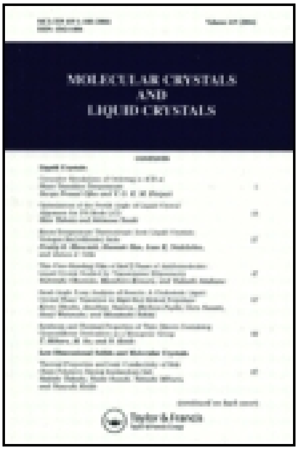

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New Properties of Cyclodextrin Complexes in Solution and in Solid State

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NEW PROPERTIES OF CYCLODEXTRIN COMPLEXES IN SOLUTION AND IN SOLID STATE

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ABSTRACT. Chiroptical property studies of conformational enantiomers are difficult. However, in association with cyclodextrin, one chiral conformer is favoured by complexation and leads to optical activity in solution. Therefore crystallographic studies of the cyclodextrin complex can provide absolute configuration of the guest. Further results are discussed. We show that all β cyclodextrin clathrates with head to head dimers can be classified in three classes with the same dimer sheets. This fact may be useful for future crystallographic studies. A remarkable peculiarity may be pointed out : all these structures display a very similar partial water network.

INTRODUCTION

Cyclodextrins (cyd) are able to form complexes in solution as well as in the crystal state. There seem to be few restrictions on the nature of possible guests which can form inclusion compounds as seen from the variety of molecules studied so far [1].

In aqueous solution, the cyd cavity presents a definite preference for inclusion of guest molecules presenting hydrophobic interactions. Obvious applications arise then from the solubilization in water through complex formation of hydrophobic species.

The intrinsic chirality of cyd leads to a stereospecificity of the interaction which is reflected in the spectroscopic properties of guest molecules. The modification or appearance of guest optical activity is of particular interest as it provides a quick and easy way of testing the effective inclusion of the guest in solution.

Moreover inclusion of a guest molecule within the cyd cavity can be utilized to increase the stability of the guest species in both solution and solid state.

A large number of molecules form inclusion compounds even though they are too large to be completely included within the cyd cavity. Meanwhile, until now, only complexes with guests which fit into cavity were found to crystallize easily.

We report here how cyd can be used to separate labile conformers , a general crystallographic study of β cyd clathrates and an attempt to classify these structures.

I SELECTIVE COMPLEXATION OF CONFORMATIONAL ENANTIOMERS

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 activity. Several chemical families have been studied.

a) Bile pigments.

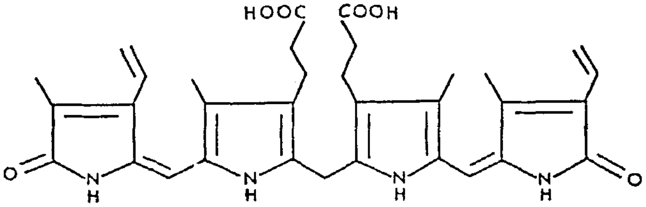


Figure 1. Bilirubin IX α

A well known example of a conformationaly labile molecule in biology is bilirubin (fig.1), where the two enantiomeric conformations ,as found in crystalline bilirubin, interconvert rapidly in solution at room temperature (fig.2). Thus, free bilirubin solution in achiral organic solvents does not exhibit optical activity. But, selective complexation of one conformational enantiomer is achieved by cyd in aqueous solution, allowing the determination of chiroptical properties of bilirubin as shown below.

We describe first the biological implication of this structural study. Bilirubin is the end product of heme catabolism in man and most animals. This pigment is normally carried in blood by serum albumin until it is excreted by the liver. All forms of jaundice are a manifestation of an excess of bilirubin over the binding capacity of serum albumin. Then the aqueous insoluble unbound pigment leaves the intravascular system, diffuses into lipophilic tissues and, in the case of newborn babies, it may reach the brain and cause irreversible damage. In order to rapidly 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 [2]. We have shown that a solubilization effect is also obtained by association with cyd. However, this is achieved only at pH > 8.

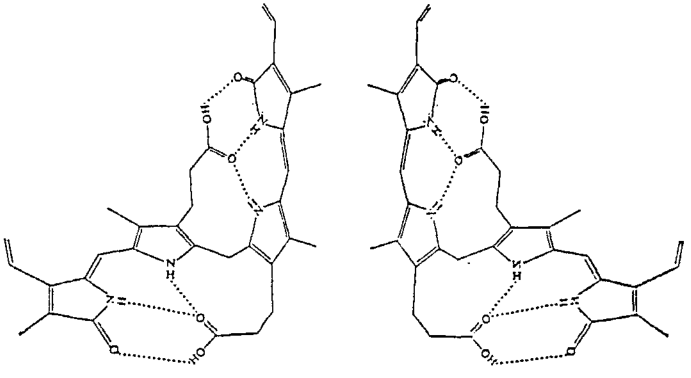


Figure 2. The two enantiomeric conformations of crystalline bilirubin.

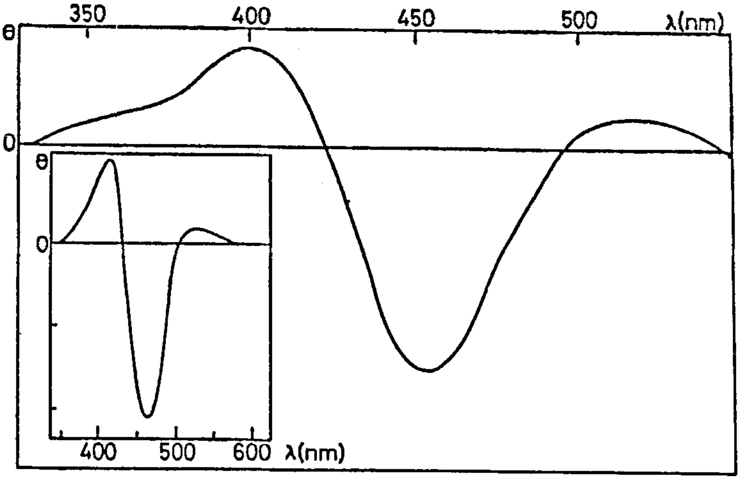


Figure 3. CD spectrum of bilirubin β-cyd complex ($\lambda = 455$ nm, $\theta = -2.7\ 10^{4}$ deg.cm^{2}.dmole-1), pH = 10.2. Inset shows the CD spectrum of bilirubin-ligandin complex, pH = 7.4.

The detection of this complex is precisely assured through the remarkable chiroptical properties of bilirubin. Indeed, the crystallographic analyses of free bilirubin displays an internally hydrogen-bonded chiral conformation [3]. All crystalline forms studied up to now are racemic, the two enantiomers being associated by an inversion center.

In solution the two labile enantiomers are in dynamic equilibrium. But association with an auxiliary stable chiral molecule displaces the conformer equilibrium and leads to optical activity. Indeed, the physiologically important complexes with serum albumin [4] or ligandin [5] (liver protein) give rise to an intense circular dichroism spectrum in the region of the visible absorption bands of bilirubin. It is important to emphasize that the spectral form of bilirubin complexed with β cyd [6] (8 10^{-1} M bilirubin, 10^{-2} M β cyd) shown in fig. 3 is practically identical with that obtained in the ligandin (rat liver) complex. It appears that β cyd acts here as a biomimetic molecule. The analogy of the spectra shows clearly that the same conformer, of the same chirality, is selected as well in association with cyd as with the protein.

b) Helicenes.

We have obtained (in aqueous solution) the CD spectrum of 4-helicene complexed with γ cyd. This result completes the optical activity study of helicene series, all higher homologues having known CD spectra.

The helicene series represents a class of classical examples of chromophores termed inherently dissymetric. The optical activity measurements of these molecules can provide the basis for comparison with theoretical calculations. Though optical activity of higher homologues has been extensively studied, ORD and CD spectra of 4-helicene have not been reported. Indeed, the optical antipodes of 6-7-8-9 helicenes are stable and easily resolved [7,8] ; 5-helicene racemizes at room temperature but the energy barrier separating the two antipodes is sufficient to allow resolution [9] . whereas the enantiomeric conformers of 4-helicene (fig.4) interconvert rapidly in solution, even at the lowest accessible temperature, and can not be separated. Fig. 5 shows the CD spectrum of aqueous solution of complex 4 helicene - γ cyd (10^{-4} M 4H, 10^{-2} M γ-cyd) [10] . This spectrum can now be compared with theoretical calculation [11] .

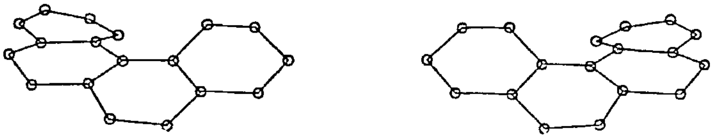


Figure 4. Two enantiomeric conformers of 4-helicene

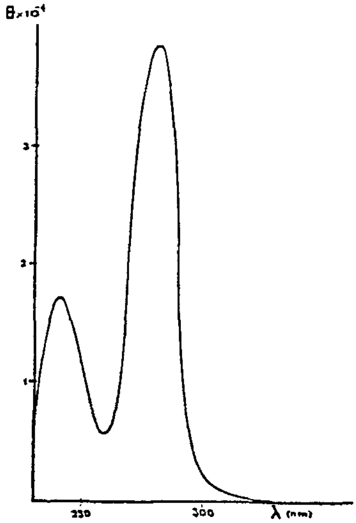


Figure 5. CD spectrum of 4-helicene complexed with γ-cyd. θ in deg.cm^2.dmole^{-1}.

c) Benzil.

CD spectrum of benzil complexed with β cyd has been recorded in aqueous solution and a crystallographic study of the complex has been undertaken.

The benzil molecule exhibits conformational freedom arising from the rotation around the central C-C bond. The CD spectrum of benzil-β cyd complex solution is given fig. 6 (3.5 10^{-4} M benzil , 10^{-2} M β-cyd). The structure of the benzil complex exhibits head to head dimers of β- cyd connected by hydrogen bonds involving all secondary hydroxyl groups .Despite the disorder of the guest molecule in the cyd cavity, a model of one preferred chiral conformer has been provided and its absolute configuration is that of fig.7.

We note finally that the CD spectrum of cyd complexed with several other molecules have been recorded [12].

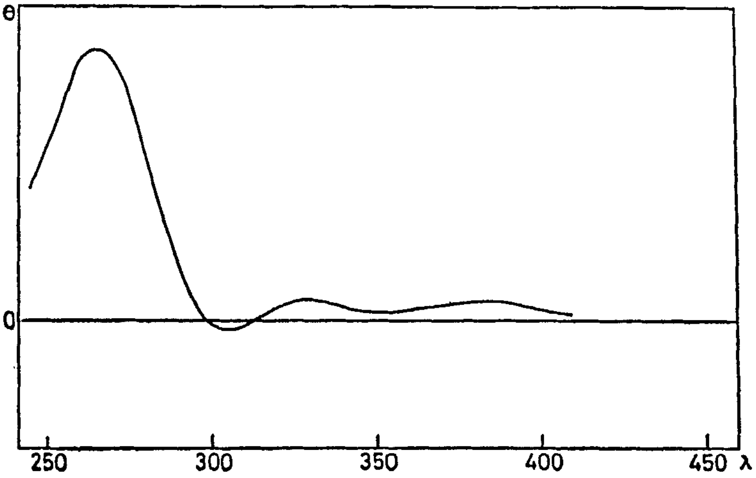


Figure 6. CD spectrum of the complex benzil-β cyd θ max = 10^4 deg.cm^2.dmole^{-1}.

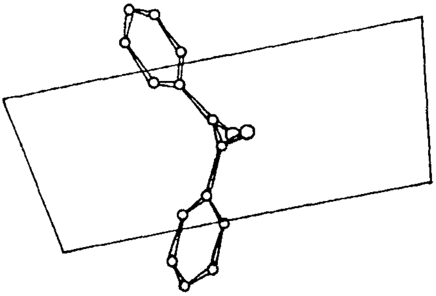


Figure 7. Absolute configuration of benzil in β-cyd clathrate.

Correlatively with selective complexation of enantiomers ,it is worth noting the cage environnement's effect on stable enantiomers . Enantiomeric separation has been explored by Mikolajczik et al[13] . Optical purity may reach 66%. We note also chromatographic separation [14] and asymetric synthesis whithin cyd cages [15] .

Figure 8. Class A clathrate (β-cyd-benzophenone)

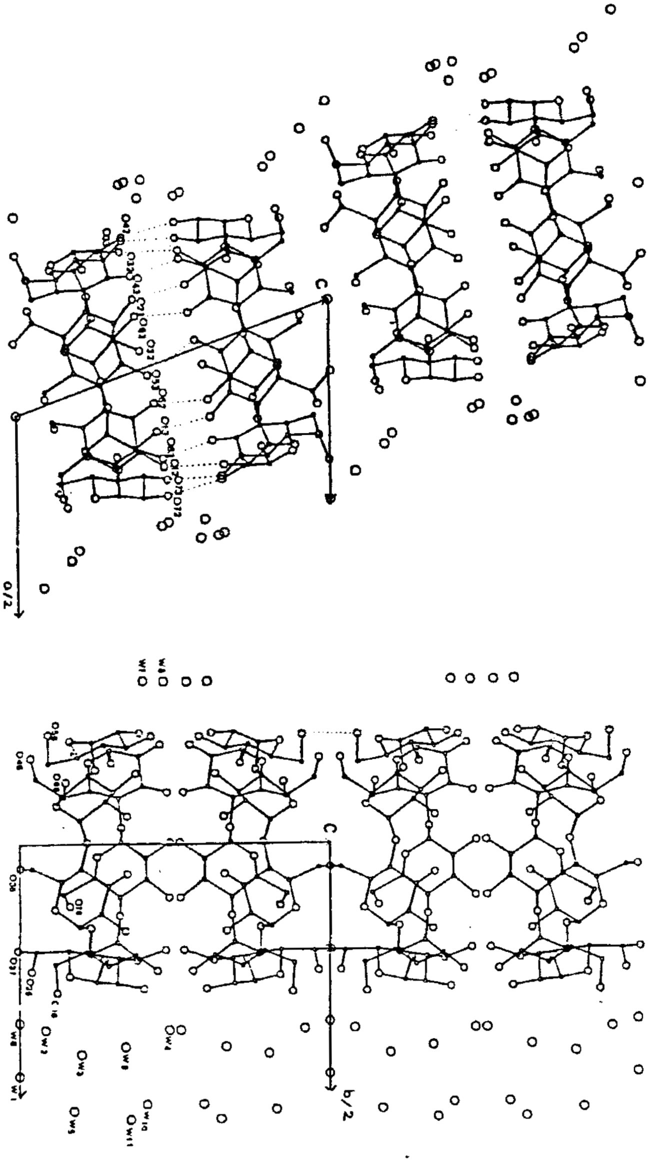


Figure 9. Class B clathrate (β-cyd-benzil)

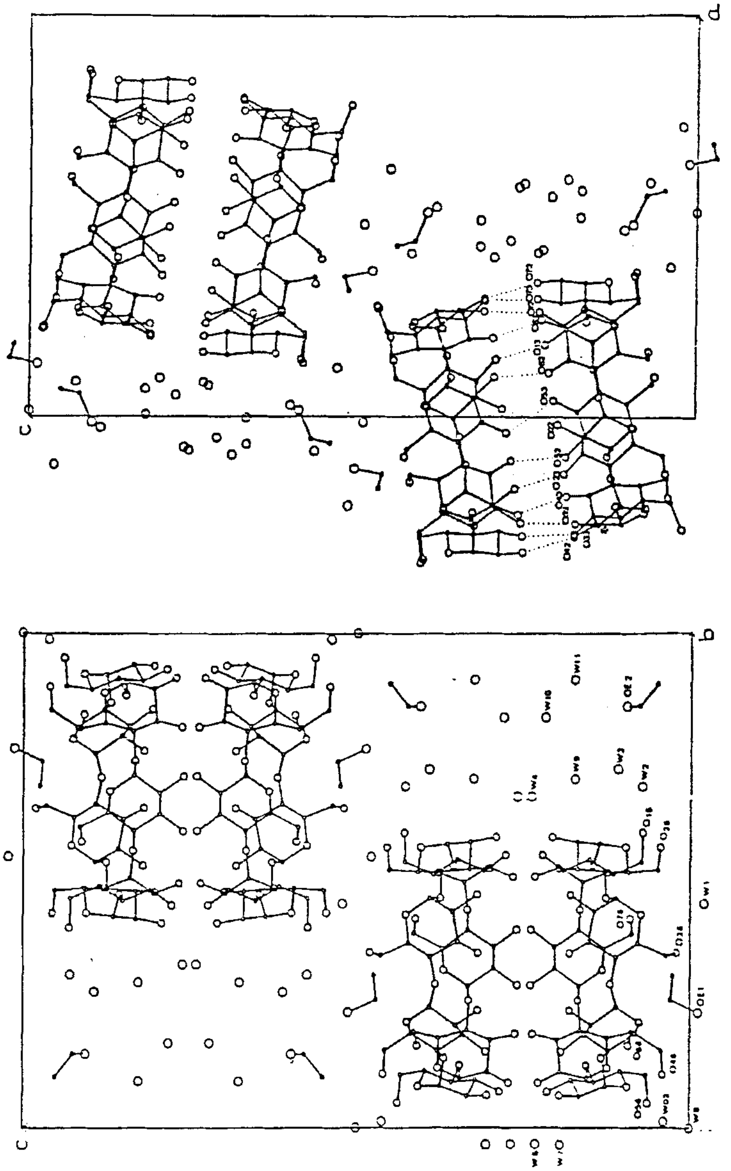
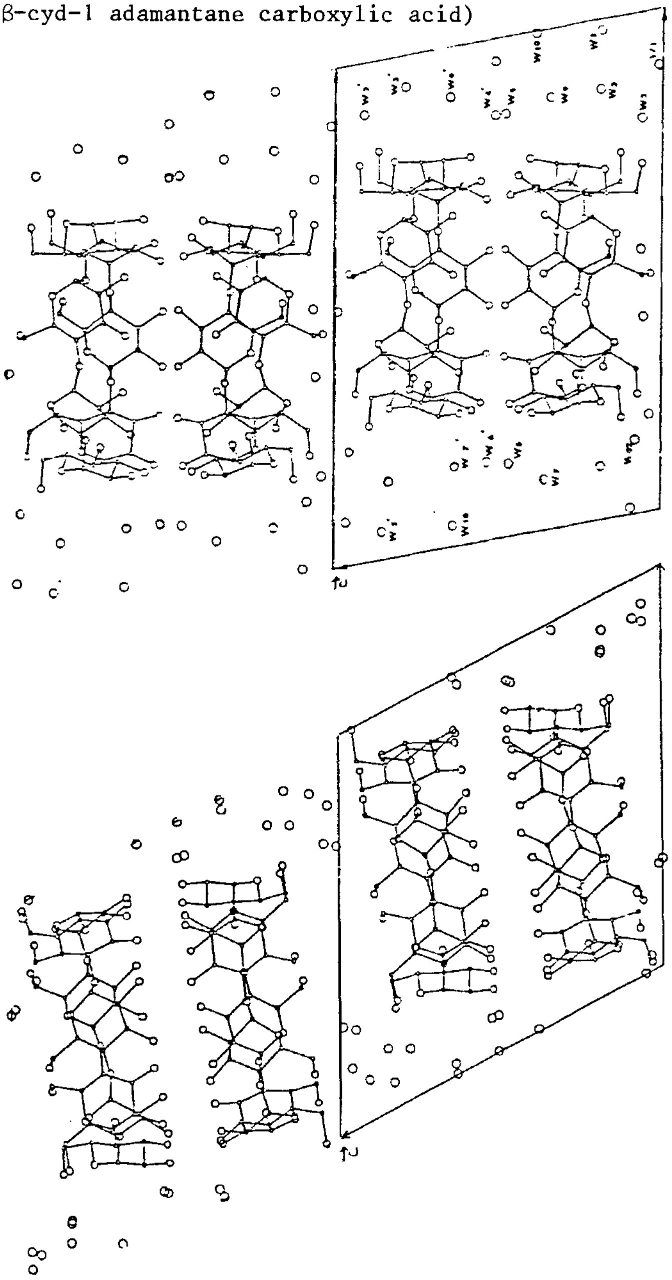


Figure 10. Class C clathrate
(β-cyd-1 adamantane carboxylic acid)



II COMPARISON BETWEEN β-CYCLODEXTRIN CLATHRATES AND THE ASSOCIATED WATER NETWORK.

Most of the β-cyd clathrates display head to head dimers. We show here that they can be classified in three classes which have in common the presence of the same dimer sheets. Furthermore, from the study of the crystal structures of several clathrates, a remarkable peculiarity emerges; they all display a very similar partial water network

Within a dimer all secondary hydroxyl groups of two partners are connected by hydrogen bonds (fig.8). The two halves of the dimer are always related by a molecular twofold axis which in some structures is also a crystallographic axis. Many crystalline structures are quasi-isomorphous to one an other, eventually, after a unit cell change. Structures on which we have data, in total seventeen, enter into three classes [16] .

In the first class crystals, titled class A, these dimers are stacked along the c axis to produce columns ,with interdimer hydrogen bonds involving some of the primary hydroxyl groups. Typical examples of this class are the clathrates of β-cyd n-propanol [17] or β-cyd benzophenone [10,16] shown in fig.8. These columns, which contain the guest molecules, are closely packed, spaces between the columns being filled with water molecules. The columns are linked by hydrogen bonds, involving hydroxyl groups either directly or through intermolecular water network.

In the B class crystals, no dimer columns are observed (fig.9). However individual sheets are still present with almost identical conformation of β-cyd molecule, with the same orientation of dimer axis with respect to the plane, and the same packing arrangement of dimers within a sheet. Moreover, within the dimer sheet the hydrogen bonded framework involving hydroxyl groups and water molecules is closely resembles that of class A but the connection between sheets is different. One sheet is related to its neighbour by a 2_1 axis along the c direction so that a dimer is located above a space filled with solvent, while in the class A clathrates, one dimer is superposed on another dimer. Direct hydrogen bonds between the primary hydroxyl groups of dimers of two adjacent sheets, as in class A, do not exist. Instead, each primary hydroxyl end is attached to one or more water molecules inducing a new intermolecular water network between sheets.

In the C class (fig.10) (the complex β-cyd-1-adamantane carboxylic acid is an example) the same dimer sheets are found again to display the leading structural features[18] i.e., same conformation of β-cyd molecule, same orientation of dimer axis with respect to the plane direction, same packing of dimers, and also a very similar water network within the same layer. But the sheet arrangement is different from classes A and B. As in class A, the sheets are interrelated by translation along c, but as the angle between the translation axis and the dimer axis is very large, the intramolecular channel considerably shrinks and we note also that each dimer is more surrounded by water molecules than in class A.

From the above analysis it follows that two characteristics are invariant for all classes :

a) dimer sheets seem to be the common building block for all structures

b) within the sheets the water network surrounding the cyd dimers is approximately invariant.

Up to now we have essentially described the structures and made a classificaton attempt. A further step would be establishing a relationship between the molecular structure of the guest and the crystal structure of the complex. Such an achievement, as is usual in this domain, is beyond today's state of the art. However we can explore different directions of research.

A first correlation would be the hydrophilic/hydrophobic balance of the guest. Class A packing may be viewed as an expansion of the hydrophobic region of cyd to enhance the binding of an hydrophobic substrate or an hydrophobic part. Indeed several representative guests of this class are either hydrophobic (biphenyl) [14] or have an hydrophilic part "hidden" in the middle of the cyd cavity (benzophenone). In these both cases it is an hydrophobic part of the guest which "sees" the corresponding part of the next dimer. Conversely, in classes B and C a greater part of the dimer is exposed to water contact. One would then expect a preference for polar molecules (for example, class B : β-cyd phenobarbital [19] ; class C : β-cyd 1-adamantane carboxylic acid [18]). An interesting fact corroborates this statement. It has been observed that crystals of β cyd complex with hydrophilic n-propanol belonging to class A are metastable, the stable crystals being of class C [20].

Another correlation would be considered with respect to the guest's size or length. Clearly if the included molecule is too long as compared to the dimer's length, class A is disfavoured (for example : benzil clathrate belongs to class B as shown in fig.7).

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