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CRYSTAL STRUCTURE OF THE γ-CYCLODEXTRIN·n-PROPANOL INCLUSION COMPLEX; CORRELATION OF α-,ß-,γ- CYCLODEXTRIN GEOMETRIES*

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SUMMARY

Crystals of the hydrated n-propanol inclusion complex of γ-cyclodextrin (γ-CD; cyclo-octaamylose) have space group P4, *a* = *b* = 23.759(7), *c* = 23.069(7) Å and six quarter γ-CD *per* asymmetric unit. The structure was solved by YZARC and refined to R = 14% using 6300 X-ray counter data. The γ-CD are stacked, n-propanol (not located) occupies the channel-type cavity and 27 water sites populate interstices between stacks. Within the stacks γ-CD are arranged head-to-head as well as head-to-tail and H-bonded with O(2), O(3), O(6) hydroxyls. In the series α-,ß-,γ-CD, angles C(1')-O(4)-C(4) reduce from 119°-117.7°-112.6°, virtual O(4')····O(4) distances increase 4.23-4.39-4.48 Å, intramolecular H-bonding distances O(2)···O(3) between adjacent glucoses, 3.00 Å in α-CD are wider than ∿ 2.83 Å in ß- and γ-CD, indicating a greater flexibility of the former.

INTRODUCTION

As pointed out in the preceding contribution (1), cyclodextrins (CD; cycloamyloses) are used successfully as models to study non-covalent intermolecular interactions and enzyme mechanisms. Another point of interest is the possible extension of CD geometry, which can be obtained very accurately from single crystal X-ray data, to the polymeric analogue amylose (starch), the helical structure of which can only roughly be derived from X-ray fibre diffraction analysis aided by computer modeling (2-6). Since amylose is known to be polymorphic and to display 4- to 8- fold helices depending on added precipitating agent or chemicals (6), the α-,ß- and γ-CD with 6 to 8 glucoses per macrocycle are ideal model substances. Further, in this homologous series of cyclic oligosaccharides, it is of general interest to follow changes in conformation and

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[*] Part XIV of the series on "Topography of Cyclodextrin Inclusion Complexes". For part XIII, see M. Noltemeyer, W. Saenger (1980) J. Amer. Chem. Soc. in the press.

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glucose geometry when going from one macrocycle to the next. In this paper, the channel-type structure of the hydrated γ-CD·n-propanol complex as opposed to the cage-type structure of the "empty" hydrated γ-CD (1) will be described and some correlations concerning α-,ß- and γ-CD will be presented.

METHODS

When a hot, saturated solution of γ-CD in 60% (v/v) n-propanol was allowed to cool down slowly, square bipyramidal crystals truncated at both ends were obtained. A specimen of dimensions 0.3 x 0.3 x 0.6 mm was sealed with some mother liquor in a quartz capillary and used for all X-ray studies. Over 7000 intensity data were collected at 20°C on a STOE four circle diffractometer using Ni-filtered CuK_α radiation, $2\theta_{max} = 118^\circ$, $2\theta/\omega$ scan mode, stationary background counts on both sides of each scan, absorption correction according to (7).

The structure was solved by direct methods. After several attempts applying the multisolution method (MULTAN 78,(8)) had failed, the approach of Baggio et al (9,10) with 100 start phases chosen randomly, refined by least squares and expanded by tangent formula showed the whole structure except O(6) atoms and solvent molecules. The atomic parameters were subsequently refined against the 6300 data above 3σ level (ORXFLS4 (11)) and missing atoms located from difference Fourier maps. The present R-factor is 14% with all atoms vibrating anisotropically, 27 water sites accounting in total for an occupancy of 21.4 but the included n-propanols could not yet be traced unambiguously.

RESULTS AND DISCUSSION

The crystal structure of hydrated γ-CD·n-propanol is characterized by stacked γ-CD yielding channel-type "endless" cavities in which the n-propanol is accomodated. There are two different stacks centered around the two fourfold rotation axes passing through the center of the unit cell (stack I) and through the origin (stack II). Each stack contains three γ-CD molecules, A,B,C in stack I and D,E,F in stack II (Fig. 1), such that the asymmetric unit is composed of six quarter γ-CD molecules (Fig. 2).

In stack I, molecules A and C point in the same direction (O(2;3) side up) while B is in opposite orientation and in stack II, molecule E is O(2;3) side up but D and F are down. In total, three γ-CD molecules point up, three down. The odd number of molecules in each stack and the opposite polarities imply that the γ-CD are in head-to-head an in head-to-tail orientations within the same stack. The head-to-head arranged γ-CD molecules are linked pairwise by O(6)···O(6) and by O(2;3)···O(2 ;3) hydrogen bonds (A,B; B,C; D,E; E,F) and the head-to-tail pairs (A,C; D,F) are H-bonded O(6)···O(2;3). This crystal packing pattern is unique in CD structures as α-and ß-CD stacks are only of the head-to-head or of the head-to-tail type.

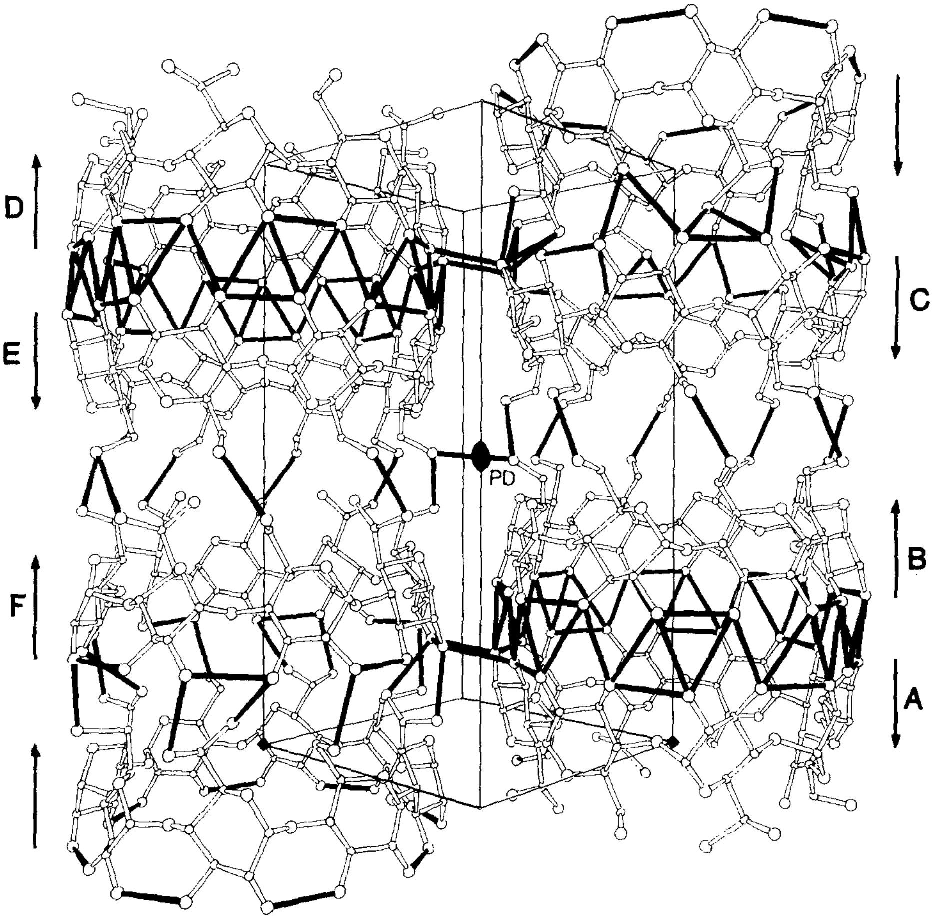

Figure 1. View of the crystal structure of γ-CD·n-propanol inclusion complex, looking along [110]. Only γ-CD molecules drawn for sake of clarity. The outlined prism represents one quarter unit cell and shows fourfold axes at 0,0,0 (molecules D, E, F) and at 1/2, 1/2, 0 (molecules A, B, C). Arrows indicate polarity of γ-CD, from O(2;3) to O(6) side. PD marks the location of pseudo-diad relating the two stacks. O(6) atoms are twofold disordered in A, D, F. Covalent bonds drawn with open lines, H-bonding contacts < 3.0 A with solid lines.

The X-ray reflection intensities are nearly consistent with the higher symmetry space group P422, and the crystal packing reflects a pseudo-twofold symmetry as indicated by the pseudo-diad between stacks I and II in Fig. 1. This diad relates molecules A,D; B,E; C,F and also like interactions such as head-to-head and head-to-tail in the two stacks. The symmetry, however, is broken by pair C,F because the O(6) atoms in C are all well ordered with torsion angles O(5)-C(5)-C(6)-O(6) in the preferred *(-)gauche* orientation (12) while they

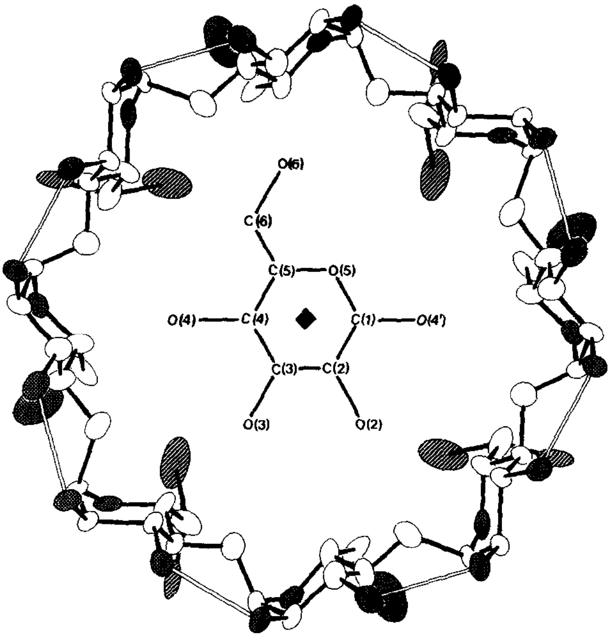

Figure 2. Molecule A as a representative of all six γ-CD. Position of fourfold axis is marked ◆. O(2)···O(3) H-bonds drawn with open lines, oxygen atoms indicated by stippling, disordered O(6) atoms by hatching. The inset shows the atom numbering used in the text.

are partly disordered in F, *(-)gauche* and *trans*. Other disordered O(6) atoms are in pair A,D while O(6) atoms in pair B,E are ordered and *(-)gauche*.

Between the stacks there are some direct H-bonds bridging O(2;3) and O(6) hydroxyls, indicated in Fig. 1. Not shown in this drawing are 27 water sites filling interstices between γ-CD stacks and giving rise to an intricate H-bonding pattern.

Although the present R-factor is quite high, the occurence of six independent γ-CD molecules allows us to derive some averaged geometrical details and to correlate these with data obtained from the lower homologs α- and ß-CD, see Table 1.

There are some obvious trends in average geometrical data when going from α-CD to γ-CD. Thus the O(4)···O(4) distance giving the virtual bond length *of the glucose (3), increases from 4.23 Å in α-CD to 4.39 Å in ß-CD to 4.48 Å in* γ-CD and the angle at the glucosidic link, C(1')-O(4)-C(4), is reduced from

Table 1.

Some averaged geometrical data for α-, ß- and γ-CD. Data from α- and ß-CD are from (15,16). Torsion angles Ø, Ψ are defined as O(4)···C(1)-O(4')-C(4') and C(1)-O(4')-C(4')···O(4''); primed and double primed atoms belong to adjacent glucoses.

Cyclodextrin	Angle (°) C(1')-O(4)-C(4)	Torsion Angle(°) Ø	 Ψ	Distance(Å) O(4)···O(4)	Distance(Å) O(2)···O(3)
α	119.0	166	-169	4.23	3.00
ß	117.7	169	-172	4.39	2.86
γ	112.6	165	-169	4,48	2.81

119° in α-CD to 117.7° in ß-CD to 112.6° in γ-CD. (The latter angle is very different from those in α- and ß-CD but the variation of the twelve angles in the γ-CD crystal structure, from 106.4° to 116.9°, indicates a significant trend) These data reflect the widening of the CD-macrocycle from 6 to 8 glucoses, which is accompanied by a reduction of curvature and can be understood from mechanical reasonings with a wire model. It is remarkable that the relative orientations of adjacent glucoses, represented by torsion angles Ø and Ψ, is comparable in all three CD but the length of the O(2)···O(3) H-bonds between adjacent glucoses shows an interesting trend. This distance, 3.00 Å for α-CD, is much longer than for ß- and γ-CD, about 2.83 Å, and indicates a tighter ring of H-bonds around the O(2), O(3) rim in the latter two molecules. This finding is corroborated by theoretical calculations which predicted a decreased macrocycle stability of α-CD relative to ß- and γ-CD (13) and adds more weight to the spectroscopically (14) and X-ray crystallographically (12) observed flexibility of α-CD.

Computer studies based on X-ray structural data of α-CD alone tried to predict geometrical features of ß- and γ-CD (6). Although the C(1')-O(4)-C(4) angle was confined to a narrow range of 119°-120°, the trend in O(4)···O(4) distances was predicted. It is hoped that with the new, more extended data now at hand, better computer simulations of amylose structures are possible and that not only the variation of C(1')-O(4)-C(4) angles but also the disorder of O(6) atoms and intermolecular H-bond interaction schemes give new impetus to such studies.

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