1.411	0.005
C(2)–O(2)	1.427 (4)	1.423 (4)	1.434 (4)	1.422 (4)	1.425 (4)	1.412 (4)	1.424	0.007
C(3)–O(3)	1.441 (4)	1.432 (4)	1.437 (4)	1.422 (4)	1.428 (4)	1.441 (4)	1.434	0.008
C(4)–O(4)	1.445 (3)	1.440 (4)	1.432 (3)	1.435 (4)	1.432 (4)	1.444 (4)	1.438	0.006
C(5)–O(5)	1.432 (4)	1.438 (4)	1.445 (4)	1.438 (4)	1.447 (4)	1.441 (4)	1.440	0.005
C(6)–O(6)	1.434 (4)	1.407 (5)	1.422 (5)	1.430 (5)	1.432 (5)	1.465 (6)	1.432	0.019
C(1)–C(2)–C(3)	107.9 (2)	109.6 (2)	109.2 (3)	109.2 (3)	109.9 (2)	110.8 (2)	109.4	1.0
C(2)–C(3)–C(4)	109.7 (3)	111.6 (2)	110.4 (2)	110.4 (2)	108.5 (2)	112.7 (2)	110.6	1.5
C(3)–C(4)–C(5)	111.5 (2)	109.7 (2)	112.1 (2)	111.8 (2)	109.8 (2)	114.0 (2)	111.5	1.6
C(4)–C(5)–C(6)	112.6 (3)	114.2 (3)	112.3 (3)	111.8 (3)	112.0 (3)	113.4 (3)	112.7	0.9
C(2)–C(1)–O(5)	109.9 (2)	110.6 (2)	108.6 (2)	110.2 (2)	109.7 (2)	109.3 (2)	109.7	0.7
C(2)–C(1)–O(4)	106.4 (2)	107.9 (2)	107.6 (2)	108.3 (2)	108.9 (3)	109.2 (2)	108.1	1.0
C(1)–C(2)–O(2)	110.2 (3)	110.0 (2)	108.7 (2)	107.6 (2)	112.2 (2)	108.5 (2)	109.5	1.6
C(3)–C(2)–O(2)	109.3 (3)	112.6 (3)	111.0 (2)	112.0 (3)	109.3 (2)	112.9 (2)	111.2	1.6
C(2)–C(3)–O(3)	109.5 (2)	108.9 (2)	111.5 (2)	108.6 (2)	108.1 (2)	106.7 (2)	108.9	1.6
C(4)–C(3)–O(3)	110.3 (2)	110.4 (2)	107.3 (2)	110.6 (2)	111.9 (2)	110.7 (2)	110.2	1.5
C(3)–C(4)–O(4)	107.8 (2)	104.4 (2)	105.1 (2)	105.5 (2)	107.7 (2)	102.3 (2)	105.5	2.1
C(5)–C(4)–O(4)	108.5 (2)	109.7 (2)	109.3 (2)	107.4 (2)	108.5 (2)	112.2 (2)	109.3	1.6
C(4)–C(5)–O(5)	108.7 (2)	109.1 (2)	110.8 (2)	110.9 (2)	109.4 (2)	112.0 (3)	110.2	1.3
C(6)–C(5)–O(5)	106.5 (3)	106.4 (2)	106.1 (2)	105.9 (3)	106.5 (3)	102.4 (3)	105.6	1.6
C(5)–C(6)–O(6)	112.0 (3)	110.1 (3)	111.4 (3)	111.3 (3)	110.8 (3)	110.4 (3)	111.0	0.7
C(4)–O(4)–C(1)	115.9 (2)	119.5 (2)	118.7 (2)	119.7 (2)	117.5 (2)	118.5 (2)	118.3	1.4
C(1)–O(5)–C(5)	113.6 (2)	113.6 (2)	114.3 (2)	114.9 (2)	113.8 (2)	116.5 (2)	114.5	1.1
O(5)–C(1)–O(4)	111.1 (2)	110.9 (2)	110.7 (2)	111.0 (2)	111.3 (2)	111.1 (2)	111.0	0.2

Table 4. Selected torsion angles (°) describing glucose conformations in  $\alpha$ -CD.6H<sub>2</sub>O, form (II)

Standard deviations are  $\pm 0.3^\circ$ . Atoms marked \* and † belong to next and second next glucose units.

	Glucose unit						Mean	$\sigma$
	1	2	3	4	5	6		
C(1)–C(2)–C(3)–C(4)	–55.7	–51.2	–56.3	–55.5	–57.9	–49.9	–54.4	3.1
C(2)–C(3)–C(4)–C(5)	54.8	51.8	50.0	51.4	57.4	41.3	51.1	5.5
C(3)–C(4)–C(5)–O(5)	–54.6	–54.0	–48.3	–49.5	–56.8	–40.3	–50.6	6.0
C(4)–C(5)–O(5)–C(1)	59.9	60.6	56.1	55.1	59.0	52.4	57.2	3.2
C(5)–O(5)–C(1)–C(2)	–63.7	–62.1	–63.1	–60.5	–59.6	–61.6	–61.8	1.6
O(5)–C(1)–C(2)–C(3)	59.7	55.7	61.8	59.3	58.3	58.7	58.9	2.0
O(5)–C(5)–C(6)–O(6)	74.0	–62.4	–23.5	–62.6	69.2	–57.3	–	–
O(2)–C(2)–C(3)–O(3)	63.2	63.9	64.7	64.1	56.9	66.4	63.2	3.3
C(1)–O(4)*–C(4)*–C(3)*	140.4	132.9	121.8	113.2	164.6	111.4	147.4	37.0
O(5)–C(1)–O(4)*–C(4)*	111.3	112.8	109.6	104.0	95.1	104.9	106.3	6.5
C(1)–O(4)*–C(4)*–C(5)*	–99.8	–106.6	–118.8	–128.1	–72.8	–127.7	–109.0	21.0
C(2)–C(1)–O(4)*–C(4)*	–129.2	–125.9	–131.8	–134.8	–143.8	–134.4	–133.3	6.1
O(4)–C(1)–O(4)*–C(4)*	168.6	172.2	167.8	163.0	154.4	165.2	165.2	6.1
C(1)–O(4)*–C(4)*–O(4)†	–158.8	–167.8	–178.7	–186.9	–134.7	–187.7	–169.1	20.1

Table 7. Hydrogen-bonding scheme for  $\alpha$ -CD.6H<sub>2</sub>O, form (II)

A—H...B		Distances (Å)			Angle (°)	Symmetry code <sup>a</sup>
A...B	A—H	H...B	H—A...B			
Donor	Acceptor					
O(2)1	O(2)5	3.277 (3)	0.81 (5)	2.57 (5)	39 (3)	65501
	O(3)5	3.119 (3)	0.81 (5)	2.54 (5)	26 (4)	65501
O(3)1	O(2)6	2.795 (3)	1.11 (5)	1.71 (5)	10 (3)	
O(6)1	W(2)	2.849 (4)	0.98 (6)	1.88 (6)	5 (3)	46503
O(2)2	O(3)3	2.828 (3)	0.96 (4)	1.93 (4)	17 (2)	
	O(4)3	2.774 (3)	0.96 (4)	2.26 (4)	49 (2)	
O(3)2	O(2)1	3.048 (3)	0.94 (4)	2.15 (4)	14 (3)	
	O(4)2	2.823 (3)	0.94 (4)	2.29 (4)	47 (3)	
O(6)2	W(1)	2.848 (4)	0.78 (5)	2.07 (5)	5 (4)	46503
O(2)3	W(6)	2.669 (5)	—	1.82 (4)	11 (2)	
O(3)3	O(3)6	2.829 (3)	1.01 (4)	1.87 (4)	14 (2)	46403
O(6)3	W(1)	2.851 (4)	0.86 (5)	2.01 (5)	10 (3)	45604
	O(5)3	2.853 (3)	0.86 (5)	2.73 (5)	73 (3)	
O(2)4	W(3)	2.706 (4)	0.78 (5)	1.99 (5)	19 (3)	46403
O(3)4	O(3)4	2.872 (3)	0.78 (5)	2.50 (5)	54 (3)	
O(3)4	O(2)3	2.873 (3)	0.91 (4)	1.97 (4)	6 (3)	
	O(4)4	2.884 (3)	0.91 (4)	2.48 (4)	55 (3)	
O(6)4	W(4)	2.779 (4)	0.85 (4)	1.94 (4)	7 (3)	
	O(5)4	2.780 (3)	0.85 (4)	2.54 (4)	64 (3)	
O(2)5	O(3)2	2.846 (3)	0.77 (4)	2.13 (4)	19 (3)	46503
O(3)5	O(2)4	2.808 (3)	0.91 (4)	1.94 (4)	14 (2)	
	O(4)5	2.882 (3)	0.91 (4)	2.49 (4)	56 (3)	
O(6)5	W(5)	2.842 (5)	1.10 (5)	1.76 (5)	8 (3)	46403
O(2)6	O(6)5	2.663 (4)	0.80 (5)	2.00 (4)	29 (3)	46403
	O(3)6	2.881 (3)	0.80 (5)	2.41 (5)	47 (3)	
O(3)6	O(6)1	2.922 (3)	0.84 (4)	2.13 (4)	18 (3)	46403
O(6)6	W(5)	3.153 (5)	—	—	—	46503
W(1)1	W(2)	2.792 (4)	0.91 (5)	1.88 (5)	5 (3)	
W(1)1	O(3)1	2.969 (4)	0.90 (5)	2.14 (5)	19 (3)	45501
W(2)1	O(2)2	2.832 (3)	0.74 (4)	2.11 (4)	9 (3)	46503
W(2)2	O(6)4	2.741 (4)	0.78 (5)	1.96 (5)	6 (4)	44604
W(3)1	O(3)1	2.742 (3)	1.02 (4)	1.72 (4)	4 (2)	
W(3)2	O(5)3	2.871 (3)	0.96 (5)	2.00 (5)	20 (3)	54604
W(4)1	O(6)3	2.794 (4)	0.78 (5)	2.20 (5)	35 (4)	46702
W(4)2	W(5)	2.863 (4)	0.87 (5)	2.00 (5)	4 (3)	46702
W(5)1	O(6)1	2.881 (4)	0.91 (6)	1.97 (6)	4 (4)	
W(6)1	W(4)	2.843 (5)	0.94 (8)	1.91 (8)	2 (4)	56602
W(6)2	O(5)2	2.831 (5)	0.90 (8)	2.26 (8)	43 (5)	46602

(a) Symmetry code according to ORTEP (Johnson, 1976). If no symmetry operation is given, 55501 applies.

However, crystal forms (I) and (II) of  $\alpha$ -CD.6H<sub>2</sub>O differ in two main points: (i) the relative orientation of adjacent  $\alpha$ -CD rings is such that in form (I) crystals, the O(2), O(3) rim of one  $\alpha$ -CD is located over the cavity of the neighbouring molecule while in form (II) crystals, the O(6) rim is close to the cavity of the next neighbour; (ii) this packing allows one of the O(6) hydroxyls in form (II) crystals to protrude into the adjacent cavity, which leads to formation of a self-inclusion complex. The inclusion stoichiometry in form (I) crystals can be represented by  $\alpha$ -CD.2H<sub>2</sub>O.4H<sub>2</sub>O, with two water molecules included and four water molecules located in interstices between  $\alpha$ -CD rings while in form (II) crystals,  $\alpha$ -CD.H<sub>2</sub>O.O(6).5H<sub>2</sub>O, the  $\alpha$ -CD cavity accommodates one water molecule and one O(6) hydroxyl and five water molecules are located outside the  $\alpha$ -CD ring.

### (b) Conformation of $\alpha$ -CD

The six crystallographically independent glucose residues within the  $\alpha$ -CD molecule are in the <sup>4</sup>C<sub>1</sub> chair conformation and all endocyclic torsion angles are in

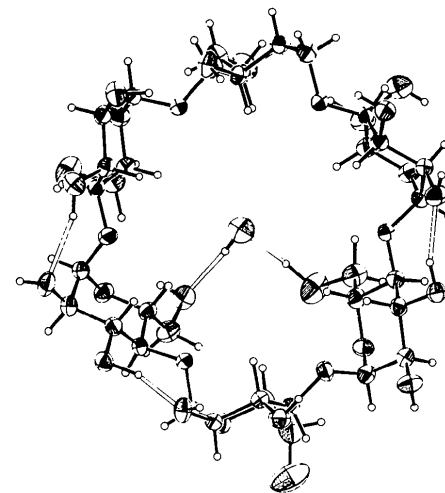
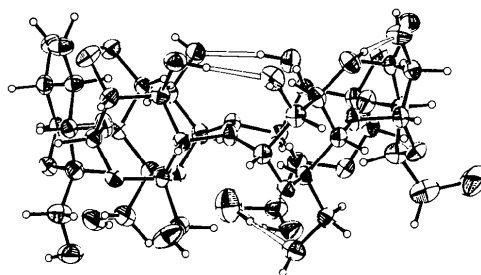


Fig. 2. Two different views of  $\alpha$ -CD.6H<sub>2</sub>O, form (II). Only the water molecule enclosed in the cavity is shown for the sake of clarity. Ellipsoids represent 50% probability distribution.

the *gauche* range (Table 4). The torsion angles with C(3) or C(4) as central atoms [C(1)—C(2)—C(3)—C(4); C(2)—C(3)—C(4)—C(5); C(3)—C(4)—C(5)—O(5)], average  $-54.4 \pm 3.1$ ,  $51.1 \pm 5.5$ ,  $-50.6 \pm 6.0^\circ$ , are in general smaller than the other three endocyclic torsion angles with C(1) or C(2) as central atoms, average  $57.2 \pm 3.2$ ,  $-61.8 \pm 1.6$ ,  $58.9 \pm 2.0^\circ$ . A similar trend is also observed with the dihedral angles between the central four-atom planes of the glucose rings [defined by C(2), C(3), C(5), O(5)] and the bow/stern three-atom planes [defined by C(3), C(4), C(5) and O(5), C(1), C(2)] [Table 5(iii), (iv)].\* The average dihedral angle between the former planes is  $46.7^\circ$ , range  $15.3^\circ$ , while for the latter planes it is  $53.7^\circ$ , range  $2.8^\circ$ . The ranges for the two dihedral angles are quite different and suggest that the glucose ring is rather rigid around C(1) but more flexible at C(4), probably because the group O(5)—C(1)—O(4) constitutes a mesomeric system. Four of the six exocyclic torsion angles O(5)—C(5)—C(6)—O(6) are in the preferred (–)*gauche* range and two adopt the

\* See deposition footnote.

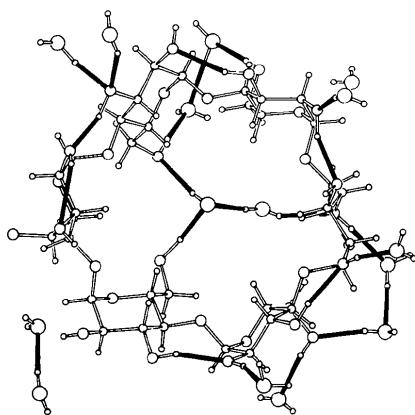
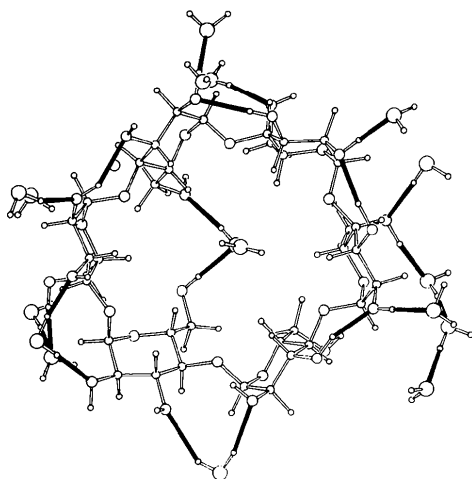


Fig. 3. The structure of  $\alpha$ -CD $\cdot$ 6H<sub>2</sub>O, form (I) (top), and  $\alpha$ -CD $\cdot$ 6H<sub>2</sub>O, form (II) (bottom), drawn on the same scale.

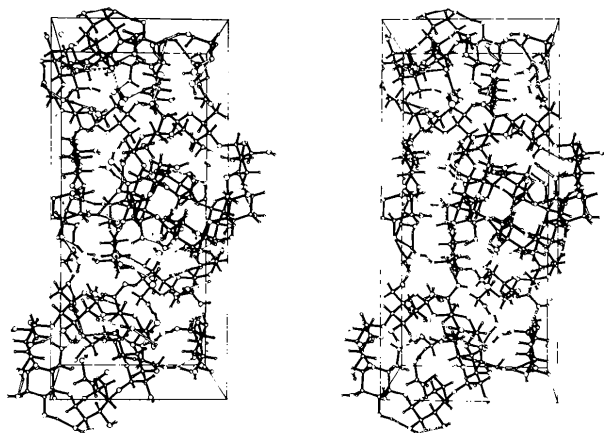


Fig. 4. A stereoscopic representation of the unit-cell content, viewed down the crystallographic  $c$  axis. Hydrogen bonds are indicated by open lines, interatomic bonds by heavy lines.

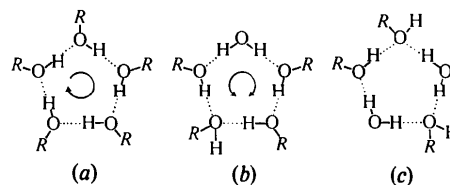


Fig. 5. Three types of circular bonds: (a) having the same sense (homodromic); (b) opposing sense (antidromic); (c) not having any particular direction (heterodromic).

(+)*gauche* conformation in order to hydrogen bond with the included water molecule.

The relative orientations of the glucose units in the  $\alpha$ -CD macrocycle are best described by the torsion angles around C(1)—O(4) and C(4)—O(4) and by the interglucose torsion angles  $\phi$ ,  $\psi$  (Table 4). While  $\phi$ , average  $165.2 \pm 6.1^\circ$ , is relatively constant for all six interglucosidic bonds, the angle  $\psi$ , average  $-169.1 \pm 20.1^\circ$ , varies considerably and, if potential-energy functions are applied as in the previous study (Manor & Saenger, 1974), the  $\psi$  angle for glucose 5 corresponds to a high-energy conformation.

This finding and the overall geometrical similarity of the  $\alpha$ -CD molecules in form (I) and (II) crystal structures (Fig. 3) indicate that the strained conformation of the  $\alpha$ -CD macrocycle is intrinsically associated with the inclusion of water while in complexes with all other guest molecules, even of Kr with comparable van der Waals dimensions to H<sub>2</sub>O (Saenger & Noltemeyer, 1976), the  $\alpha$ -CD adopts an undistorted, low-energy, round structure.

#### (c) Bond distances and angles

These data are given in Table 3 and have been discussed in detail in the previous publications (Manor & Saenger, 1974; Klar, Hingerty & Saenger, 1980). It is noteworthy that the average data for bond lengths and angles for the two crystal structures, the high-precision form (I) and form (II), are comparable within the  $\sigma$  limits. If the same bond lengths or angles for all six glucose residues are compared, one should expect a rather narrow distribution about the mean value. However, we find sometimes deviations exceeding the  $3\sigma$  limit, e.g. C(1)—C(2) for glucose 1 is  $1.541(4) \text{ \AA}$  while this distance for glucoses 2 to 6 averages  $1.520(5) \text{ \AA}$  and C(4)—C(5) for glucose 2,  $1.514(4) \text{ \AA}$ , is smaller than the mean value for the other five C(4)—C(5) distances,  $1.532(3) \text{ \AA}$ . Because systematic errors can be excluded in this case, the data differing greatly from mean values have to be attributed to internal strain within the macrocycle and to crystal-packing forces.

*(d) Intramolecular hydrogen bonding*

One of the main structural features of cyclodextrins is the ring of hydrogen bonds formed between O(2) and O(3) hydroxyl groups of adjacent glucose residues. In all the  $\alpha$ -CD inclusion complexes with guests other than water, the respective hydroxyl O atoms are so close together that hydrogen bonds are formed or they could form with only *slight* movements of the glucose units. For one of these complexes,  $\alpha$ -CD.methanol.4H<sub>2</sub>O (Hingerty & Saenger, 1976), the H atoms were located from X-ray data ( $R = 3.7\%$ ) and the hydrogen-bond circle has been established.

In the  $\alpha$ -CD.6H<sub>2</sub>O form (I) and (II) complexes, the ring of hydrogen bonds is disrupted at glucose 5 which in both structures is rotated out of alignment with the other five glucose residues, leading to an O(2)5...O(3)6 distance of 4.022 (3) Å, *i.e.* for formation of this hydrogen bond glucose 5 would have to rotate substantially, disrupting the hydrogen bond to the included water molecule, O(6)6-H...W(5).

All the other five O(2)...O(3) hydrogen bonds are formed, with O...O distances in the range 2.794 (4) to 3.048 (3) Å. The O(3)5-H...O(2)4 hydrogen bond with H...O distance 1.94 (4) Å (Table 7) indicates a tight hydrogen bond while in the form (I) crystal structure, the corresponding O(2)4-H...O(3)5 interaction with H...O distance 2.84 (2) Å is too long to be called a hydrogen bond.

Because the packing arrangements in form (I) and (II) crystals are different, the hydrogen-bonding interactions between O(2), O(3) hydroxyl groups and hydroxyls of adjacent water and  $\alpha$ -CD molecules are not identical. This implies that the directions of the intramolecular O(2)...O(3) hydrogen bonds are also different. If the O-H...OH bond is indicated by an arrow from donor to acceptor group, the following pattern is found: form (I): O(2)6 → O(3)1, O(2)1 ← O(3)2, O(2)2 ← O(3)3, O(2)3 ← O(3)4; form (II): O(2)6 ← O(3)1, O(2)1 ← O(3)2, O(2)2 → O(3)3, O(2)3 ← O(3)4, O(2)4 ← O(3)5.

*(e) The guest molecules*

The cavity in  $\alpha$ -CD.6H<sub>2</sub>O form (I) is occupied by two water molecules  $W(A)$  and  $W(B)$ .  $W(A)$  accepts a hydrogen bond from O(6)5 and donates a hydrogen bond to O(6)1 and to  $W(B)$ . In the form (II) complex, one water molecule,  $W(5)$ , is included and displays the same hydrogen-bonding arrangement to O(6)1 and O(6)5. Since only one H atom for  $W(5)$  could be located it is not certain if  $W(5)$  is also bonded to the second guest molecule, an O(6)6 hydroxyl group of a symmetry-related  $\alpha$ -CD, at a distance  $W(5)\cdots O(6)6$ , 3.153 (5) Å. Unfortunately, the location of the H atom at O(6)6 is also obscure and therefore the hydrogen-bonding scheme within the  $\alpha$ -CD cavity cannot be described.

It is of interest, however, that the water molecules bonded to the O(6)1 and O(6)5 hydroxyls,  $W(A)$  in form (I) and  $W(5)$  in form (II) crystals, display the same hydrogen-bonding arrangement. The second water molecule,  $W(B)$ , in the form (I) complex, is only fixed by a hydrogen bond to  $W(A)$  and by hydrogen bonds to an adjacent  $\alpha$ -CD, not to the including  $\alpha$ -CD, and therefore is replaceable by the O(6)6 hydroxyl of a neighbouring  $\alpha$ -CD in the form (II) crystal. It appears that  $W(A)$  is tightly bound while  $W(B)$  is only loosely bound and easy to replace. In all the crystal structures of  $\alpha$ -CD reported so far, however, both water molecules have always been replaced by guest molecules.

It is not clear under what conditions this self inclusion is preferred over the  $\alpha$ -CD.2H<sub>2</sub>O complex formation. It represents a rare case since it was only observed once in about 50 different crystallization batches.

*(f) Hydrogen-bonding scheme. Cyclic system of hydrogen bonds*

The hydrogen-bonding scheme is indicated in the unit-cell plot (Fig. 4) and outlined in Table 7 where all short H...O contacts are listed. Some of the glucose hydroxyl H atoms, *e.g.* O(2)2-H, O(3)2-H, O(6)3-H, O(3)4-H, O(6)4-H, O(3)5-H, are not only in close, hydrogen-bonding contact to hydroxyl groups of other glucose units or of water molecules but are also in short intramolecular contact with adjacent O(4) or O(5) O atoms which obviously have some attractive influence on the positions of the hydroxyl H atoms. There are also two clear indications of otherwise rarely observed hydrogen bonds to the endocyclic O(5) atoms,  $W(3)2\cdots O(5)3$  and  $W(6)2\cdots O(5)2$ , while O(4) atoms are obviously too concealed by neighbouring atoms and therefore cannot act as hydrogen-bond acceptors.

The hydrogen bonds are not randomly distributed but follow a certain pattern, forming circularly closed structures with five O-H groups linked by hydrogen bonds (Fig. 5). Such circular hydrogen bonds have been observed previously (five- and six-membered circles, Saenger, 1979) and again recently in yet another crystal form of hydrated  $\alpha$ -CD ( $\alpha$ -CD.7.57H<sub>2</sub>O; four- and six-membered circles, Chacko & Saenger, 1980). The circular hydrogen bonds can be *homodromic*, running in the same direction, *antidromic*, with counter-running hydrogen bonds and *heterodromic*, with hydrogen bonds in randomly alternating sense (Fig. 5). Besides homodromic circles (I) and (II) (Fig. 6), an antidromic circle (III) with a bifurcated hydrogen bond emanating from the H atom attached to O(2)6 and an 'infinite', homodromic chain running through the crystal lattice are observed (Fig. 6, Saenger & Lindner, 1980), leading to a cluster-like arrangement of O-H groups and indicating the influence of the 'cooperative effect' (Saenger, 1979; Lesyng & Saenger,

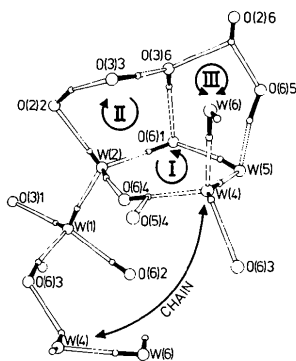


Fig. 6. The OH cluster in  $\alpha$ -CD.6H<sub>2</sub>O, form (II). The rings with homodromic hydrogen bonds are designated (I) and (II); the arrows show the directions of the O—H...O bonds. Ring (III) having antidromic hydrogen bonds contains a bifurcated hydrogen emanating from O(2)6—H. An 'infinite' chain of homodromic hydrogen bonds shown by a double-headed arrow from water molecule *W*(4) to the symmetrically equivalent *W*(4) goes through the crystal lattice. Water molecules are indicated by *W*(1) to *W*(6); the numbering of all other atoms corresponds to that given in Fig. 1.

1980). The relative frequency of these structures suggests that they may be of importance in the hydration of (macro)molecules and in the structure of water itself.

### Conclusions

We have seen that the packing schemes of form (I) and form (II) crystals of  $\alpha$ -CD.6H<sub>2</sub>O are so different that the almost identical conformation of  $\alpha$ -CD in both crystal structures cannot be attributed to crystal-packing artefacts. Rather, it appears to be intrinsically associated with the inclusion of water molecules, *i.e.* the 'empty'  $\alpha$ -CD present in aqueous solution has a conformation that differs from the conformation adopted if guest molecules other than water are included. This even holds for a recently discovered, new crystal form of  $\alpha$ -CD hydrate,  $\alpha$ -CD.7.57H<sub>2</sub>O (Chacko & Saenger, 1980) which was obtained from 1.2*M* aqueous BaCl<sub>2</sub>. It displays a 'round'  $\alpha$ -CD macrocycle with 2.57 H<sub>2</sub>O molecules included and disordered over four different, not fully occupied sites, representing 'activated water'. This  $\alpha$ -CD hydrate has been predicted as the transition intermediate when going from 'empty'  $\alpha$ -CD to an inclusion complex in an 'induced-fit'-type mechanism (Saenger, Noltemeyer, Manor, Hingerty & Klar, 1976). The conformational change of  $\alpha$ -CD occurring upon inclusion formation has also been observed by circular dichroism spectroscopy (Rees, 1970). The 'induced-fit'-type mechanism

is valid only for  $\alpha$ -CD. For  $\beta$ - and  $\gamma$ -CD, the homologous compounds with seven and eight glucose residues, no conformational differences between 'empty' and complexed  $\beta$ -CD are observed but release of highly disordered water within the cavity ('activated water') upon complex formation seems to provide substantial driving force for this process (Lindner & Saenger, 1978; McLennan & Stezowski, 1980; Bender & Komiyama, 1978).

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