03.X–8 CRYSTALLOGRAPHIC AND MOLECULAR MODELLING STUDIES ON POLYCYCLIC AROMATIC HYDROCARBONS. Stephen Neidle, CRC Research Group, King's College London, WC2B 5RL, 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 species, typified by the 7,8-diol 9,10-epoxides of benzo-(a)pyrene. This compound has four stereoisomers, with widely differing carcinogenicities and reactivities to DNA. Crystallographic studies have now been performed on the racemates of both syn and anti isomers; the latter is probably biologically the more significant. No structural data is as yet available on benzo(a)pyrene-oligonucleotide adducts. We have used the X-ray data on the 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 differences shown by the (+) and (-) enantiomers of the anti diol 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. D. 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 metabolic 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-tetrahydronaphthalene-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 ($\sin\theta/\lambda < 0.85$ A^{-1}) have been collected at 110 K. Phases for the observed structure factors in the acentric space group $Pca2_1$ have been taken from the model phases of a MOLLY multipole 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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03.X–10 STEREOCHEMICAL PROPERTIES OF NUCLEOSIDES ALKYLATED BY ACTIVATED CARCINOGENS. Jenny P. Glusker, H. L. Carrell and John J. Stezowski, Institute for Cancer Research, Fox Chase Cancer Center, 7701 Burholme Avenue, Philadelphia, Pennsylvania 19111, U.S.A. and Universität Stuttgart, D-7000 Stuttgart 80, Federal Republic of Germany.

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 N^6 by related aralkyls of differing carcinogenic potential has been prepared. We report here the crystal structure determinations of four of these compounds: N^6-(anthracenyl-9-methyl)adenosine; N^6-(10-methylanthracenyl-9-methyl)adenosine; N^6-(12-methylbenz[a]anthracenyl-7-methyl)adenosine and N^6-(10-methylanthracenyl-9-methyl)-2'-deoxyadenosine. Results are compared with those for a previously published analysis 6, N^6-(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 copounds are similar, the base lying approximately perpendicular 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 of 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 puckerings C3'-*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, is of impcrtance 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 helical 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 puckerings alternate 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-azauridine, display antileukaemic action. Structure analyses have demonstrated that this drug exhibits unusual conformation which explains its biological action.