CRYSTAL PACKING PATTERNS OF CYCLODEXTRIN INCLUSION COMPLEXES*

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ABSTRACT. Cyclodextrin inclusion complexes crystallize in two basically different patterns, the cage and the channel type. The cage type occurs when cyclodextrins are packed crosswise (fishbone) or, if they are packed side-by-side, in layers and adjacent layers are displaced by about one half molecule. In each case, the internal cavity of one cyclodextrin is closed on both sides by neighbouring cyclodextrins. On the other hand, channel complexes are formed if cyclodextrins are stacked like coins in a roll so that cavities line up to produce long channels. In these crystal structures, cyclodextrins can be arranged in head-to-head or head-to-tail mode. In the smaller α-cyclodextrin, cage type structures are formed with small, molecular guests whereas long molecular guests and ionic guest molecules induce channel type structures. The latter are generally preferred with the ß- and γ-cyclodextrin series which is probably due to the higher tendency for self aggregation in these two members of the cyclodextrin family.

INTRODUCTION

In the past 20 years, a large number of cyclodextrin inclusion complexes and also the "empty" cyclodextrin molecules which were crystallized from pure water have been studied by X-ray and neutron diffraction methods (1-4). On the basis of the available data, some conclusions can now be drawn concerning the overall packing tendency of the cyclodextrin molecules which in some cases depends on the type of the guest molecule (5,6). Since the cyclodextrin complexes are becoming of increasing importance for industrial purposes, it is of interest to be able to predict the packing arrangements of crystalline specimens. It is the purpose of the present contribution to summarize the packing patterns of α-, ß- and γ-cyclodextrin inclusion complexes and to draw some general conclusions.

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1. GENERAL FEATURES OF CYCLODEXTRIN PACKING PATTERNS

The macrocyclic structure of cyclodextrins resembles a truncated cone with the wide side occupied by O2, O3 hydroxyls and the narrow side by O6 hydroxyls. This polarity gives the cyclodextrins properties which are essential if packing in crystal lattices is discussed.

Before describing the individual packing modes of α-, ß- and γ-cyclodextrins, let us have a look at general packing motifs that are obtained with these molecules. If cyclodextrins pack in a crosswise or fishbone type arrangement (Fig. 1a), both sides of the internal cavity of each cyclodextrin are closed by the adjacent cyclodextrins in the crystal lattice. This gives rise to individual cages, in which the guest molecules are enclosed and are separated from each other such that there is no direct contact between the guest molecules.

A cage type arrangement can also be produced if cyclodextrin molecules are arranged side-by-side so as to form layers in which the (O2,O3) sides and the O6 sides of the cyclodextrin molecules form the two surfaces of these layers. Adjacent layers are displaced by about the radius of a cyclodextrin molecule such that a motif reminiscent of bricks in a wall is generated. The cavities of individual cyclodextrins are closed on both sides by neighbouring molecules (Fig. 1b).

This kind of brick-type cage structure has until now been observed only with α-cyclodextrin and not with ß- and γ-cyclodextrin. With ß-cyclodextrin, another type of cage structure occurs in which larger cages are formed by head-to-head arranged dimers or even by tetramers. These dimers or tetramers are arranged side-by-side in layers and adjacent layers are displaced so that the cavities of the dimers or tetramers are closed on both ends (Fig. 2b).

In the channel type complexes (Fig. 1c), cyclodextrin molecules are stacked on top of each other like coins in a roll such that the cavities align in the form of endless channels. This packing mode is stabilized by hydrogen bonding between the cyclodextrin molecules and we observe two kinds of arrangements, head-to-head and head-to-tail. In the head-to-head arrangement, the (O2,O3) side of one cyclodextrin is hydrogen bonded with the (O2,O3) side of the adjacent molecule to form a dimer and the O6 sides of the dimer are hydrogen bonded with O6 sides of adjacent dimers. In the head-to-tail arrangement, (O2,O3) sides are hydrogen bonded with O6 sides and vice versa. There is one case, found in γ-cyclodextrin, where we have both head-to-head and head-to-tail hydrogen bonding in alternating sequence in the same channel structure.

This latter kind of arrangement appears to be special for γ-cyclodextrin as it was not observed until now in α and ß-cyclodextrin crystal structures. For α-cyclodextrin, channel-type complexes in both head-to-head and head-to-tail arrangements have been found whereas for ß-cyclodextrin, only the head-to-head arrangement has been visualized thus far.

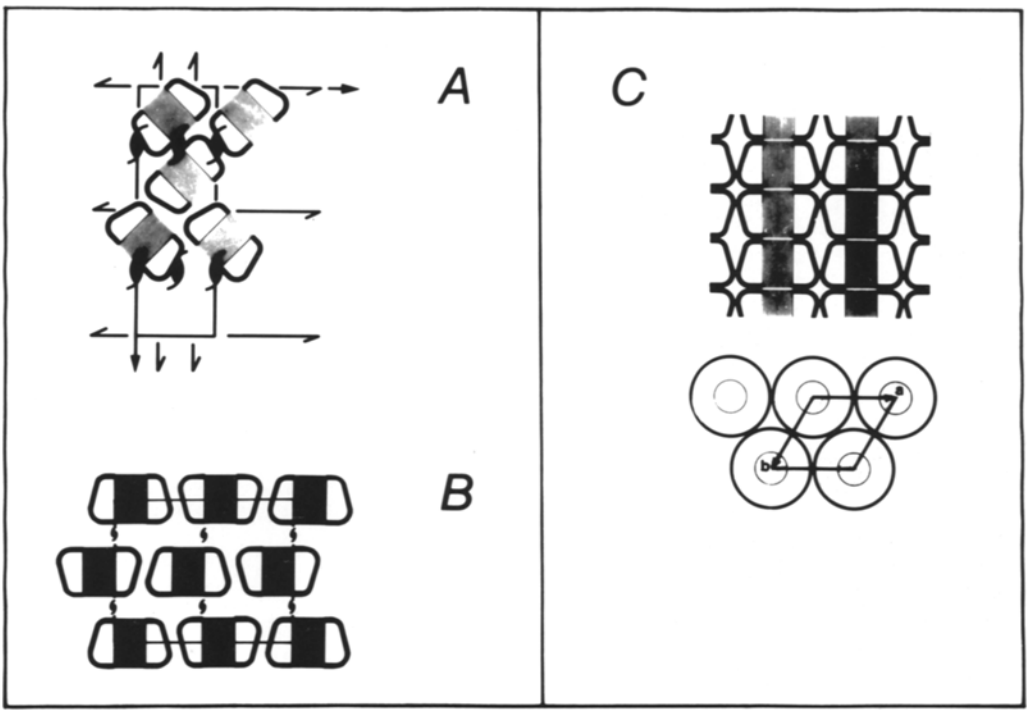
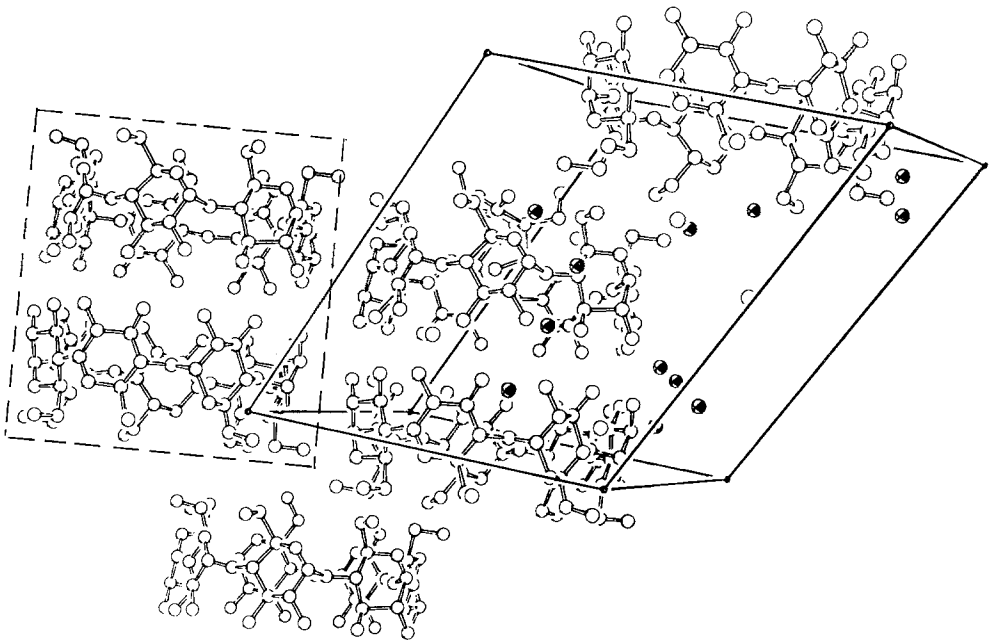
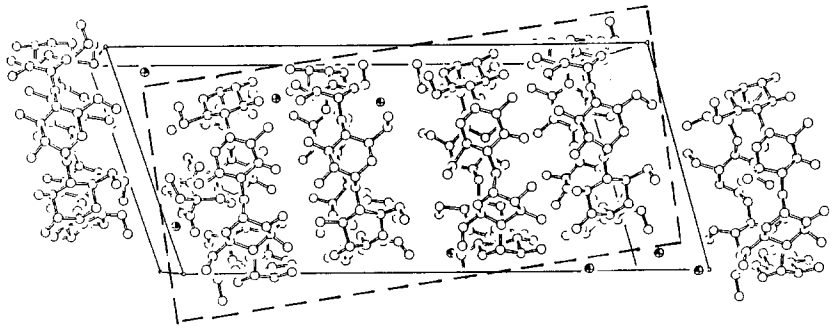
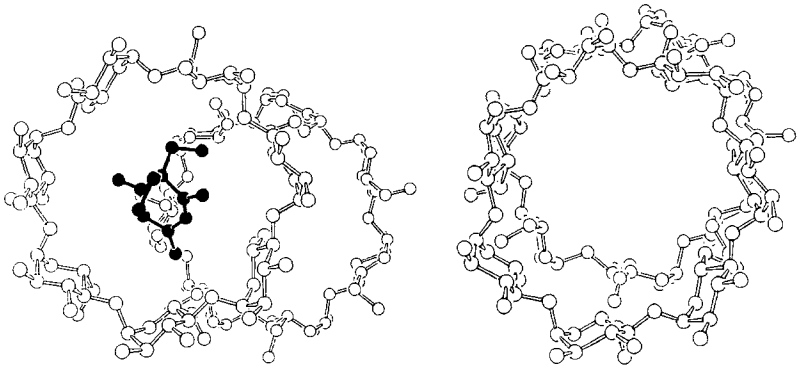


Figure 1.
General packing schemes of cyclodextrin molecules in crystalline lattices. Cyclodextrins are seen from the side, the cone-like structure is indicated by wider (02,03 hydroxyls) and narrower (06 hydroxyls) dimensions; cavities are marked by hatched areas. (A) Fishbone-type cage, (B) brick-type cage, (C) channel-type arrangement (a head-to-head packing of cyclodextrin molecules is shown).







2. PACKING PATTERNS IN α-CYCLODEXTRIN INCLUSION COMPOUNDS

In crystalline α-cyclodextrin inclusion compounds, the packing depends largely on the type of guest molecule. Since the cage type patterns allow only small molecules to be enclosed, this kind of arrangement is found with molecular guests which fit into the cavity. If the size of the guest is so large that it protudes on both sides of the cavity, a rearrangement into channel type form is observed. This behaviour has been found with fatty acids of which acetic, propionic, and butyric acids are so small that they can be accommodated in the cage type structure whereas from valeric acid on, the channel type structure is preferred (6).

Another systematic change in packing pattern is observed if we go from a small molecular guest to an ionic guest. Thus, acetic acid forms a cage type structure whereas the ionic potassium acetate prefers a channel type arrangement (7). The anions are located within the channels whereas the cations are outside the channels and in interstices between cyclodextrin molecules. A similar behavior was found with iodine which as molecular I_2 is accommodated in cage type arrangement whereas if metal iodide is added to the crystallization batch, polyiodide is formed which is enclosed in channel type structures (8). The metal ions are again located between the cyclodextrin stacks and the polyiodide occupies the channels.

With small aromatic guest molecules, the brick-type cage motif is often found. The reason might be that the benzene moiety is wedged into the α-cyclodextrin cavity which is somewhat distorted into an elliptical shape (9). It appears that this gives the cyclodextrin molecules a tendency to pack laterally and to produce layers. The layers are stacked with slight lateral displacement with respect to each other so that the cavities of one layer are closed on both ends by adjacent α-cyclodextrin molecules. This kind of brick-type cage arrangement has until now only been observed with α-cyclodextrin and not with ß- and γ-cyclodextrins.

Figure 2
ß-Cyclodextrin barbital crystallizes in two different cage forms. Individual cages are outlined by broken lines. (top) Head-to-head dimer formation, with adjacent dimers laterally displaced so that cages are closed on both ends by neighbouring molecules. (bottom) Two dimers are stacked linearly to form a tetramer and adjacent tetramers are displaced laterally so that individual, long cages are obtained. The two views of the bottom of this figure display lateral displacement of stacked ß-cyclodextrin molecules, with (right) dimer-dimer stack and (left) tetramer-tetramer stack. In the latter illustration, a guest molecule (barbital) is drawn in solid lines to indicate the cage-effect produced by the displacement.

Individual dimers (top) and tetramers (bottom) are indicated by dashed lines, unit cells are drawn with solid lines. These illustrations were kindly provided by Prof. T. Fujiwara (Osaka) before publication.

The channel structures of α-cyclodextrin are found in the head-to-head and head-to-tail forms. They are stabilized by extensive hydrogen bonding between (02,03) and 06 hydroxyls. Based on our present knowledge, it is not possible to predict which type of channel structures will form. It appears that if the guest molecule has the proper size to be enclosed in two cyclodextrin molecules (a dimer) like e.g. the pentaiodide (8), a head-to-head situation will be favoured.

3. ß-CYCLODEXTRIN PREFERS DIMERIC HEAD-TO-HEAD TYPE ARRANGEMENT

The behaviour of ß-cyclodextrin is very different compared with α-cyclodextrin. Only for a few crystal structures with water, methanol and ethanol as guest molecules, a fishbone type cage arrangement has been found (10,11). Larger guests like n-propanol are accommodated in cavities which are formed by two ß-cyclodextrin molecules arranged in a head-to-head fashion although n-propanol is small enough to be enclosed in a monomeric cavity (12). It appears that the head-to-head dimer formation is favoured for ß-cyclodextrin because it has a more rigid structure due to rather strong hydrogen bonds formed between 02 and 03 hydroxyls of adjacent glucoses in the same molecule which give rise to an intramolecular ring of hydrogen bonds. The hydrogen bonds can be in general of the flip-flop type as observed in the ß-cyclodextrin hydrate structure (13,14) and if so, hydrogen bonding between molecules arranged head-to-head will contribute to the stabilization of these dimeric structures.

The dimers are then stacked on top of each other so that their 06 sides are in hydrogen bonding contact. The stacking is not in all cases linear and we observe more often lateral displacement so that the cavity formed by one dimer is closed on both ends by adjacent ß-cyclodextrin dimers. This leads to cage type formation although, by and large, the ß-cyclodextrin molecules are arranged in channel type form (Fig. 2a). In fact, all the channels formed by ß-cyclodextrin are more or less irregular because this molecule has 7 glucoses in one ring and therefore twofold or other crystallographic symmetry axes cannot coincide with the channel axis as is frequently observed with α- and γ-cyclodextrin. In α- and γ-cyclodextrin, the even number of glucose units per ring allows two, three, four or six fold rotation axes to lie within the channel axes and to produce really linear channels.

A special case is observed in one of the two morphologically different complexes formed between ß-cyclodextrin and barbital where two dimers of ß-cyclodextrin are stacked almost linearly and these tetramers then are displaced laterally with respect to the next tetramers above and below so that long cages consisting of four ß-cyclodextrin cavities are produced (15), Fig. 2b.

The preferred tendency of ß-cyclodextrin to form dimer structures is also illustrated by a series of polyiodide complexes containing different metal ions, which always produce the same crystal form in space group $P2_1$ (8,16). In contrast, the α-cyclodextrin series gives

rise to a number of different space groups and packing arrangements, depending on the kind of counterion involved in complex formation. This finding suggests that the head-to-head dimer formation of ß-cyclodextrin is so strong that it determines the crystal packing. In the α-cyclodextrin series, the self-aggregation of the α-cyclodextrin molecules is less pronounced and therefore the packing is influenced by the different coordination schemes of the metal ions located in interstices between the α-cyclodextrin stacks and bound to α-cyclodextrin hydroxyls and water molecules.

γ-CYCLODEXTRIN PACKING PATTERNS ARE REMINISCENT OF ß-CYCLODEXTRIN

For γ-cyclodextrin, there are only a few crystallographic data available so that general conclusions cannot be drawn at the moment. It appears, however, that there are mainly two types of packing patterns, which are even more limited compared with the ß-cyclodextrin.

If γ-cyclodextrin is crystallized as "empty" molecule from water, it arranges in a fishbone type cage structure similar as observed for α- and ß-cyclodextrins (17). If, however, a small guest like n-propanol is added, a channel type structure is formed in which the γ-cyclodextrin molecules with eightfold symmetry are stacked along a fourfold symmetry axis and therefore exactly linear channels are produced (18), Fig. 3.

These channels, however, are unique in that they have in one asymmetric unit three cyclodextrin molecules. These are arranged in head-to-head and head-to-tail mode in alternating sequence so that the whole structure is built up of trimers of γ-cyclodextrin. In detail, however, the crystal packing is even more complicated because there are two independent stacks per asymmetric unit which differ only in very slight atomic displacements and disorder. In total, this crystal structure contains therefore six quarter γ-cyclodextrin molecules per asymmetric unit (Figure 3).

Since the γ-cyclodextrin channel structure exhibits a fourfold crystallographic symmetry axis coinciding with the channel axis and since the enclosed molecule (n-propanol) has no fourfold symmetry axis, it has to be disordered. The disorder is so bad that there is an almost continuous, very low electron density filling the channel. A similar complex has also been obtained with prostaglandin (Hirayama, Zabel, Saenger, unpublished) and it appears that this channel-type crystal form is more general for γ-cyclodextrin inclusion complexes.

The simultaneous head-to-head and head-to-tail trimer arrangement is unique for γ-cyclodextrin and has not been observed for the α- and ß-analogues. Since the small n-propanol as well as the rather extended prostaglandin give rise to the same γ-cyclodextrin packing mode, there is clearly no specific influence due to the guest molecule. It is rather to conclude that the trimer stack formation is a property of γ-cyclodextrin itself, and is associated with the crystallization in a tetragonal space group (P4) where the fourfold rotation axis coincides with the molecular axis. The alternating head-to-head and head-to-tail aggregation cannot be explained with exclusive inter-

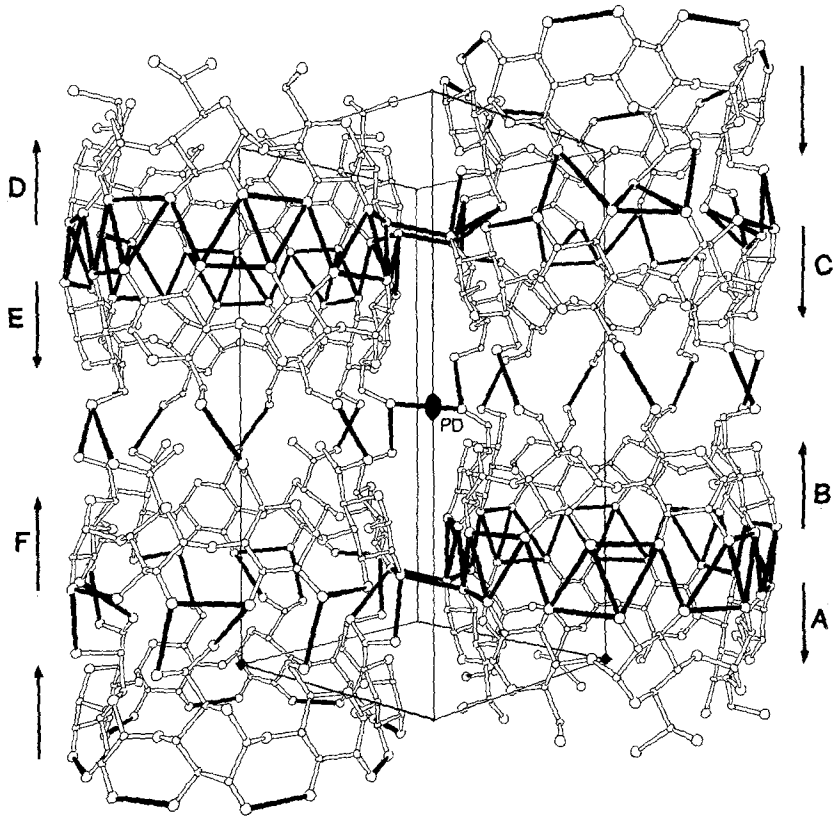


Figure 3.
Packing of γ-cyclodextrin molecules in the complex with n-propanol. If cocrystallized with prostaglandin, γ-cyclodextrin molecules arrange in the same pattern. A crystallographic fourfold axis coincides with the molecular and stack axis. There is alternating head-to-head and head-to-tail orientation of γ-cyclodextrins along the same stack, and due to slight atomic displacement, there are two independent stacks per asymmetric unit containing six quarter (fourfold axis!) γ-cyclodextrin molecules, indicated by letters A to F. Arrows indicate different orientations of γ-cyclodextrin molecules, PD marks a pseudo dyad relating molecules A, B, C and D, E, F. Intermolecular hydrogen bonding contacts given by solid lines, hydration water molecules omitted for clarity.

actions along the channel axis and must be caused by lateral contacts between adjacent stacks and with water molecules embedded in interstack interstices.

CONCLUSIONS

In summary, it is possible to predict the crystal packing patterns for the cyclodextrins on a broad basis. For α-cyclodextrin, small molecular guests will produce cage structures of the fishbone type whereas small aromatic guests will produce cage structures of the brick-type. Long molecular guests and small as well as large ionic guests will lead to channel type arrangement where head-to-head as well as head-to-tail packing of the cyclodextrin molecules is possible.

As for ß-cyclodextrin, only a very limited number of small molecular guests will produce a fishbone type cage arrangement and in general, a head-to-head dimer formation is preferred, with these dimers then either stacked in a channel type form or slightly displaced to produce cage type structures. It is also possible that two dimers stack linearly; the thus formed tetramer acts as a building unit and adjacent tetramers are stacked and slightly displaced laterally so that cages are formed.

As for γ-cyclodextrin, very small molecular guests produce the fishbone type cage arrangement whereas larger guests, no matter what their nature is, crystallize in a channel type structure with tetragonal space group. The channel axis coincides with the crystallographic fourfold axis and the γ-cyclodextrins are arranged alternately head-to-head and head-to-tail along the channel axis. Since, however, not enough crystallographic data are available until now for γ-cyclodextrin, it might be that other crystal packing types will emerge in the near future.

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