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CONFORMATIONAL AND ENANTIOMERIC DISCRIMINATION IN CYCLODEXTRIN INCLUSION COMPOUNDS

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ABSTRACT:Cyclodextrins open great possibilities for studying both the crystal structure and the spectroscopic properties in solution of the same compound. In the present paper new inclusion compounds are studied. Two conformationaly labile molecules (cyclopentanone, bilirubin), the pheromone of the olive fly with chiral stable conformation and p-nitroaniline with non linear optic properties are investigated.

Cyclodextrins (cyd) open great possibilities for studying both the crystal structure and the spectroscopic properties in solution of the same compound.

The interaction between the host cavity and the guest causes a structural perturbation of the guest and consequently a modification of its physical, chemical and biological properties. Circular dichroism is one of the properties which are particularly sensitive to conformational changes induced by the cyd environment (1).

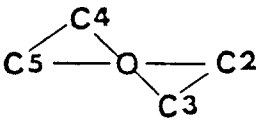
It was shown that bilirubin, biliverdin and 4-helicene in solution acquire a preferential chiral conformation exhibiting a very strong circular dichroism spectrum upon interaction with cyd ; crystallographic study has provided experimental evidence that the CD spectrum of benzil molecule in β cyd complex is to be ascribed mostly if not entirely to a conformational isomerism (2,3). This provides a novel method of studying the chiroptical properties of conformationaly labile molecules.

In the present paper we report new inclusion compounds:

1.Cyclopentanone 1 in α cyd

1 has two enantiomeric conformations in solution. The CD spectrum of 1 complexed with α cyd shows a minimum at

λ = 290 nm. Such an extremum for the n-π* transition was attributed to the R isomer(4).



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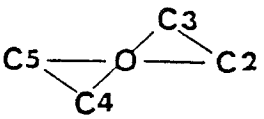

R

Figure 1. The two enantiomeric conformations of 1 ,looking behind the axis of C=O bond.

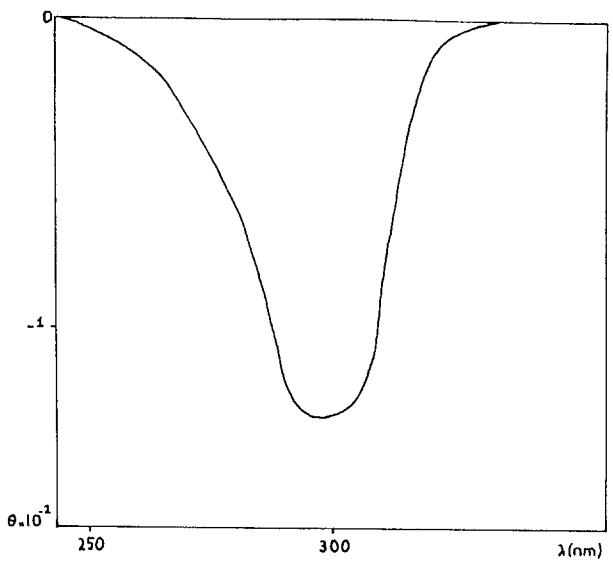

Figure 2. CD spectrum of the complex α-cyd-1.

In crystal structure ,conformational analysis is often impaired by disorder exhibited in the guest and the host molecule as well, however significant phenomena can be observed: host/guest interaction and the nature of the formed bonds.

A typical example is the complex α-cyd - 1.

α-cyd - 1, 6(H_2O) complex crystallizes as a head to tail channel (figs.3,4).

CRYSTALLOGRAPHIC DATA

space group	P6
a = b (Å)	23.64
c (Å)	8.00
V (Å^3)	3941
Z	3
Nref	1940
Nobs	1713
R	0.06

It is noteworthy to observe the high symmetry of this structural arrangement. There are two symmetrically independant molecules in the cell, one hexagonal, the other trigonal. To our knowledge, these ideal symmetries for α-cyd molecules have not been found, up to date.

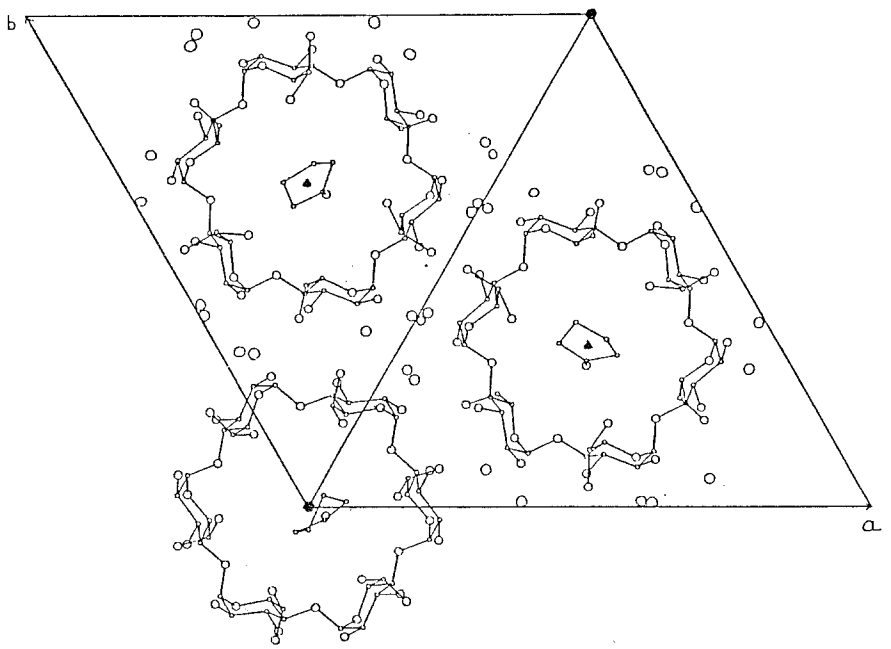

Figure 3. Projection of the structure on the (a,b) plane.

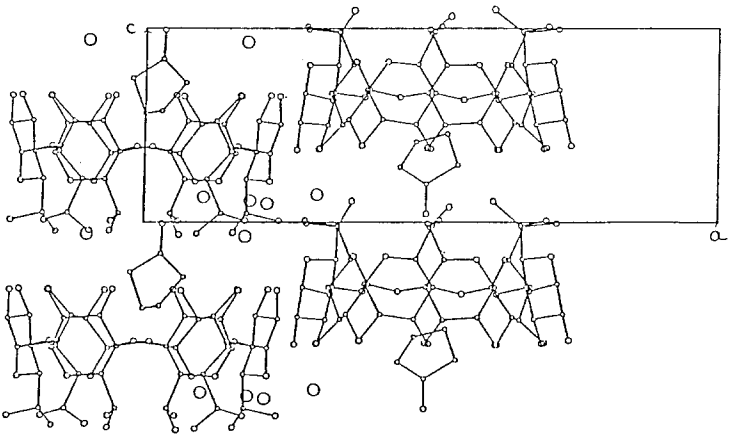

Figure 4. Projection of the structure on the plane (a,c).

The two guest molecules in the unit cell are disordered, one along the six fold axis, the other along the three fold axis.

The primary hydroxyl groups are disordered between the gauche-gauche and the gauche trans conformation. In the model suggested by X-ray analysis, the occupancy factor of the gauche-trans conformation is about:

- 1/6 for the cyd molecule at the 6 fold axis,
- 1/3 for the molecule at the 3 fold axis, but for only three primary hydroxyl groups, the other three being entirely in the gauche-gauche conformation.

The most remarkable fact exhibited by this crystal structure is that the disorder of the primary hydroxyl groups of the host depends directly upon the orientations of the guest molecule. In all cases H-bonds are established between the primary hydroxyl groups of the host and the carbonyl groups of the guests.

The positions of most of the hydrogen atoms were determined. Secondary hydroxyl groups of the hexagonal cyd molecules O (2) H and O (3) H are respectively acceptor and donor. In the trigonal molecule, the two secondary hydroxyl groups are donors in one glucose residue and acceptors in the other residue of the asymmetric unit.

In order to specify the hydrogen positions and the dynamic disorder, neutron diffraction and X-Ray diffraction at low temperature will be undertaken.

2. Bilirubin in permethyl A cyd

Let us describe the biological implication of this study. Bilirubin is the end product of heme catabolism in man and most animals. This lipophilic pigment is normaly carried in blood by serum albumin until it is excreted by liver. All forms of jaundice are a manifestation of an excess of bilirubin over the binding capacity of serum albumin. Then the aqueous insoluble pigment leaves the intravascular system, diffuses into the lipophilic tissues and, in the case of newborn babies, it may reach the brain and cause irreversible damage. In order to urgently remove the bilirubin excess, massive U.V. irradiation is applied. The generally admitted mechanism involves transformation into "photobilirubins" which are more soluble in water and readily excretable(5).

We have shown that a solubilization effect is also obtained by association with cyd. The detection of this complex becomes effective through the remarkable chiroptical properties of bilirubin. The two enantiomeric conformations stabilized by six intramolecular hydrogen bonds, as found in crystalline bilirubin (6) interconvert rapidly in solution at room temperature by breaking and remaking all six H-bonds (fig.5).

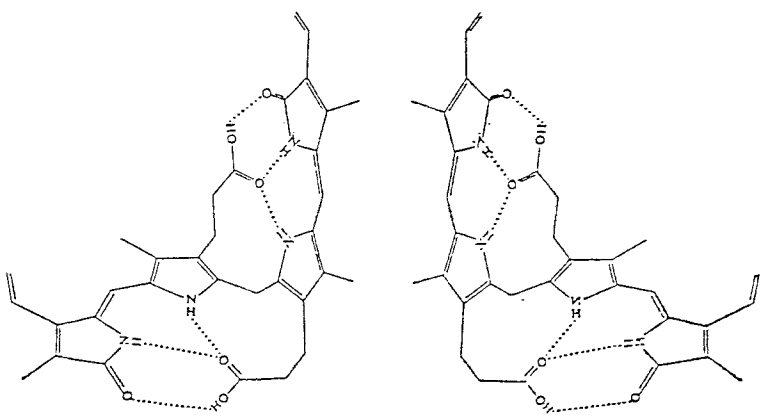

Figure 5. The two enantiomeric conformations of cristalline bilirubin.

Selective complexation of one enantiomer is achieved by cyd in aqueous alkaline solution which leads to optical activity (fig.6) (2).

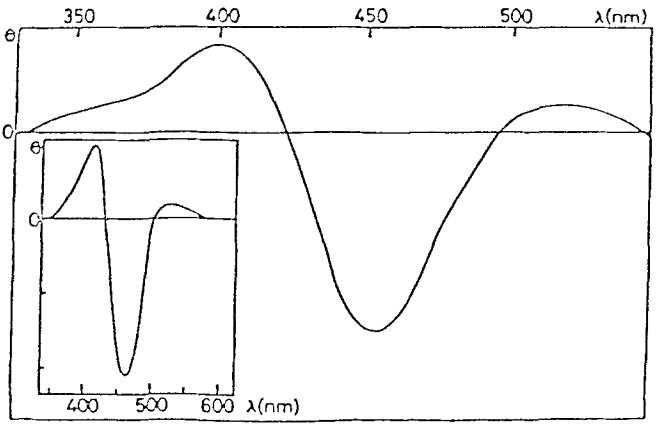

Figure 6. CD spectrum of bilirubin-β cyd , pH=10.2, (λ=455nm,θ=-2.7 10^{4} deg.cm^{2}.dmole^{-1}). Inset shows the CD spectrum of the complex bilirubin-ligandin.

We report now the chiral recognition of bilirubin by permethylated β cyd. A basic requirement for the complexation of bilirubin with cyd derivatives is a common solvent. The CD spectrum shown below has been obtained in $CH Cl_3$. Besides,it seems that $CH Cl_3$ may be enclathrated and therefore, there is a competition with bilirubin for cyclodextrin cavity. This fact can explain the poor quality of the spectrum compared to that of β cyd (fig.7). We are presently pursuing the experimental study.

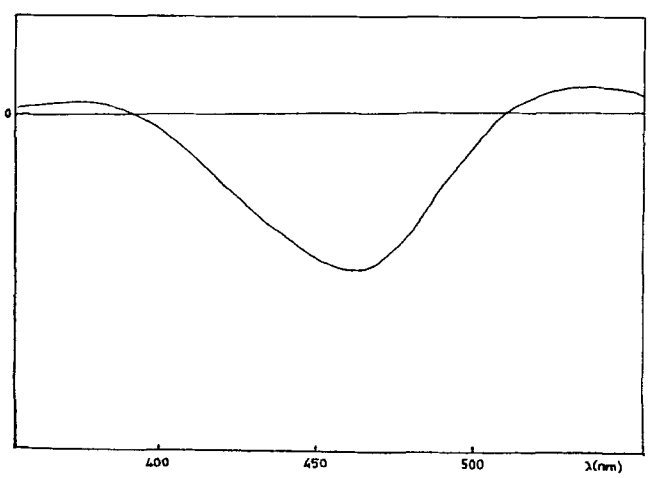

Figure 7. CD spectrum of permethyl β cyd - bilirubin at a molar ratio of permethyl β cyd to bilirubin of 50 : 1 in chloroform, (λ = 455nm, θ = -5.0 10^{3} deg.cm^{2}.dmole^{-1}).

3. The pheromone of the olive fly: 1,7 dioxaspiro (5,5) undecane 2.

The first biological experiments have shown that the pheromones are considerably stabilized and therefore slowly released after enclathratation in cyd.

The cell parameters of 2 complexed with A-cyd are given:

space group	P1
a(Å)	15.60
b	15.72
c	15.93
α(°)	101.4
β	101.7
γ	103.2

2 is chiral and cyd can be used in order to isolate or to enrich the more biologically active enantiomer R-(-)-2.(fig.8)

S R

Figure 8. Two enantiomeric isomers of 2.

4. Non linear materials.

A prerequisite for non linear optic material is the absence of inversion center . Cyd can be used as a tool in order to achieve a non centrosymmetric crystal .Cyd offers a new procedure for the evaluation of the order of a molecular non linearity.

p-nitroaniline 3 is one of the most interesting molecules. The CD spectrum demonstrates a complexation with α cyd.

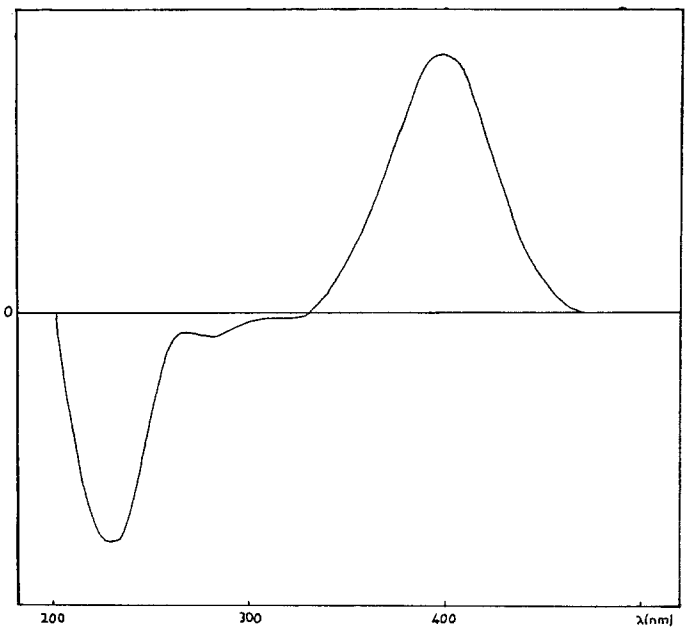

Figure 9. CD spectrum of α-cyd-3 with the molar concentrations: α-cyd = 10.10^{-3} M/l, 3 = $1.5.10^{-3}$ M/l. (λ = 400nm, θ = $7.6\ 10^{3}$ deg.cm^{2}.dmole^{-1}) .

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