04.X-4 CYCLODEXTRIN INCLUSION COMPOUNDS

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Cyclodextrins are cyclic oligosaccharides consisting of six or more D-glucose units, which are connected by the α-1,4-linkage to form a macrocycle. These doughnut-shaped molecules form inclusion compounds by taking a variety of guest molecules into the intramolecular cavity. The inclusion phenomena of cyclodextrins have been extensively studied by the X-ray method as well as theoretical and physicochemical methods. The only obvious requirement for complex formation is that the guest molecule must fit geometrically into the annular void, even if only partially. The geometrical feature of the host-guest interaction differs depending on the size, shape, and chemical proterties of the included guest as well as the cavity size of the host cyclodextrin. Relatively small molecules tend to be enclosed within the "cage" formed by blocking both ends of the host cavity with adjacent host molecules in the crystal. Some long molecules or ionic guests are included within the "column" which is formed by the stack of cyclodextrin rings in a head-to-head or head-to-tail mode. Chemical modification of cyclodextrins changes the size and shape of the host cavity and affects the geometry of the host-guest interaction. When cyclodextrins are methylated, the hydrophobic cavity is extended and guest molecules are rather loosely bound in the wider cavity. Permethylation markedly distorts the round structure of parent cyclodextrins and brings higher ability of chiral recognition in the complex formation with optically active guests.

04.X-5 CHIRAL INTERACTION AND FINE STRUCTURAL FIT IN CYCLODEXTRIN CLATHRATES.

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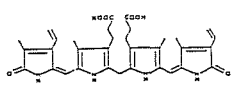
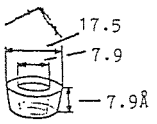
The inclusion of guest molecules in cyclodextrins has a wide range of applications in chemistry and biology. Recent developments allow a certain choice among modified cyclodextrins as a "host candidate" for a given guest.The aim of this work is to give, with a few examples, a finer insight onto the notion of fit, and to illustrate this approach in a case of great practical importance, the controlled inclusion and release of pheromones.

1. Conformational and enantiomeric selectivity

The bile pigments bilirubin and biliverdin are achiral, but upon interaction with cyclodextrin, they acquire a preferential conformation resulting in a very strong circular dichroism spectrum ($\Delta\varepsilon > 10$). The size of the γ-cyclodextrin cavity is smaller than that of bilirubin.



Bilirubin IXα



This suggests that bilirubin is "sitting on" rather than "included in" the cavity. Thus complete inclusion may not be a prerequisite for the manifestation of markedly different properties of the guest molecule upon complexation. On the contrary, in the β-cyclodextrin·cyclopentanone clathrate, the guest fits comfortably in the cavity, and we have observed new phenomena upon inclusion: mutual dependence between the disordered orientations of the guest and a conformational disorder of the primary -OH groups of the host. In conclusion we have to be very careful when reasoning with rigid geometrical models: a conformational feedback of statistical or dynamic origin may radically alter the expected picture of host/guest fit.

2. Pheromones

Pheromones, sex attractants produced by insects, can be used in agronomy to attract insects into a "trap", i.e. a surface area containing small quantities of pesticide. The practical implementation of this process is impaired by the volatility of pheromones and their chemical instability in the air. This drawback can be greatly reduced or totally overcome by inclusion of pheromones in cyclodextrins. The pheromone of the olive fly Dacus Oleae, 1,7-dioxaspiro 5-5 undecane has been included in β-cyclodextrin, but the clathrate is "too stable", i.e. the release rate of the guest is too low. This is a "molecular and crystal engineering" problem. The crystal structure (space group C2, Z=4, a=19.33 Å, b=24.42 Å, c=15.94 Å, β=108.72 Å, R=12.7% for 4400 reflections) may account for the stability of the clathrate: continuous columns of cyclodextrin intercalating to pheromone molecules constitute "rigid pillars" of the structure. On the other hand, guided by molecular models to obtain a less stable clathrate, we achieved inclusion in 2,6-dimethyl-β-cyclodextrin. The first experiments have shown that this clathrate is indeed less stable than that of β-cyclodextrin. In conclusion, the notions of geometrical fit, feedback in conformational changes and chiral discrimination must be critically studied in order to understand the inclusion phenomenon.

04.X-6 DRUG - Z-DNA INTERACTIONS: CRYSTAL STRUCTURE OF DEOXY CpG - MITOXANTRONE COMPLEX

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Mitoxantrone is a new anticancer drug effective against breast cancer and leukemia. We report here the structure of its complex with left handed Z-DNA d CpG sequence.

Crystals were grown from an aqueous solution containing deoxy CpG, mitoxantrone and NH_4Cl by acetone liquid diffusion. Crystals belong to triclinic P1, with a = 10.583, b = 13.738, c = 16.920 Å; α = 107.81°, β = 101.22°, γ = 102.3°. Three dimensional intensity data were collected on a CAD-4 diffractometer using CuK_α radiation up to θ = 70°. 7200 out of 8600 reflections collected, were considered observed. Lorentz and polarization corrections were made.

Structure was solved using vector search rotation function combined with DIRDIF methods. Anisotropic refinement of 122 non hydrogen atoms converged at R = 13.5%.

There are two independent d CpG molecules in the unit cell. They form a mini Z-DNA double helix with G.C Watson-Crick base-pairs. The side-chains of the drug are on opposite side of the anthraquinone chromophore which is pseudo intercalated between two d CpG duplexes related by the unit cell translation along 'a' axis as shown in figure. The structure of the complex is stabilized by H-bonds from the NH_2^+ and the terminal OH groups of the side-chains of the drug to N7 and O6 atoms of the guanine bases on the major groove side.