03. CRYSTALLOGRAPHY IN BIOCHEMISTRY AND PHARMACOLOGY

03.X-8 CRYSTALLOGRAPHIC AND MOLECULAR MODELLING STUDIES ON POLYCYCLIC AROMATIC HYDROCARBONS. Stephen Helde, CRC Research Group, King's College London, WC2B 6NL, U.K.

Polycyclic hydrocarbons do not themselves bind to nucleic acids, their likely biological targets. Instead, a complex series of metabolic steps leads to reactive oligonucleotide adducts. Instead, a complex series of metabolic steps leads to reactive oligonucleotide adducts of benzo(a)pyrene. Results of this work will be presented, with especial reference to electron distribution and the electrostatic potential, a molecular property which may also be obtained, we hope by the present methods. 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.

Research sponsored by the Cancer Association of Greater New Orleans.


The mechanism of chemical carcinogenesis by "activated" carcinogenic polycyclic aromatic hydrocarbons is believed to involve alkylation of DNA. A series of adenines and 2'-deoxyadenosine substituted at N6 by related alkyls of differing carcinogenic potential has been prepared. We report here the crystal structure of one of these compounds: N6-(anthracenyl-9-methyl)adenosine; N6-(10-methylanthracenyl-9-methyl)adenosine; N6-(12-methylbenz[a]anthracenyl-7-methyl)adenosine and N6-(10-methylanthracenyl-9-methyl)-2'-deoxyadenosine. Results are compared with those for a previously published analysis of N6-(12-methylbenz[a]anthracenyl-7-methyl)-2'-deoxyadenosine. All five compounds have the syn-conformational relationship between the sugar and the base. The overall conformations of all five compounds are similar, the base lying approximately parallel to the polycyclic aromatic ring system. The packing consists of alternations of adenine 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 modelling techniques have been used to construct a tentative model of the interaction of alkyl substituents with Z-DNA.

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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. D. Stevens, Dept. of Chemistry, University of New Orleans, New Orleans, Louisiana 70148.

Many polycyclic hydrocarbons (PAH), such as benzo(a)pyrene (BP), are known to be environmental pollutants and potent chemical carcinogens. The most active forms 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-tetrahydrophthalene-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 acen­tric space group Pca2₁ 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.

Research sponsored by the Cancer Association of Greater New Orleans.

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 puckerring C₂'-endo in A and C₂'-endo in B, and display different helical parameters. The biologically active species is B-DNA which is found in superhelical form in chromatin, 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 can transform into A-DNA which is transiently observed in DNA transcription when DNA/RNA hybrids exist. The latter as well as double helical RNA can adopt only the A-form for reasons not yet fully understood. If DNA has a certain alternating sequence poly[d6-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 is Cβ-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 the nucleotides, are themselves biologically active. They can be modified chemically and, in case of 6-azaoadine, display antileukaemic action. Structure analyses have demonstrated that this drug exhibits unusual conformation which explains its biological action.