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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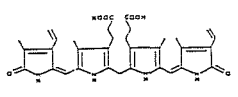
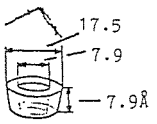
The inclusion of guest molecules in cyclodextrins has a wide range of applications in chemistry and biology. Recent developments allow a certain choice among modified cyclodextrins as a "host candidate" for a given guest.The aim of this work is to give, with a few examples, a finer insight onto the notion 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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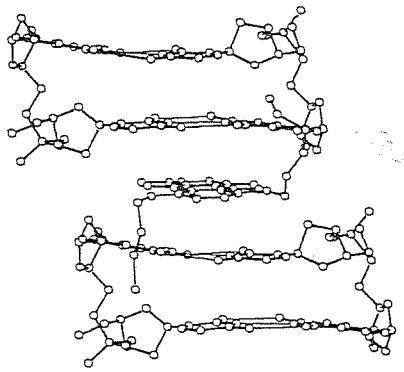
Mitoxantrone is a new anticancer drug effective against breast cancer and leukemia. We report here the structure of its complex with left handed Z-DNA d CpG sequence.

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.

The interactions observed in the crystals show an interesting correlation with the pharmacological activity of mitoxantrone related drugs.



04.1-1 THE FIRST DETERMINATION OF THE ENERGY DIFFERENCE BETWEEN SOLID STATE CONFORMERS BY X-RAY DIFFRACTION: 1. THE CRYSTAL STRUCTURE OF THE PSEUDO-JAHN-TELLER COMPLEX (NITRITO)BIS(2,2'-BIPYRIDYL)COPPER(II) NITRATE AT 20, 100, 165, AND 296 K. 2. THE POSSIBILITY OF USING X-RAY DIFFRACTION TO CHARACTERIZE ADIABATIC POTENTIAL ENERGY SURFACES AND RELATIVE LIGAND STRENGTHS. By Charles J. Simmons, Chemistry Department, University of Puerto Rico, Rio Piedras, Puerto Rico 00931; Brian J. Hathaway, Chemistry Department, University College, Cork, Ireland; Bernard D. Santarsiero, Chemistry Department, California Institute of Technology, Pasadena, California 91125; Abraham Clearfield, Chemistry Department, Texas A&M University, College Station, Texas 77843.

The crystal structure of $[Cu(bpy)_2(ONO)]NO_3$ has been determined at 20, 100, 165, and 296K. It is found that the molecular geometry of the CuN_4O_2 chromophore is temperature dependent: the Cu-O bonds are 2.051(2) and 2.536(2)Å at 20 K and 2.230(5) and 2.320(5)Å at 296 K. The distortional behavior of $[Cu(bpy)_2(ONO)]NO_3$ and other similar systems is rationalized in terms of a pseudo-Jahn-Teller formalism. The proposed adiabatic potential energy surface, which is consistent with both theory and the crystallographic results, consists of a double-minimum ground state, which, depending on crystal-packing forces, may or may not be equivalent. A methodology which uses the observed metrical data from the structures of the CuN_4O_2 chromophore from 20-296 K and Boltzmann statistics will be presented which allows an accurate determination of the energy difference between the two conformers (77 cm^{-1}).

A formalism which allows these energy surfaces to be calculated from crystallographic and ESR data will be discussed. The energy gap between the ground and first-excited electronic states for an undistorted complex, obtainable from the calculations, is proportional to the ligand strength of the OXO^- group (OXO^- = CH_3CO_2-, etc.).

04.1-2 STRUCTURE-FUNCTION RELATIONSHIPS IN $Z-PR_3$ COMPOUNDS. By B.J. Dunne, R.B. Morris and A.G. Orpen, Department of Inorganic Chemistry, The University, Bristol BS8 1TS, U.K.

We have sought to understand R_3P-Z bonding in tertiary phosphine-metal complexes (Z = metal), phosphine oxides (Z = O) and PPN^+ salts (Z = N) from analysis of structural data. The P-Z bond is usually depicted as having both σ and π interactions. The nature of the π component has been a subject of debate, notably for transition metal-phosphine complexes. Traditionally the phosphorus 3d orbitals have been invoked as the site of phosphorus π-bonding, but recently this view has been challenged and the importance of the P-R σ^* orbitals postulated on the basis of molecular orbital calculations (*e.g.* D.S. Marynick, *J.Am.Chem.Soc.*, 1984, 106, 4064).

We have tested this theory by two analytical approaches to illustrate data. The first, which concerns the case where Z = metal, rests on comparison of pairs of complexes where the structures of $[L_nM-PR_3]$ and $[L_nM-PR_3]^+$ are known. In cases where the effect of oxidation on metal-phosphine bonding is largely limited to the M-P π bond the M-P bond is lengthened and P-R bonds shortened. These changes together with others in the PR_3 geometry support the "new" view of metal-PR_3 bonding. The second approach which is more widely applicable, rests on comparison of the geometries of large numbers of $Z-PPh_3$ structures taken from the Cambridge Structural Database (CSD). These show patterns of structural deformations which relate the nature of Z, the length of the P-Z bond, and other geometrical parameters of the PPh_3 unit. The observed correlations may be understood with the aid of qualitative molecular orbital theory.

04.1-3 ON THE LATTICE PACKING RULES REVEALED BY THE PAIRS OF QUASI-ISOSTRUCTURAL CARDENOLIDES AND ANALOGOUS BUFADIENOLIDES. A. Kálmán, Gy. Argay and V. Fülöp Central Research Institute for Chemistry, Hungarian Academy of Sciences, H-1525 Budapest, POB 17, Hungary; B. Ribár and D. Lazar, Institute of Physics, Faculty of Sciences, 21000 Novi Sad, POB 204, Yugoslavia.

Quasi-isostructural relationship between two or more related steroid crystals first was recognized when we reported (Kálmán et al (1984) Croat.Chem.Acta 57, 519) the X-ray analysis of digirezigenin (Fig. 1) formed from digitoxigenin via 14,15β-epoxy-ring-closure. Although this alters the puckering of ring D (Karle & Karle (1969) Acta Cryst. B25, 434) the packing (e.g. hydrogen bonds) of the crystal lattice remains unaltered:

	a(Å)	b(Å)	c(Å)	packing coeff.
digitoxigenin:	7.250(2)	15.015(4)	18.464(8)	0.693
digirezigenin:	7.288(2)	14.686(3)	18.480(3)	0.691

Continuing X-ray studies of the analogous bufadienolides isolated also from Ch'an Su, the dried venom of the Chinese toad (Fig. 1) we found a second isostructural pair formed by gamabufotalin and arenobufagin which differ in a 12-oxo group (Kálmán et al (1987) Acta Cryst. in press). This was followed by the observation that the 5-OH group of cinobufotalin also does not spoil the lattice found for cinobufagin (Declercq et al (1977) Abstr. of ECM-4 Oxford, p. 279). In contrast with this the related bufotalin is not isostructural with them, since its 14-OH takes part in hydrogen bonding. Consequently, in this case the closure of 14,15β-epoxy ring has to destroy the already existing molecular packing. In other words: quasi-isostructural pairs or groups (e.g. methyl-digitoxigenin (Prasad & Gabe (1983) Acta Cryst. C39, 273) is also isostructural with digitoxigenin) may exist only if the alteration of the molecular structures does not disturb the existing hydrogen bonding of the system.