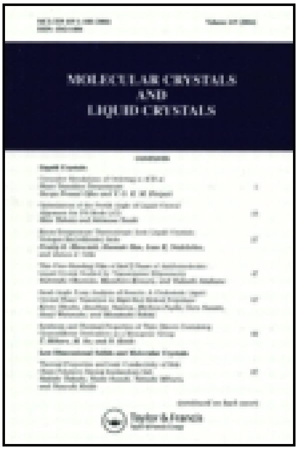

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Host-Guest Interaction in Cyclodextrins

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HOST-GUEST INTERACTION IN CYCLODEXTRINS

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ABSTRACT
Interaction between cyclodextrin (host) and cyclopentanone (guest) has been studied by joint use of crystallographic information and molecular graphics. The proposed model is characterized by a host-guest hydrogen bond whose direction is controlled by crystallographic symmetry.

INTRODUCTION

Cyclodextrins (CDs) are cyclic oligosaccharides composed of six, seven or eight α-1,4 linked D(+)-glucopyranoses and are able to form inclusion compounds, both in solution and in the solid state, with a large variety of molecules[1]. This combination is characterized by the absence of ordinary chemical bonds and gives an interesting model for studying intermolecular forces.

The interaction between host and guest causes a structural perturbation of the guest and consequently a modification of its physical, chemical and biological properties. This opens up a major field of application which has begun to be extensively explored.

Moreover, the included molecule, in turn, may induce conformational changes in the cyclodextrin cavity. The final picture is of a mutual dependence of the host and guest conformations. The aim of this work is to examine the relationships between the geometry of both guest and host molecules.

In crystal structures of inclusion compounds the problem of conformational analysis is often impaired by disorder of the atomic positions, both in the guest and certain primary hydroxyl groups of the host molecule, but significant information can still be obtained. Graphic systems can then be used to further investigate structural models differing in :(a) position, orientation and conformation of the guest : (b) conformation of the host.

I- DESCRIPTION OF THE CRYSTAL STRUCTURE OF α-CYD-CYCLOPENTANONE.$6H_2O$

Several α-CD inclusion compound structures have been determined (review article by Saenger[2]). Most of them had relatively low symmetry (monoclinic, orthorhombic) with the cyd molecule in a general position where the inclusion compound is often disordered.

A striking example of this behavior is provided by the α-cyclodextrin cyclopentanone clathrate where the disorder is associated with an exceptionally high crysallographic symmetry. This inclusion compound crystallizes in channels which are formed by the stacking of host molecules in a head to tail mode (figures 1 and 2).

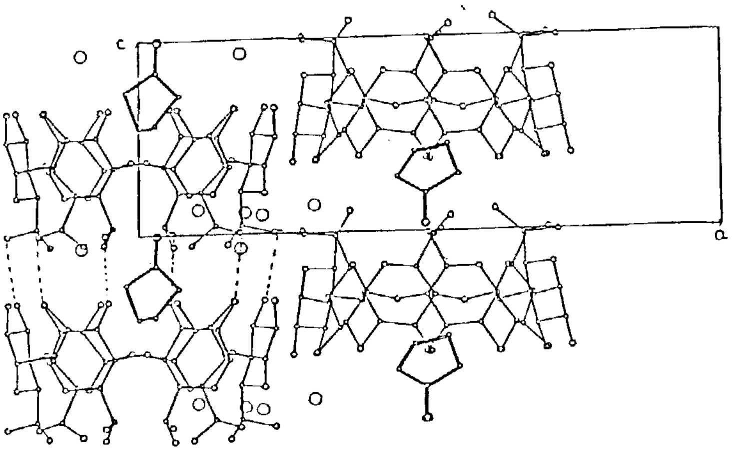

Figure 1: Projection of the structure on the (a,c) plane

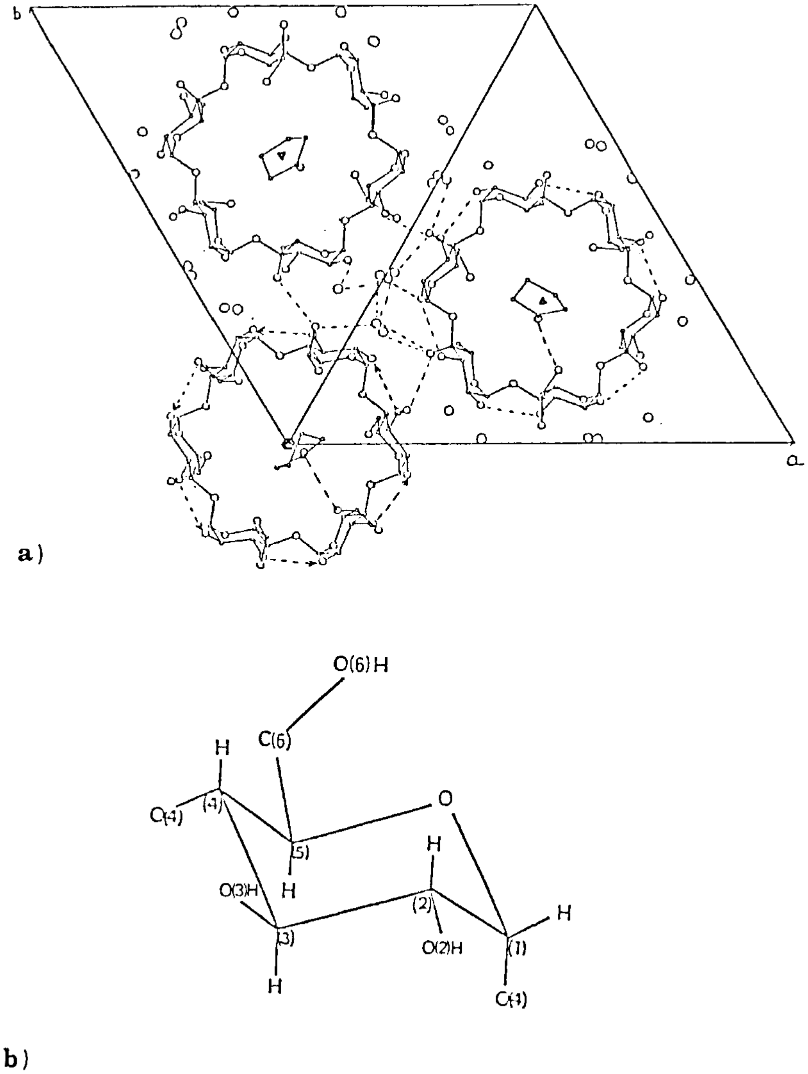

Figure 2: a) projection of the structure on the (a,b) plane. Only one guest molecule is represented in each case.

b) shows the nomenclature of a glucopyranose residue of the cyclodextrin molecule.

Crystallographic data :
space group : P6 Z = 3
a = b = 23.86 Å
c = 8.00 Å
V = 3941 $Å^3$
λ= 1.541 Å N =1940 N =1713 R = 6.5%

There are two non crystallographic related host molecules in the asymmetric unit, one on the 6-fold axis, the other on the 3-fold axis. The two independent host molecules pack in columns parallel to the c axis. One column presents the narrow side (primary hydroxyl) up, the other down. Both guest molecules in the asymmetric unit are disordered. Six positions are equally occupied along the six-fold axis while three are found along the 3-fold axis. The guest molecules are considerably smaller than the cavity they occupy. This suggests that they can be distributed among the partially occupied positions found in the crystal structure.

The positions of some hydrogen atoms were located from difference Fourier synthesis. As usual in CD-structures, a crown of intermolecular hydrogen bonds is found between the secondary hydroxyl groups of the α-CD molecules. Around the 6-fold axis it appears clearly that the hydroxyl groups O(2)H and O(3)H are respectively acceptor and donor. Within the columns there are intermolecular hydrogen bonds between O(3)H and O(6)H which surround the guest molecule. These hydrogen bonds are shorter around the 6-fold axis. Certain primary O(6)H of the CD molecules exhibit two different conformations, one oriented away from from the center of the macrocycle (gauche-gauche conformation), the other oriented "inwards", i.e. towards the cavity (gauche-trans conformation). The most remarkable feature revealed by this crystal structure is that the disorder of the conformation of the primary hydroxyl O(6)H groups depends directly upon the orientation of the guest molecules.

In all cases, the distance between the positions of the carbonyl group of the guest and the primary hydroxyl group of the host O(6)H in the "inwards" reveals an H bond.

TABLE I - Distances concerning primary hydroxyl groups

Around the 6-fold axis

O161; primary hydroxyl in "away" conformation
host-host, intra column O161-O13 : 2.81 Å
host-host, inter column O161-O26 : 2.92 Å
host-water O161-W04 : 2.92 Å

O162; primary hydroxyl in "inwards" conformation
host-guest O162-OX : 2.78 Å
host-host, intra column O162-O13 : 2.87 Å

Around the 3-fold axis

O26; primary hydroxyl always in "away" conformation
host-host, intra column O26-O23 : 3.00 Å
host water O26-W04 : 2.91 Å
O26-W03 : 3.08 Å

O361; primary hydroxyl in "away" conformation
host-host, intra column O361-O33 : 3.11 Å
host-water O361-W01 : 3.01 Å
O361-W05 : 2.58 Å

O362; primary hydroxyl in "inwards" conformation
host-guest O362-OY : 2.70 Å
host-host intra column O362-O33 : 3.12 Å

In the "away" conformation, the primary hydroxyl group forms hydrogen bonds with water molecules which are outside the macrocycle. There are no water molecules inside the macrocycle or even inside the columns.

The 3 water molecules (WO) in the asymmetric unit are found in 5 positions between the cyclodextrin molecules. The too short distances observed between water and host molecules may well arise from such disorder.

In order to complete the description of the network of hydrogen bonds that maintains the crystal structure, neutron diffraction experiments are being carried out at low temperature, in particular, in order to derive information about the dynamic and static disorder of the water, cyclopentanone molecules and the cyclodextrin primary hydroxyl groups.

II- CRYSTALLOGRAPHIC DISORDER AND THE USE OF GRAPHIC SYSTEMS

The problem of the determination of exact positions for the guest molecules is a difficult one. However, the difference Fourier maps clearly revealed peaks attributed to the oxygen of the carbonyl. This is corroborated by the observed distance between this oxygen atom (OX or OY) and the hydroxyl group "inwards" of the host which seems normal for an H bond of this type.

Figure 3: The two enantiomorphic conformations of cyclopentanone, as seen from behind the axis of the C=O bond.

The positions of the carbon atoms of the cyclopentanone are superimposed as a result of the disorder. An approximate model has been constructed and subsequently refined as a rigid block. We have adopted the R-conformation which was suggested by the study of circular dichroism in solution[4]. However, as a result of the disorder, it is unlikely that it will be possible to distinguish between the R and S configurations with certainty (figure 3).
The R factor of the final model is R=6.5%, considerably smaller than the 7.9% if the cyclopentanone molecule around the 3-fold axis is removed. However, the distances between the carbon atoms of the guest and some atoms of the host are too short. This shows that, despite the indication of the R factor, the guest position and orientation cannot be determined from X-ray data alone.

The use of graphic systems (Evans and Sutherland, MOGLI and SYBYL programs) allows a convenient visualization of the disorder and an "on line" checking of interatomic distances throughout the exploration of positional, orientational and conformational disorder.

In this work we have studied only the host-guest interaction in the macrocycle located around the 6-fold axis.

The previous model from X-ray analysis has been used as a starting point. The cyclopentanone molecule has been minimized and slightly moved on account of the steric hindrance.

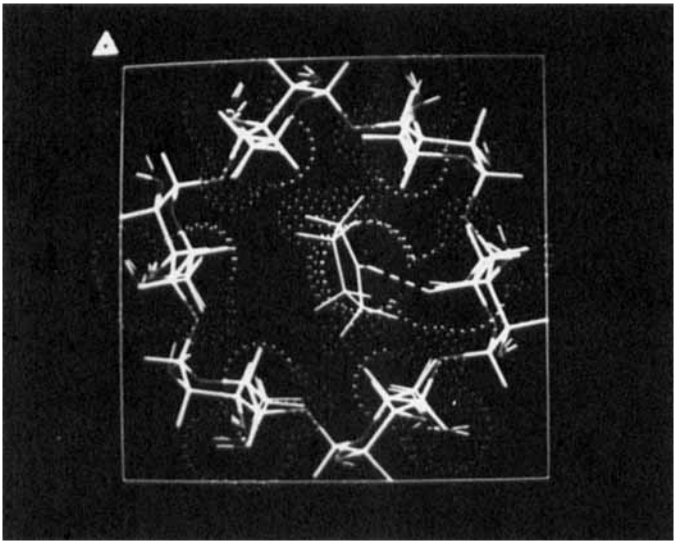

Photo No 1: Optimized model with z-clipped sections of the Van der Waals surfaces and unclipped molecules. The host-guest H-bond is marked by dashed lines. **See Color Plate I.**

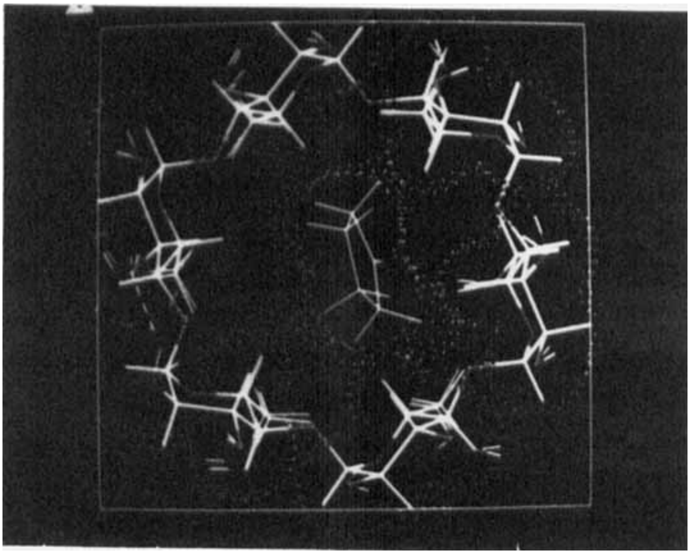

Photo No 2: Optimized model with different z-level clipping showing the best adjustment between host and guest surfaces. **See Color Plate II.**

The energy minimization program[5] now gives a model where the positions of the H atoms of cyclodextrin are slightly different from the starting model and for which there are no abnormal distances. Starting with this optimized model, we rotate the cyclopentanone molecule around the 6-fold axis. Thus a maximum energy value is found for a rotation of approximately 18°.

The difference between this maximum and the minimum energy is 8 kcal/mole.

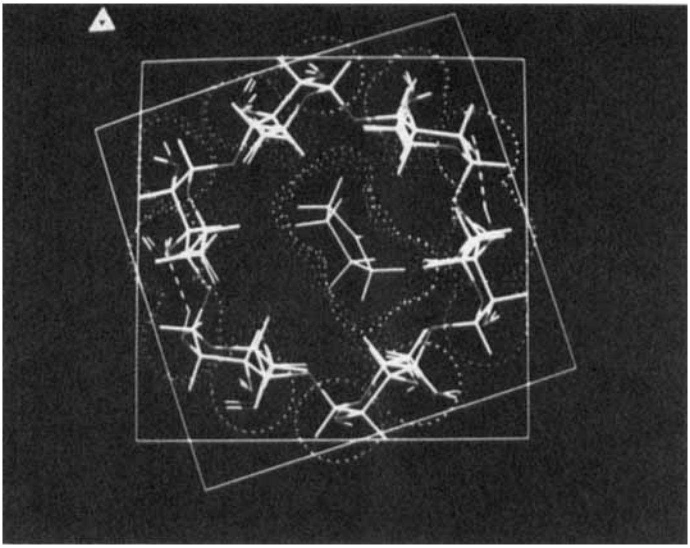

Photo No 3: After 18° rotation around the z axis of the cyclopentanone, showing the poor contact between the host and guest Van der Waals surfaces. **See Color Plate III.**

We consider that the optimized model represents a good approximation. We are carrying on additional work in order to obtain final numerical values for the energy as a function of orientational and conformational changes.

We wish to thank P. Floersheim and P. Boucherie from Evans and Sutherland for their collaboration in the use of graphic systems and software.

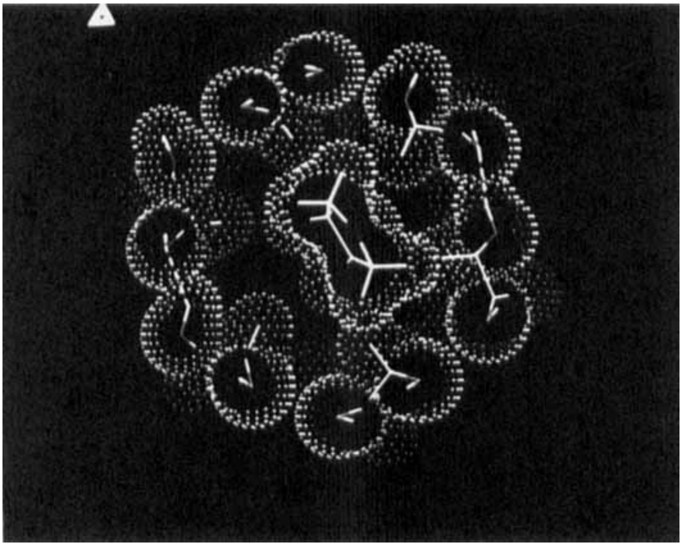

Photo No 4: After 18° rotation around the z axis of cyclopentanone. Both the surfaces and molecules are z-clipped sections. See Color Plate IV.

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