**04-Crystallography of Biological Small Molecules**


**04.02 - Structure of Nucleic Acids and Nucleic Acid Complex**

MS-04.02.01 Structural study of DNA/RNA and their complexes with antitumor drugs by X-ray crystallography

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Our lab has been investigating the problems associated with the structure and dynamics of DNA/RNA and their complexes with antitumor drugs. We are particularly interested in the unusual DNA structures, possibly required by certain sequences. In addition, we have studied the interactions of several types of antitumor drugs (including minor groove binder, intercalator, nucleoside analog) with DNA oligonucleotides. In this paper, I will focus on the structural analyses of several complexes of anthracycline drugs and DNA. For example, the interactions of cytosine-5-fluorouracil with anthracycline, a promising potent adriamycin derivative, with DNA have been analyzed using the structure obtained from the high resolution (better than 2 Å) X-ray diffraction analysis. We also study the binding of other anthracyclines (e.g., aclacinomycin A and nogalamycin) with DNA oligonucleotides by NMR. The structures derived from the solid state and solution state are then compared carefully to understand the forces that are used to stabilize the structure and the mechanism of the drug binding. (Supported by NIH)

**MS-04.02.02 Structural Studies on DNA Minor-Groove Recognition by Drugs**

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Compounds that interact in the minor-groove of B-form DNA, primarily at A-T-rich regions, have usage in both animal and veterinary medicine. For example, the bis-phenylmethyl compound pertemscan, is one of the agents of choice in the treatment of pneumocystis carinii, the opportunistic infection that affects about 70% of AIDS patients. We have been studying the interactions of this and other compounds with DNA sequences, in part to provide a rational basis for the discovery of new, more effective agents, and in part to developing models for the recognition of specific DNA sequences. A number of structure analyses of such drug complexes with DNA sequences have now been performed by us. Several of these have been reported by us in the present literature. These structures are currently forming the basis of molecular modelling studies which are resulting in the rational design of new analogues with defined sequence recognition properties.

The X-ray analysis of the drug-oligonucleotide complexes have revealed a number of new aspects of minor-groove recognition.

(i) Water molecules can play an active role in drug-DNA recognition, mediating between them. They can also help to maintain the drug in its bound state; a novel type of "spine of hydration" has recently been observed in one of these complexes.

(ii) The hydrophobic nature of the minor groove walls plays an important role in drug binding.

(iii) The effect of sequence on structure are important for defining the nature of a drug complex. In particular, the effects of changes in parameters such as roll and propeller twist can determine which, particular base pairs are recognized by a drug.

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**PS-04.01.27 THE CRYSTAL AND MOLECULAR STRUCTURE OF N-METHYL-11-HYDROXY-12,10-TRIMETHOXY APORPHINE. By A. Hamid Ohman and Ikrar M. Said, Department of Chemistry, Universiti Kebangsaan Malaysia, 43600 Bangi, Malaysia.**

The above mentioned compound, an alkaloid was extracted from fresh leaves and bark of *Debussia incrustata* and its crystal and molecular structure has been determined from three dimensional X-ray diffraction data for 2914 unique reflections taken on a CAD-4 diffractometer. Crystal data: C₁₃H₂₂NO₂, M₀ = 240, orthorhombic, P2₁2₁2₁, a = 7.748(1), b = 23.576(6), c = 1753.5(3), µ = 0.964 cm⁻¹, Z = 4.

The structure was solved by direct method and refined by full matrix least-squares procedure. All calculations were done using XTAI 3.6 program system (Hall, S.R. and Stewart, J.M., (1990) Eds Xal (Reference Manual), Universities of Western Australia and Maryland) on a PC-AT microcomputer. The final R value was 0.071 for 1848 I > 3σ(I) reflections. The final cycle of refinement gave R = 0.089, for all the 2914 reflections. The molecule contains two planar aromatic rings with inter-planar angle of 32°. The bonds and angles and intermolecular contact distance all have regular and acceptable values.