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03. CRYSTALLOGRAPHY IN BIOCHEMISTRY AND PHARMACOLOGY

03.X-8  CRYSTALLOGRAPHIC AND MOLECULAR MODELING STUDIES ON POLYCYCLIC AROMATIC HYDROCARBONS. Stephen Helk3, CRC Research Group, King's College London, WC2B 5RL, U.K.

Polyaromatic hydrocarbons do not themselves bind to nucleic acids, their likely biological targets. Instead, a complex series of metabolic steps leads to reactive polycyclic DNA. Crystallographic studies have been performed on the covalent and intercalative metabolite structures in computerized molecular modelling studies on both the covalent and intercalative adducts of benzo(a)pyrene. Results of this work will be presented, with especial reference to the dihydrodiol epoxide.

03.X-9  ELECTRON DENSITY MAPPING OF MODELS FOR THE ACTIVATED METABOLITES OF CARCINOGENIC POLYAROMATIC HYDROCARBONS. By C. L. Klein, Dept. of Chemistry, Xavier University, New Orleans, Louisiana 70125 and E. O. Stevens, Dept. of Chemistry, University of New Orleans, New Orleans, Louisiana 70148.

Many polyaromatic hydrocarbons(PAH), such as benzo(a)pyrene(BP), are known to be environmental pollutants and potent chemical carcinogens. The most active forms of the molecules are metabolite derivatives of the parent hydrocarbons. Although a large number of metabolites of BP have been identified, the ultimate carcinogen is believed to be a dihydrodiol epoxide.

We have begun a study of the electron density distribution of a series of naphthalene derivatives which model the metabolites of BP. One of these, anti-3,4-dihydroxy-1,2,3,4-tetrahydropyrene-1,2-oxide(NDE), has been chosen as a small molecule model for the ultimate carcinogenic metabolite of BP. Room temperature x-ray data show extensive structural similarities between NDE and the dihydrodiol epoxide of BP. To map the electron density distribution, extensive high-resolution x-ray data (sin θ/λ < 0.85 Å⁻¹) have been collected at 110 K. Phases for the observed structure factors in the asymmetric unit group P4₃2₁2 have been taken from the model phases of a MOLLY multiple deformation refinement. Maps of the electron deformation density at the reactive site of the diol epoxide will be presented. From the electron distribution and the electrostatic potential, a molecular property which may also be obtained, we hope to predict sites and modes of chemical reactivity and to correlate this information with carcinogenic activity.

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The mechanism of chemical carcinogenesis by "activated" carcinogenic polycyclic aromatic hydrocarbons is believed to involve alkylation of DNA. A series of adenosines and 2'-deoxyadenosine substituted at N⁶ by related aralkyl substituents with aromatic and polycyclic aromatic ring systems in columns through the crystal. The propensity of these adducts to adopt the syn-conformation may be indicative of a preference for alkylated DNA for the Z-conformation (even if the form that is initially attacked is B-DNA). Computer-based molecular modeling techniques have been used to construct a tentative model of the interaction of aralkyl substituents with Z-DNA.

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03.X-11  DNA AS TARGET MOLECULE FOR DRUGS AND ACTION OF THE ANTIMETABOLITE 6-AZAURIDINE. By W. Saenger, Institut für Kristallographie, Freie Universität Berlin, Takustr. 6, D-1000 Berlin 33.

In nature there are two types of nucleic acids, RNA and DNA. The latter occurs in two principal right-handed double helical forms A and B which exhibit sugar puckering C₂'-endo in A and C₃'-endo in B, and display different helical parameters. The biologically active species is B-DNA which is found in superhelical form in chromatin, is of importance for protein-DNA interactions and is the target for drug intercalation. If B-DNA is dehydrated or subjected to high salt conditions, it transforms into A-DNA which is transiently observed in DNA transcription when DNA/RNA hybrids exist. The latter as well as double stranded RNA can adopt only the A-form for reasons not yet fully understood. If DNA has a certain alternating sequence poly(dG-dC), it can transform into Z-DNA, a left-handed double helix. In this form, the Watson-Crick base-pair is still maintained, yet the sugar puckering alternates C₃'-endo for dG and C₂'-endo for dC. The C₈-position of guanine is exposed at the periphery of the Z-DNA helix and can become a prime target for drugs such as aflatoxin.

The building blocks of nucleic acids, called nucleotides, are themselves biologically active. They can be modified chemically and, in case of 6-azaudidine, display anti-leukaemic action. Structure analyses have demonstrated that this drug exhibits unusual conformation which explains its biological action.