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Two-dimensional hydrogen bond network in β-cyclodextrin complexes

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The formation of invariant layers of dimers linked by an extended dense two-dimensional hydrogen bond network governs the crystal structure organisation of the great majority of native β-cyclodextrin complexes.

Cyclodextrins (CD) are cyclic oligosaccharides built from 6,7,8,. . . (α-, β-, γ-,. . .) glucose residues. They have recently come to prominence as carriers of drugs, essential oils and various key compounds in the pharmaceutical, food, cosmetic and other industries[1–5]. Their practical applications are greatly facilitated by the fact that they are natural products which can be produced in quantity by inexpensive biotechnological processes.

We have examined previously the crystal structures of β-CD complexes with benzil (I), benzophenone (II), biphenyl (III) and phenylethylmalonic acid (IV)[6]. The data, together with those of some twenty published structures taken from the literature, have led to a reexamination of the packing and hydration characteristics of this class of compounds.

The study has led to new insight into the role of hydration in the interactions between guest-containing CD molecules and of the possible mechanisms which enable CDs to include guest molecules.

Most complexes of native β-CD crystallize as dimers. The dimers in all known structures are linked head-to-head by hydrogen bonds between the secondary hydroxyls and are stacked in the crystal with their seven-fold axes approximately parallel (Fig. 1). The dimers are linked together into infinite 2D layers by a dense network of hydrogen bonds involving primary and secondary hydroxyl groups as well as water and eventually other solvent molecules. These layers are approximately perpendicular to the dimer axis and have the width of one dimer (about 16 Å). The extended crystal structure is built up by linking together the layers by hydrogen bonds involving primary hydroxyl groups and water molecules. Partial results have been given in a previous symposium[7].

All known crystal structures of β-CD dimers are generated from a superposition of these **practically invariant layers**; they fall into three main classes which differ in the relative position of the layers (Fig. 1). In the **channel** (CH) class the dimers are aligned one above the other by a lattice translation forming columns. In the **chessboard** (CB) class the dimers of adjacent layers are related by a helical two-fold axis perpendicular to the layers. A dimer is thus located above a space filled by solvent. This arrangement leads to columns with alternating CD dimer and solvent regions and confers on this class of structures a chessboard appearance. In the **intermediate** (IM) class the layers are interrelated by a lattice translation, as in the CH class, but the intramolecular cavities of dimers belonging to adjacent layers are far from exactly aligned. Each cavity is thus partially closed by the CD atoms of the adjacent layers. A fourth type, called **screw channel**, has been reported, where the layers form another variant of deformed channel located at a helical two-fold axis[8].

Despite the different packing arrangement the hydrogen bond network within a layer is very similar in different classes. A striking characteristic is the segregation of the 2D network into two sub-networks or sub-layers containing the primary and secondary hydroxyl groups, as illustrated in Figs 2 and 3, respectively, for the complex I of the CB class and complex II of CH class. An important distinction between the two sub-networks is that in the network involving the secondary hydroxyls (secondary network), water molecules extend the intramolecular and intradimer hydrogen bond system. The primary network, on the other hand, constitutes an interface between two layers and involves principally hydroxyl-solvent and solvent-solvent interactions; in the case of the CB class, it is devoid of direct bonds between CD molecules of adjacent layers. In this study, hydrogen bonds have been characterized by geometrical criteria, hydrogen positions being not found directly by X-ray diffrac-

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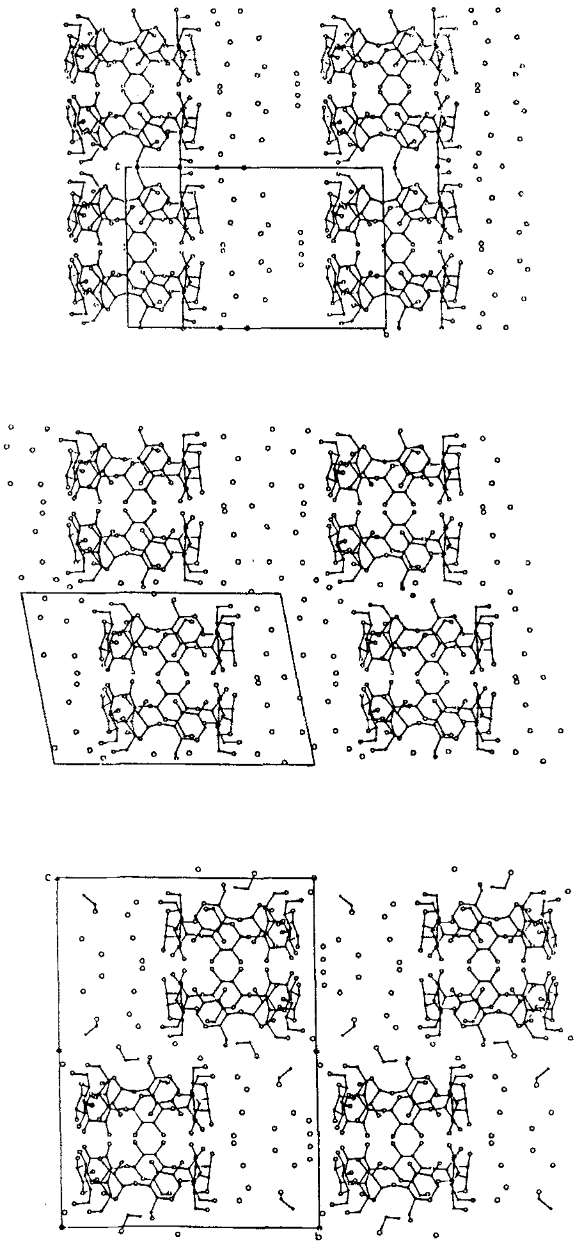

Figure 1 Packing of β-CD and solvent molecules in the three main classes. Oxygen atoms positions are indicated by small circles. For the CH class, on the top of the figure, projection on plane (b, c) of the structure of complex II (the structure of complex III also belongs to this class). The crystallographic parameters for complex II are: a = 19.24 Å, b = 24.56 Å, c = 15.94 Å, β = 109.4°, space group: C2, Z = 4. For the IM class, in the middle of the figure, the structure of β-CD complex with 1-adamantane carboxylic acid has been chosen as archetype (11). Projection of this structure on plane (c-b, a). The crystallographic parameters are: a = 17.65 Å, b = 15.26 Å, c = 15.49 Å, α = 102.5°, β = 113.5°, γ = 98.9°, space group: P1, Z = 2. For the CB class, on the bottom of the figure, projection on plane (b, c) of the structure of complex I. The crystallographic parameters are: a = 19.58 Å, b = 24.27 Å, c = 32.58 Å, space group: $C222_1$, Z = 8. The structure of complex IV also belongs to this class.
(Reproduced from Cyclodextrins and their industrial uses, Editions de Santé, Paris (1987), with permission from editor.)

tion analysis. However, we note that in the analogous case of the structure of α-CD cyclopentanone hydrate, most of the hydrogen bonds have been confirmed by a neutron diffraction study[9]. In this paper, the acceptance of hydrogen bond between two atoms is based both on the O. . .O distance (<3.1 Å) and on the value on the involved valence angles (90° – 135°). These limiting criteria are set somehow arbitrarily, yet they fall within the range of generally accepted values and they avoid exclusions from the discussion slightly displaced water or hydroxyl positions in different structures. This question is also related with an often occuring disorder in CD complexes, affecting water molecules and hydroxyl groups.

An intramolecular ring of hydrogen bonds between the secondary hydroxyl atoms O(2) and O(3) of adjacent glucose residues is found in all known structures of native CD. However, β-CD complexes forming dimers have, in addition, seven O(3). . .O(3′) bonds linking the two dimer molecules. The set of these 21 intramolecular and intradimer bonds per dimer is extended into an infinite 2D sub-network. Each CD molecule establishes 11 hydrogen bonds to the exterior of the dimer it belongs: nine of them are directed towards a water molecule and two, towards a CD molecule belonging to an adjacent dimer within the same layer. It is important to notice that this pattern is identical in all classes.

In complex I the secondary network is further strengthened by about six water-water bonds per subunit (with one CD molecule) which contains 4.5 water molecules distributed over seven distinct sites: six sites are connected via hydrogen bonds to the secondary hydroxyls groups, the seventh being connected only to another water site. The water molecule sites are comparable, yet not identical in the three classes (Figs 1 – 3). The nodes of the network form quadrilaterals and pentagons similar to that described by Saenger for the pure hydrated form; these circular structures may be combined with a flip-flop (relay) system of hydrogen bonds[10].

Thus, the absence of water molecules within the cavity and the resulting release of all hydroxyl groups, contributes to the formation of an infinite 2D **secondary sub-network of very densely packed hydrogen bonds.** This network includes the intradimer hydrogen bond system described above and is **practically invariant for the three main classes.**

In the primary network of complex I, there are five water sites and two alcohol sites per CD molecule. The remarkable fact is that the oxygen atoms of ethanol molecules are replaced in the other classes by water molecules at the same position. In complex I, all seven primary hydroxyl are linked twice by hydrogen bonds. Each residue establishes 14 hydrogen bonds: ten of them are directed towards a solvent molecule; four, towards a CD

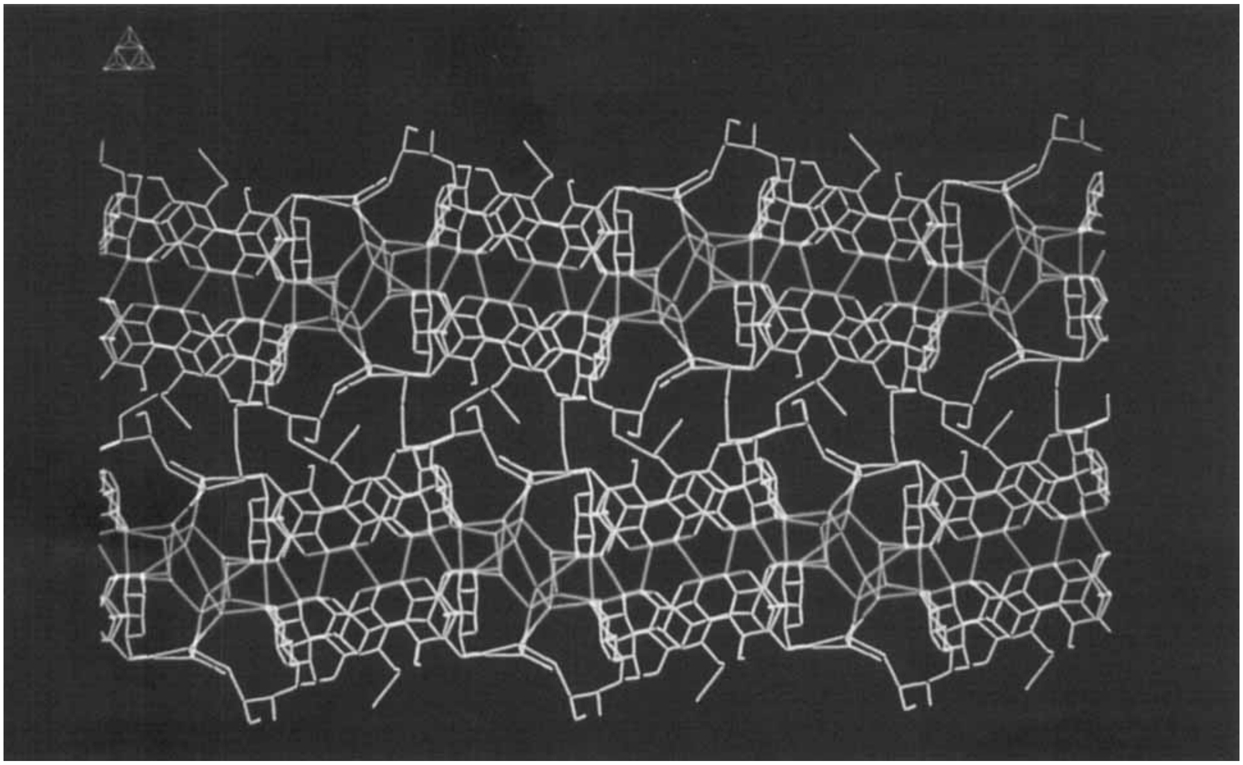

Figure 2 Projection of the structure of complex I on plane (a, c)[14]. The projection is parallel to the two-fold axis along b and perpendicular to the approximate seven-fold axis. The covalent bonds of CD and ethyl alcohol are shown in blue, the secondary hydrogen bond network in red, the primary network in green. We distinguish two bonds linking the secondary to the primary network (half green, half red). Within the dimer layers, the secondary and primary networks are clearly distinct. The secondary network extends the system of intermolecular interactions throughout the crystal. The primary network constitutes the interface between two layers. Colour Plate I

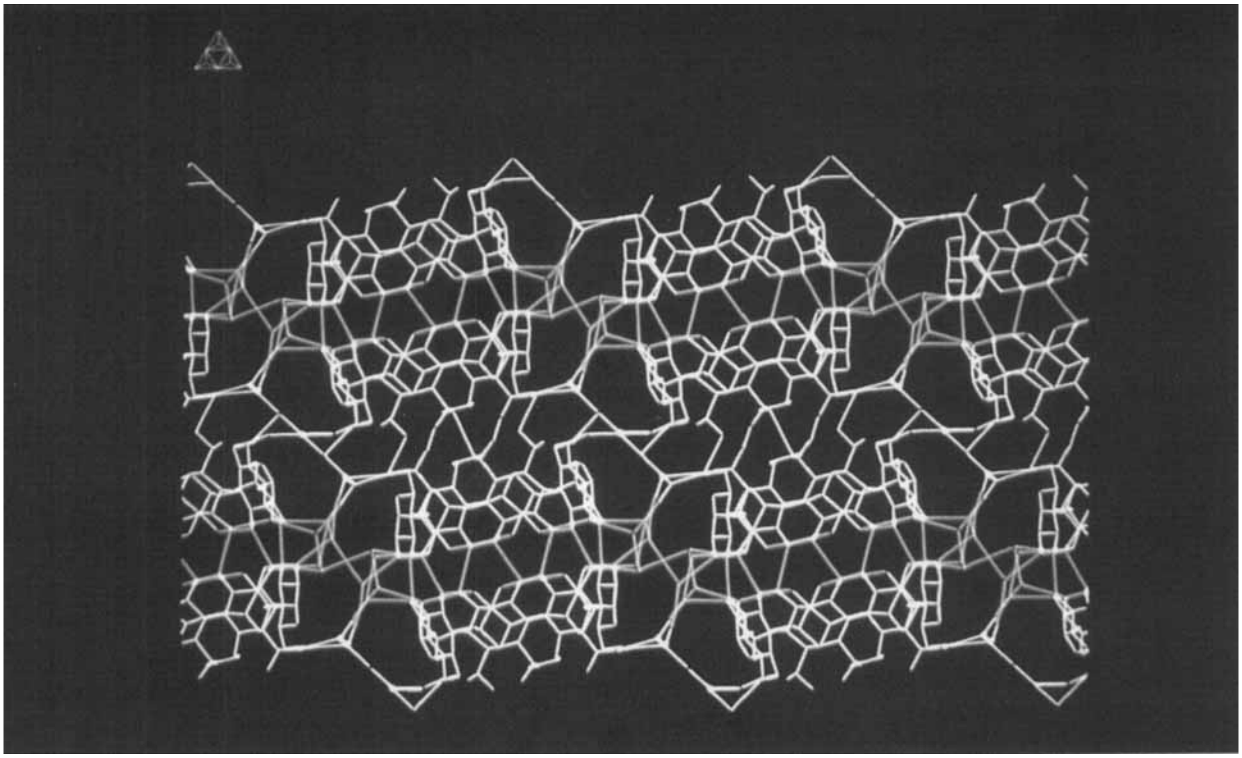

Figure 3 Projection of the structure of complex II of the CH class on plane (a, c). Color conventions are those of Fig. 2. Similarities of dimer arrangement and secondary network within a layer are striking in these different classes. Colour Plate II

molecule belonging to an adjacent dimer within the same layer. The latter four bonds form an invariant structural element in all classes. But the primary network constitutes an interface between adjacent layers and it is not surprising that it varies in the different classes: in complex 1-adamantane carboxylic acid of the IM class, eight bonds are directed towards water molecules, one towards a CD molecule belonging to an adjacent layer[11]. The corresponding figures for complex II of the CH class are, respectively, five and five.

The dense two-dimensional hydrogen bond systems within a layer suggests a three-step cooperative mechanism for the inclusion of guest molecules. In solution, as an initial step, water molecules are expelled from a few CD cavities and replaced by guest molecules. In the second step, aggregation of several CD molecules forms a stabilized layer structure over a limited domain. Any hydrated CD molecule without guest molecule included in such a domain will be relatively unstable and the water molecules in the cavity are likely to be replaced by guest molecules through the influence of the cooperative hydrogen bond system in the CD-water layer. This suggestion is in accord with the molecular model of Saenger and coworkers who postulated that the release of strain accompanying the expulsion of water plays a role in the inclusion mechanism[12]. CD dimers have also been suggested as models for biological membranes[13]. The occurence of an extended β-CD water layer suggests how such membrane might be organised in two dimensions.

Crystallization proceeds from this stage through a third step which involves the mutual positioning of the layers into a 3D array, as formed in the different classes, channel, chessboard and intermediate, described above.

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