

CHIRAL CONFORMATIONS INDUCED BY CYCLODEXTRIN

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ABSTRACT. Studies of chiroptical properties need separation or at least enrichment of enantiomers. The separation is difficult with chiral conformers of molecules with very low barriers of internal rotation. However, in association with cyclodextrin, these labile molecules can exhibit a strong Cotton effect in solution: one chiral conformer is favoured by complexation. The cyclodextrins have the advantage to yield inclusion complex in solution as well as crystalline clathrates. Therefore, the absolute configuration of the guest can be obtained by determining the structure of the cyclodextrin. In this work, the first CD spectrum of 4-helicene is recorded and crystal structures of several clathrates of labile molecules are studied.

INTRODUCTION

It often happens that chiral conformers of molecules with very low barriers of internal rotation are not stable enough, even at the lowest accessible temperature, to exhibit a detectable optical rotation or circular dichroism (CD) spectrum. Well known examples, important in biology, are the molecules of bilirubin and biliverdin. In previous work (1) we showed that these achiral molecules exhibit a strong CD spectrum in solution in association with cyclodextrin (cyd). Similarly, smaller flexible molecules such as benzil exhibited a weaker CD spectrum. In the present communication, we extend the scope to new molecules like 4-helicene (4H), biphenyl, benzophenone. These results, given below, provide the basis for a novel method of recording the chiroptical properties of conformationally labile molecules, and perhaps, of assigning the absolute configuration.

SPECTROSCOPIC STUDIES

The CD spectra are recorded in aqueous solutions of β -cyd or γ -cyd (4H complex). The complexes are prepared by mixing an aqueous concentrate solution of cyd with an alcoholic solution of the guest. The precipitate

thus obtained is redissolved in water and finally an excess (between 10 and 1000, depending on the guest) of cyd produces the intended equilibrium displacement towards complexation. For all guests except 4H, the maximum concentration of complex has been virtually reached as can be seen from the constancy of the CD spectrum above a certain concentration. For 4H, the very small quantities of host and guest available prevented us from making sure that we had reached the maximum concentration for that complex. In a general way, β -cyd is used for this size of molecule ; with 4H, the CD spectrum of the β -cyd complex was very weak ; assuming that γ -cyd leads to a stronger association, we used the available 4H to record the spectrum with γ -cyd, which has the additional advantage of being about ten times as soluble as β -cyd in water. In all these experiments, the solution is neutral. CD spectra were recorded on a Jobin-Yvon model III spectropolarimeter in a range 240-750 nm ; they are given in fig.1.

TABLE I

	γ -cyd - 4H	1-fluoro 12-methyl 4H	1,12-dimethyl 4H	5H
λ_{nm}	280	290	300	310
$(\Delta\epsilon)_{max}$	12	65	50	300

DISCUSSION

The CD spectrum of 4H complex is to be compared with 1-fluoro 12-methyl 4H, 1,12-dimethyl 4H and 5H (table I) (2) which have stable chiral conformations. From the closeness of peak wave-length, it is tempting to assume a similar assignment of these peaks ; there is an additional indication from the fact that one could expect the following order in the deviation from planarity : 4H, 1-fluoro 12-methyl 4H, 1,12-dimethyl 4H and 5H; the same order occurs in the observed wave-lengths of CD peaks. We mention that theoretical calculations are given in the literature (2). By comparison, we suggest that 4H in association with cyd (natural product) has the P configuration. We come now to the intensity of the CD peaks. The absolute value of Θ ($3300 \cdot \Delta\epsilon$) is 40000 which is one of the highest ever observed in association with cyd (cf. 34000 for bilirubin). It is about five times as small as the pure substituted 4H, and 25 times as small as pure 5H. This can be explained by several types of phenomena : the helical strain is much smaller in 4H ; in the cyd cavity, 4H may exhibit the two enantiomeric forms so that the observed spectrum is the result of the predominance of one of them ; the maximum concentration of complex could not be reached as noted above. In a similar way, the absolute configuration of biphenyl can be tentatively assigned by comparison with that of known related molecules (3) (bridged and o-substituted biphenyl). In association with β -cyd, biphenyl has the R configuration. For benzophenone, CD spectra have already been given in the literature (4) in the range 320-350 nm. In addition to the known 330-335 nm peak, new peaks are recorded (fig.1c) at 295 nm and 255 nm :

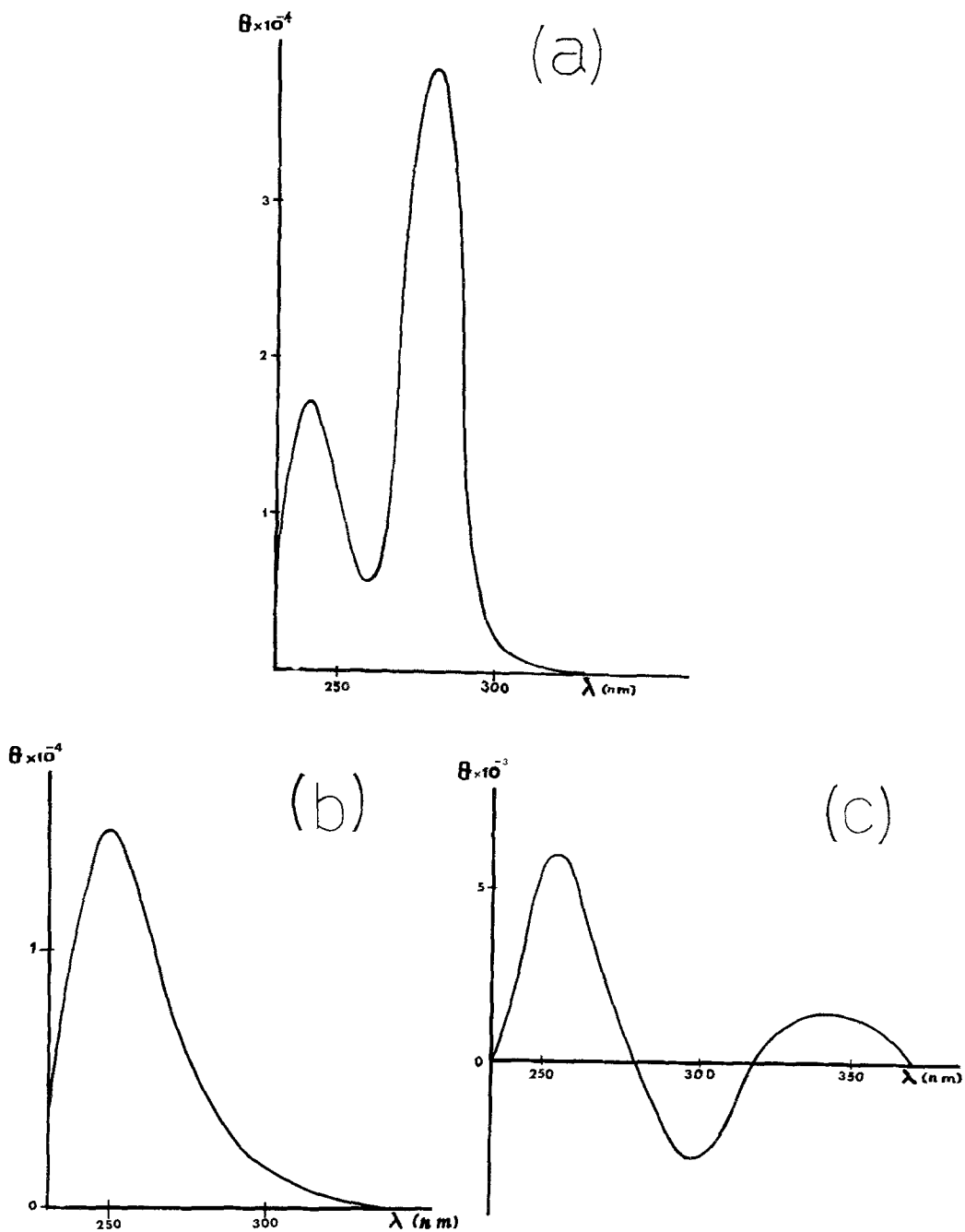


Figure 1. CD spectra. θ in $\text{deg}\cdot\text{cm}^2\cdot\text{dmole}^{-1}$.

(a) $4\text{H}(10^{-5}\text{ M/l})$ $\gamma\text{-cyd}(10^{-2}\text{ M/l})$

(b) $\text{biphenyl}(5.5 \cdot 10^{-5}\text{ M/l})$ $\beta\text{-cyd}(10^{-2}\text{ M/l})$

(c) $\text{benzophenone}(7.6 \cdot 10^{-4}\text{ M/l})$ $\beta\text{-cyd}(10^{-2}\text{ M/l})$

their interpretation is not obvious and further studies are to be undertaken.

CRYSTALLOGRAPHIC STUDIES

In order to gain better insight into this phenomenon, several X-ray analyses of β -cyd clathrates have been undertaken. The first results of the crystal structure determination of the β -cyd benzil complex were previously reported (1). Since then, this structure has been refined and those of benzophenone, biphenyl and phenyl-ethyl malonic acid complexes have been solved. We report herein the main features of these crystallographic studies.

TABLE II

	β -cyd-benzo- phenone	β -cyd bi- phenyl	β -cyd ben- zil	β -cyd phenyl ethyl malonic acid
Space group	C2	C2	C222 ₁	C222 ₁
a	19.24 Å	19.34 Å	19.58 Å	19.09 Å
b	24.56	24.49	24.00	24.27
c	15.94 $\beta=109.5^\circ$	15.80 $\beta=109.8^\circ$	32.84	32.58
Z	4	4	8	8
λ	Cu K _{α}	Mo K _{α}	Cu K _{α}	Mo K _{α}
θ_{\max}	60°	28°	55°	28°
N _{ref} *	5316	6990	5090	4350
N _{obs} *	4438	3890	4730	2300
R	0.15	0.16	0.13	0.12

* N_{ref} = measured reflection number

* N_{obs} = observed reflection number $F_{\text{obs}} > 2\sigma(F_{\text{obs}})$

In the isomorphous structure of benzophenone and biphenyl complexes, the β -cyd molecules are associated in head to head dimers : all secondary hydroxyl ends of the two partners are connected by hydrogen bonds. These dimers are stacked along the c axis to produce channels

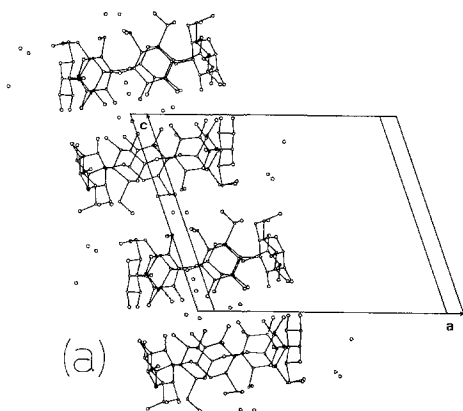


Fig.2

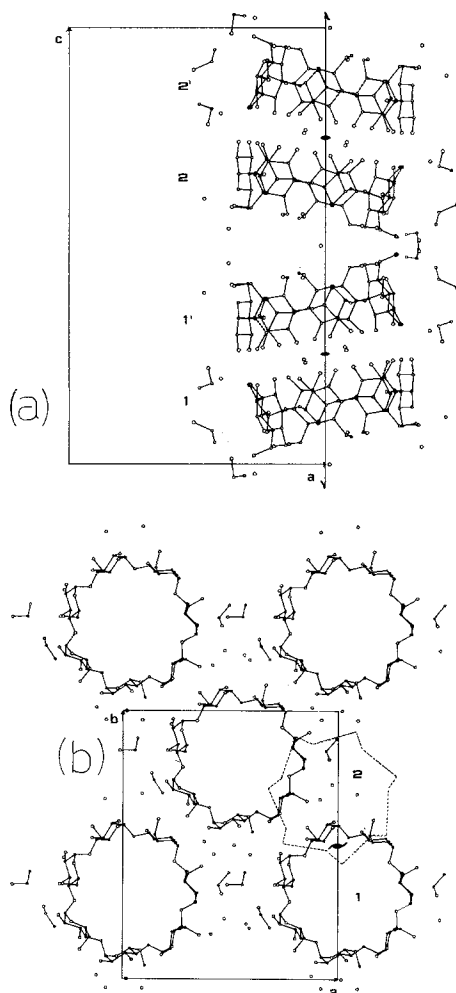


Fig.3

Figure 2. Structure of β -cyd benzophenone space group $C2$.

Figure 3. Structure of β -cyd benzil space group $C222_1$.

(a) projection on (a,c) plane showing two dimers ($1 + 1'$) and ($2 + 2'$);

(b) projection on (a,b) plane. The full line molecules belong to dimer layer between $z = 0$ and $z = 1/2$. Only one molecule of each dimer is represented (for example molecule 1 instead of molecules 1 and 1'). Molecule 2 in dotted line belongs to the sheet between $z = 1/2$ and $z = 1$, and is related to molecule 1 by axis 2_1 .

(fig.2). Within the columns, there are four hydrogen bonds between the primary hydroxyl ends of neighbouring dimers. Four out of seven primary hydroxyl ends are disordered. The columns are close packed and several primary hydroxyl ends of adjacent columns are linked by hydrogen bonds. It is worth mentioning that the two structures display exactly the same water network.

The guest molecules are disordered as they usually are in clathrates, and we could not provide a conformation model of the guest molecules. However, the contents of the channels appeared different in the two structures. In the benzophenone complex, the analysis of the electron density revealed that the guest is completely included in the β -cyd torus and that the carbonyl occupies two positions near the level of the O4 atoms of the glucose rings. In the biphenyl complex on the other hand, this fact cannot be ascertained.

The structure of benzil complex also exhibits head to head dimers of β -cyd molecules connected by hydrogen bonds involving all secondary hydroxyl groups (fig.3). The molecular conformation of β -cyd molecules, the orientation of dimer axis in relation to the (a,b) plane and the packed arrangement of dimers in the (a,b) plane sheets are the same as that of the previous structures (fig.2). Therefore, within the dimer sheets, the primary hydroxyl groups linking contiguous molecules and the partial water network are unchanged. But the crystal packing of the dimer sheets along the c axis is essentially different : direct hydrogen bonds between the primary hydroxyl ends of dimers of two adjacent sheets do not exist. Instead, each primary hydroxyl end is attached to one or more water molecules which make a new intermolecular water network.

The guest molecule still shows disorder but here it is relatively easy to provide a conformation model of the benzil molecule. This tentative model is chiral and its absolute configuration is that of fig.4. It corresponds to the CD spectrum given in 1981 (1).

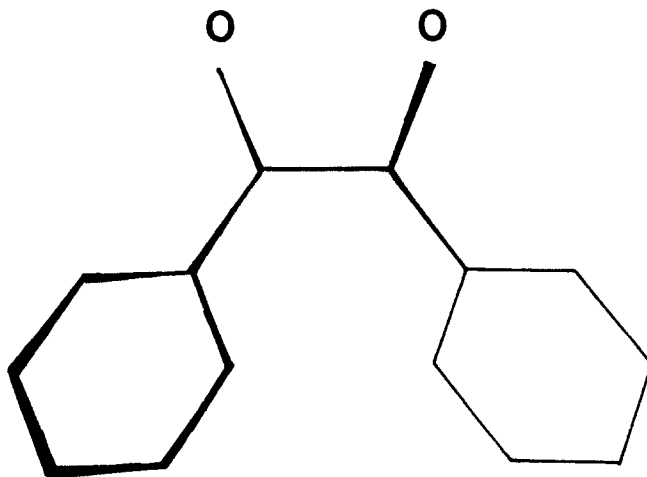


Fig.4

An interesting point for the future is understanding the origin of the disorder and subsequently trying to introduce more appropriate flexible molecules to be tightly held in the cyd cavity. We mention here a recent success with the determination of the structure of β -cyd phenyl ethyl malonic acid complex which is isomorphous to the structure of β -cyd benzil complex. Most of the guest atoms are reasonably fixed, mainly a consequence of hydrogen bond interaction. Although the motivation of the study is different (5), the results are highly encouraging for "molecular and crystal engineering".

In conclusion, despite the wealth of information provided by the crystallographic studies, the ever present disorder of the guest prevented a definite assignment of an absolute configuration. However, the combined information from CD spectra and crystallography leaves practically no doubt about the geometrical origin of the Cotton effects : the cyclodextrin molecule stabilizes the chiral conformation of the guest.

REFERENCES

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