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CLATHRATES AND INTERCALATES

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Abstract Clathrates and intercalates are not any more laboratory curiosities. The specific situation where a given matrix is able to include a large range of guests suggests a variety of experiments useful both in fundamental research and in applied fields : specific chemical reactions, polymerization, stabilization of unstable species, isomer and enantiomer separations, contribution to elucidating reaction mechanisms, etc... The determination of the crystal structure by X-ray analysis often allows the rationalization and sometimes the prediction of above phenomena. Several tens of different clathrate and intercalate matrices are known; among those which are extensively studied, we present the most recent results.

INTRODUCTION

Clathrates are molecular crystals formed of two species: host molecules form a three dimensional assembly which allows cages of channels containing guest molecules.

In intercalates the host species form two dimensional layers allowing the guests to insert in between.

It is interesting to recall the early historical discovery of clathrates. In 1811, Davy observed the formation of a crystalline compound ($Cl_2.8H_2O$) when chlorine was bubbling into cooled water; the clathrate structure was finally established by Pauling and Marsh in 1948. Several tens of clathrates are known today. In the present contribution a few

are chosen in order to illustrate the variety of the structural types and the ability of these inclusion compounds to display different physicochemical phenomena, as specific chemical reactions, isomer and enantiomer separations, stabilization of unstable species, stereospecific polymerization within channels (the last topic is developed in a separate contribution). The common trend of these phenomena is the influence of the surrounding host on the guest molecules, resulting in a change of the reaction path, or in general of the guest's behaviour, as compared with the free guest (in absence of clathrate). A gain of knowledge about these phenomena may open new possibilities, especially in crystal engineering. Finally, an advantage of clathrates is isomorphism between crystals containing different guest molecules, resulting in an identical microenvironment of the guests.

In Triorthothymotide (TOT) clathrates the cohesion is assured only by Van der Waals or residual forces. Photochemical reactions and enantiomeric separations of the guest molecules have been studied recently.

Deoxycholic acid forms channel clathrates. Host-guest photochemical reactions have been extensively investigated.

Cyclodextrins have the outstanding property of forming with the same guest complexes in solution, as well as crystalline clathrates. Crown ethers and cryptands may also exhibit this dual ability. But for all other known clathrates, dissolution in a solvent results in a practically complete loss of the inclusion ability of the host.

In Sheet Silicates (as in graphite and chalcogenides) the inorganic host crystal allows the intercalation of organic guests which may undergo chemical reactions catalyzed by the host. This important topic has been reviewed recently (J. M. Thomas in Intercalation Chemistry, Academic Press, 1982)

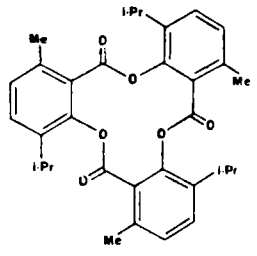
and will not be developed in this contribution. We will finally mention the DNA Intercalation as an interacting case of simultaneous intra- and inter-molecular intercalation.

TRI-ORTHO-THYMOTIDE

Tri-o-thymotide (TOT) is a labile chiral molecule forming clathrates in a variety of space groups with different guests[1-2]. Pure TOT crystallizes in a racemic group, $Pna2_1$,Z=4[3]. But, in presence of certain achiral molecules, TOT may form chiral clathrates, i.e. undergoes spontaneous resolution[4]. Two types can be distinguished:

- cage, space group $P3_121$, with molecules of largest dimensions smaller than 9 A.

- channel, space group $P6_1$, $P6_2$, $P3_1$, with long chain molecules. Another remarkable aspect of TOT is its flexibility[5]; in solution TOT exists in helical or propeller conformation, the latter being predominant. For each conformation, a rapid interconversion in solution between the M- or P- configuration occurs, the racemization barrier being 21 kcal/mole. In the crystal state, TOT acquires the propeller conformation (a related molecule, N,N',N''-trimethyltrianthranilide[6], crystallizes in the helical conformation).



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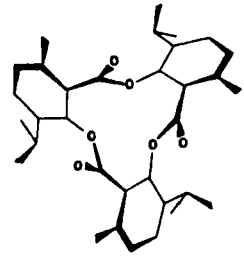


Enantiomeric Resolution

The chiral cages or channels exhibit preferential inclusion of one enantiomer over the other. But as a result of the rapid interconversion of P- and M-TOT, crystallization of TOT in presence of a racemic guest results in a mixture of enantiomeric crystals. Separation and identification of these crystals as (+)- or (-)-TOT is achieved by Pasteur's method, which consists in taking a chip from each crystal, dissolving in chloroform and then measuring its rotation. In a few cases optically active guests were used and then only the correlation of TOT and guest chirality was made[7-8-9]. The following values of enantiomeric excess in % (given in parenthesis) are the most striking. In cage-TOT: 2-Chlorobutane, 1, (32^8,45^9); 2-Bromobutane, 2, (34^8,35^9); Trans-2,3-dimethyloxirane, 3, (47^8); Trans-2,3-dimethylthiirane, 4, (30^8); Propylene oxide, 5, (5^8); 2-Methyltetrahydrofuran, 6, (2^8); Methyl Methanesulfinate, 7, (14^8); Ethyl Methylsufoxide, 8, (83^9). The interpretation is facilited by X-ray analysis of several cage $P3_121$ clathrates [7-10-11-12-13-14-15].

The absolute configuration of the preferred guest enantiomer is such that homologous atoms or groups in related molecules occupy similar positions in space. Therefore, for a given chirality of TOT clathrate crystal and in a series of homologous molecules, the absolute configuration of the preferred guest enantiomer can be predicted. Moreover, the absolute configuration of TOT has been assigned by determining the relative configuration of TOT to guest, for several guest molecules of known absolute configuration : (+)-TOT has a P-propeller like configuration[16-17].

The cavity picture is shown in fig.1. Its dimensions explain well the upper limit (~9Å) in the size of the guest. Also, the cavity has the crystallographic symmetry 2, and

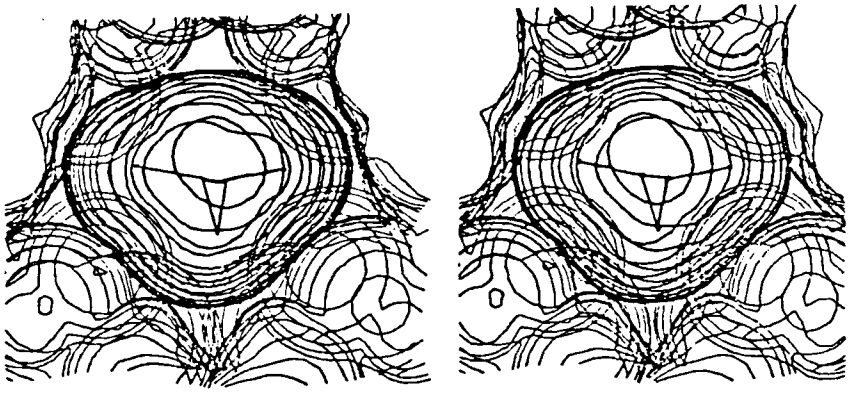


FIGURE 1 Stereoview of the contours of the van der Waals envelope of the volume accessible of guest atoms.

can explain to some extent a tendency for high discrimination undergone by guests (3 and 4) whose molecular symmetry is also 2. However, it has been found that disorder occurs in clathrates like 3 or 4, grown from optically pure guest. The cage appears as a deformed ellipsoid and its ability for enantiomeric discrimination is not obvious ; even less is so the prediction of the configuration of the preferentially included guest. On the other hand, an intriguing fact is the quite high discrimination exhibited by guests like 1, 2 or 8 despite the lack of symmetry 2, implying an increased degree of disorder. The discrimination in channels (for instance, 2-Bromooctane), about 4-5 %, is quite small, yet significant, presumably as a consequence of disorder.

Despite these difficulties, tentative discrimination mechanisms have been proposed. Another relevant fact illustrating the stabilizing influence of the cage on the guests is provided by racemization of 7 within the cage: crystals

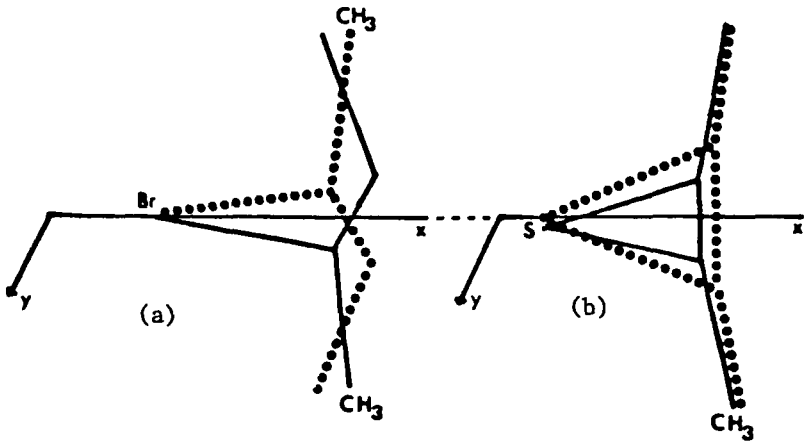


FIGURE 2 View of guest molecules along c. (a) TOT-2: two positions of 2 (b) TOT-4:major and minor (dashed lines) enantiomers

heated to 115° for up to 12 hours showed no racemization, whereas in solution racemization takes place at that temperature[7].

Finally, it is important to emphasize that the enantiomeric excess given above concerns a crystal grown from a racemic solution of guest, but enantiomeric enrichment can be considerably increased by repeated crystallization[7].

Photochemical reactions

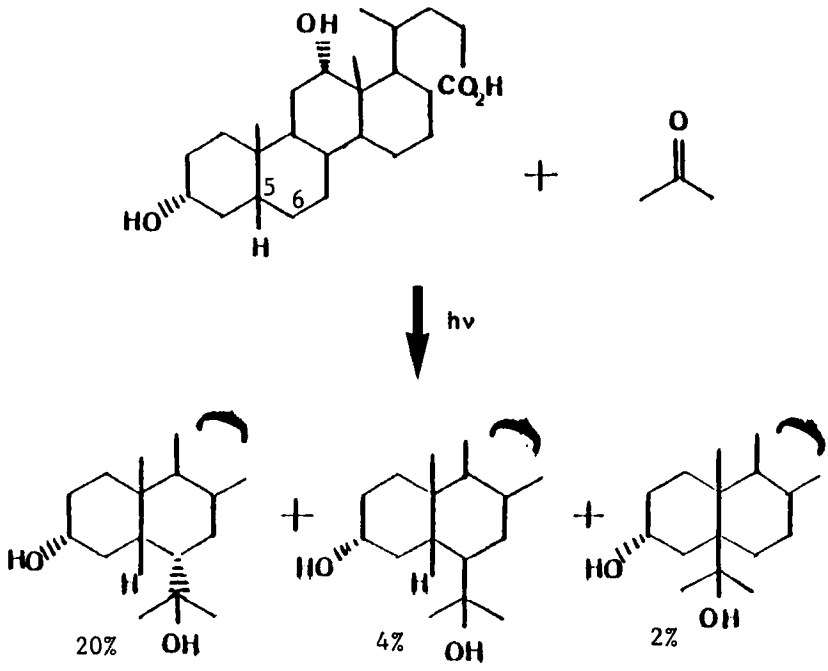
The irradiation by UV of cis and trans-stilbene clathrates provides another striking illustration of the influence of the cage, as shown in the following scheme[18]:

in solution		in clathrates	
cis ⇄ trans		cis → trans	
80%	20%		100%
		cis ↛ trans	

Here, the guest's crystalline environment dramatically modifies the photochemical behaviour as compared to that in solution: cis-stilbene isomerises completely to trans-stilbene, (after a certain irradiation time depending on temperature), but the trans-isomer is photostable. On the contrary, irradiation of either cis- or trans-methylcinnamate leads in both cases to a c.a. 50% photoequilibrium. These results can interpreted essentially by a symmetry controlled mechanism. The crystal structure of all these clathrates (space group $P\bar{1}$) are isomorphous. The host matrix allows cavities which communicate through narrower tubes to form channels running through two mutually perpendicular directions. Thus, TOT presents an intermediate type of clathrate, between cavities and quasi uniform channels. The cavities are located at inversion centers. Only trans-stilbene has the required symmetry to occupy the cavities without disorder, as confirmed by X-ray analysis. Clearly, a non centrosymmetric guest cannot achieve the same favoured interactions within the centrosymmetric cavity and is less stable. Thus, cis-stilbene completely converts into the more stable trans-stilbene clathrate, whereas the smaller molecules of cis- or trans-methylcinnamate (both lacking $\bar{1}$ symmetry) convert into a mixture.

CHOLEIC ACIDS

In a series of elegant experiments combining chemical studies and low temperature X-ray analysis, stereospecific photochemical reactions between the host deoxycholic acid (DCA) molecule and included ketones have been studied[19-20-21-22-23]. These reactions involve hydrogen abstraction from DCA by the photoexcited ketones which then add to form a new carbon-carbon bond. In each such reaction, a chiral center



is created on the steroid and, if the ketone is prochiral, a new chiral center is formed at the carbonyl carbon atom.

The ratio of diastereomers varies with the guest, being highly selective for acetophenone, where half of the guest molecules react. The selectivity can generally be understood in terms of the orientation and distances between the carbonyl group and the potentially reactive H-C groups on the steroid. Perhaps the most intriguing aspect of these studies was the discovery of a topochemical, strictly lattice-controlled, reaction in the DCA-acetophenone complex wherein the stereochemical outcome is the opposite of that anticipated on the basis of bond formation along the path of least motion. Thus, the 10:4 DCA acetophenone complex gave, on irradiation under argon, only one photoproduct for addition to

position 5. From the X-ray analysis of unreacted and partially reacted crystals a model has been proposed (Fig.3). It is essentially a superstructure extended over five unit cells along axis $\underset{\sim}{c}$, the channel direction, and involving four acetophenone molecules (two crystallographically independant molecules, G and G', and their images through a 2_1 axis).

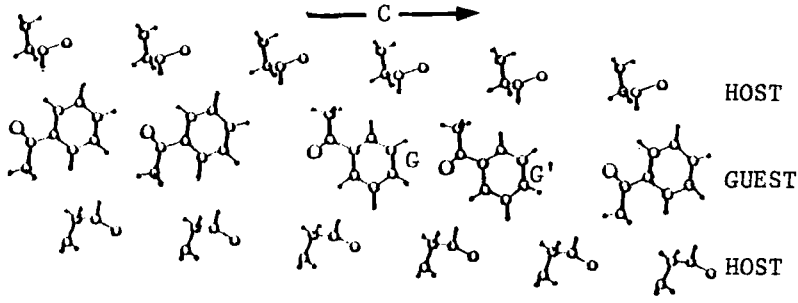


FIGURE 3 Chain of guest acetophenone molecules within the channel. The two independant guest molecules G and G' are related by pseudo translation of $\underline{C} + \underline{\Delta C}$ where $\underline{\Delta C}$ = 0.8 Å.

Despite the disorder (imagine the projection on one unit cell !) and the complexity of the problem, the model reasonably fits most chemical and crystallographic data. The unexpected fact is that the ketone adds from that face of acetophenone which is the most distant from the steroid in the starting structure. This implies the need for unusual motion of the guest acetyl group around the bond C(phenyl)--C(OH) CH_3 during the process of H abstraction from C5.

This work illustrates the interest of clathrates in elucidating reaction mechanisms, arising from the exact knowledge of the spatial dispositions of reactants before reac-

tion and of the stereochemical configuration of the product revealed in situ. But, the often occuring disorder is a major handicap requiring very high precision X-ray work. The idea of a superstructure of guest molecules presiding over topochemical reactions may well constitute an important progress in this difficult field.

CYCLODEXTRINS

Cyclodextrins (Cyd) are uniquely situated within the inclusion compound family : they are able to form complexes in solution as well as in the crystal state[24]. There does not seem to be restrictions on the nature of possible guests as seen from the variety of molecules studied so far, e.g. esters, acids, alcohols, sulfoxides, sulfinates, phosphinates, amines, ketones. Cyclodextrins are formed of 6,7,8... glucose molecules, named correspondingly, α-,β-,γ-...cyd. The diameter of the intramolecular cavity is respectively, 4.5 Å,7.0 Å 8.5 Å... They are obtained industrially by the action of bacillus macerans and related bacteria on starch ; the biological "motivations" of these bacteria are the subject of speculation. The crystal structures are being extensively studied and present several interesting aspects. Crystallized from water, α-cyd•$6H_2O$ presents a curiously "strained" form, considerably lacking 6-fold symmetry (Fig. 4). This has been considered tentatively as a driving force towards inclusion of guests, where strain would be relieved upon inclusion resulting in a unstrained or less strained ring[25-26-27].

β-cyd clathrates present a variety of space groups, but in most of these structures the cyd molecules associate through H-bonds and water molecules to form dimers, which allow a larger space for guest inclusion.

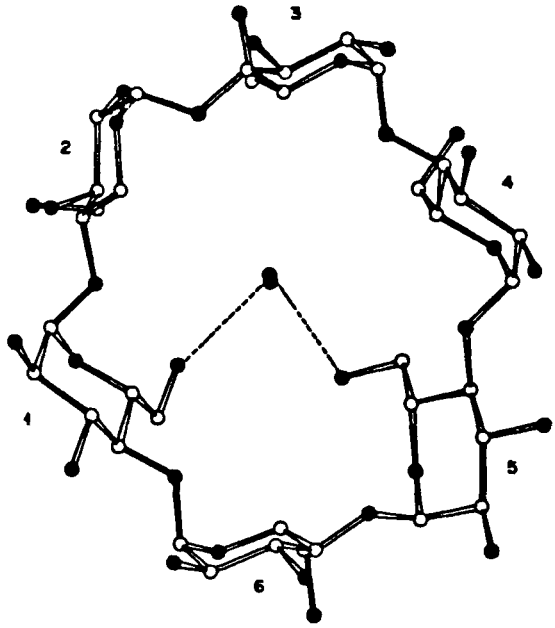


FIGURE 4 α-cyd viewed along a direction parallel to the torus axis

There is a definite preference for inclusion of molecules presenting hydrophobic interactions[24]. Obvious applications arise then from the solubilisation in water, through complex formation of hydrophobic species, especially in pharmacology. Also, stabilization of unstable species, both in solution and solid state, is naturally achieved by inclusion. We deal below with two domains, where the influence of the host is manifested in a finer scale.

Chemical reactivity

In solution, cyd can catalyse reactions through inclusion complex formation of substrates, displaying many of the kinetic features of enzymes[24] :

- covalent catalysis,via formation of covalent intermediates, as in hydrolysis of phenyl esters, amides, organophosphates, etc...

- non covalent catalysis; cyd provides its cavity as an apolar or sterically restricted reaction field without the formation of any covalent intermediates. A typical example is decarboxylation of anions of α-cyano and β-keto acids.

- asymmetric catalysis occurs in hydrolysis of chiral carboxylic esters and organophosphates.

In solid state, the chiral environment of the guest can result in asymmetric synthesis, illustrated by the following reaction. When the β-cyd phenylethylmalonic acid complex is heated at 100°C in its crystalline adduct form, CO_2 is evolved. Among the extracted products, 2-phenylbutyric acid is formed with an enantiomer excess of S-(+) over the R-(-) of 7.2 %.[7]

Enantiomer Selectivity and Induced Chiroptical Properties

The chiroptical properties of the guest may be modified upon inclusion. The physical nature of the modifications may be of two kinds : asymmetric perturbation of the electronic distribution of the guest, termed electronically induced circular dichroism (cd) and chiral modifications of the guest's geometry, called geometrically induced cd . In particular, it often happens for molecules with very low barrier of internal rotation, that chiral conformers are not stable enough in solution, even at the lowest accessible temperature, to exhibit a detectable ORD or cd spectrum. But, association with an auxiliary stable chiral molecule may allow the determination of chiroptical properties of labile enantiomers. Thus, induced cd arising from the $n-\pi^*$ transition appears for several derivatives of benzophenone, benzobenzoic acid[28]

-[29], benzil and diacetyl [30-31]. All the above molecules are likely to be included into the β-cyd cavity. This is not possible for bilirubin and biliverdin[30] whose dimensions are larger than that of the cyd cavity. They exhibit however intense induced cd spectra, with respectively θ_{max} ~ 27000 and 35000 deg $dmol^{-1}$. The association with cyd can be accounted for by a "sitting on top" model, or by the formation of a cyd dimer allowing a larger cavity. Similarly, a very strong cd spectrum (θ_{max} ~ 40000 deg $dmol^{-1}$) has been observed for 4-helicene[31].

A parallel enantioselectivity appears also in the crystal state. Since cyd is optically pure, all the precipitating crystals have the same chirality and the guest optical purity can be determined with polycrystalline samples. The observed selectivities are generally small with the exception of methyl isopropyl sulfinate (68 %)[32] and phosphinate (66 %)[33].

DNA - INTERCALATORS

Intercalation of flat molecules into DNA, oligo-DNA, or RNA molecules is considered as a possible first step in the action of carcinogenic and anticarcinogenic drugs[34]. We quote the structure of the complex of 1, as an interesting example of simultaneous intra- and extra-molecular intercalation[35]. Indeed as shown in fig. 5, the "minihelix" formed by two dinucleotide molecules contains one molecule of the intercalator ; another intercalator molecule is located outside this complex so that a column of planar molecules stabilized by π-interactions is formed.

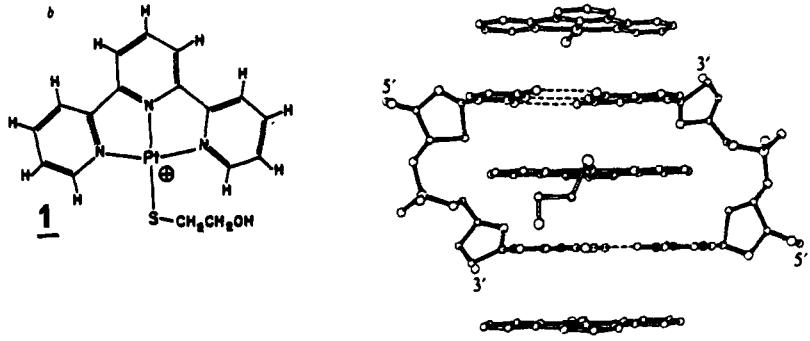


FIGURE 5 View of the structure as seen down the a axis

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