Syntheses of the Adducts Formed by Carcinogenic Metabolites of Polycyclic Aromatic Hydrocarbons with DNA

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There is significant evidence for involvement of three pathways in the metabolic activation and mechanisms of carcinogenesis of PAHs. These pathways differ in the natures of the active metabolites involved. On this basis, they may be designated as: (1) the diol epoxide path, (2) the quinone path, and (3) the radical-cation path. They are not mutually exclusive, and all three mechanistic pathways may play a role. A long-range goal of our research is to determine the relative importance of these activation pathways for cancer in human populations. The investigations to be reported have as their principal objective development of methods for efficient syntheses of the adducts formed with DNA by the active metabolites of PAH carcinogens, such as benzo[a]pyrene (BaP) and benz[a]anthracene (BA). Because satisfactory methods for synthesis of the adducts formed via the diol epoxide pathway already exist, the principal focus of these studies is on synthesis of the adducts formed via the quinone and radical-cation pathways. The quinone mechanism of PAH carcinogenesis proceeds via initial activation of PAH dihydrodiol metabolites, such as BaP 7,8-dihydrodiol, by aldo-keto reductase (AKR) enzymes to yield the corresponding PAH catechols. These intermediates enter into redox cycles with O2 to generate the related PAH quinones, such as BaP 7,8-dione (BPQ) along with reactive oxygen species (ROS) that attack DNA. Formation of low levels of PAH quinones can result in formation of large amounts of ROS, as a consequence of the cyclic nature of the process, leading to extensive DNA damage. The PAH quinones themselves also interact directly with DNA to form both stable and depurinating adducts. In addition, PAH quinones, such as BPQ, can afford stable hydrated adducts of dA and dG. Thus, the AKR pathway can give rise to a spectrum of DNA adducts. The radical-cation pathway involves PAH activation by cytochrome P450 peroxidases to form reactive PAH radical-cation intermediates that combine with DNA to generate several types of depurinated adducts. The syntheses to be reported include: (1) synthesis of the "stable adducts" formed by the quinone metabolites of BaP (BPQ) and BA (BAQ) with both 2\\\'-deoxyadenosine (dA) and 2 \\\'-deoxyguanosine (dG); (2) synthesis of 15N-labelled analogs of these adducts (all five nitrogen atoms 15N-labelled); (3) synthesis of the depurinating adducts formed by BPQ and BAQ with both adenine and guanine covalently linked at either the N7 or N9 positions of the purine bases; (3) synthesis of 13C-labelled BaP, BPQ, and BaP 7,8-dihydrodiol (each containing 13C-atoms at the 5- and 11- positions of the BaP ring system); and (4) new synthetic approaches to the adducts formed by radical-cations of BaP with adenine and guanine. The compounds whose syntheses are reported have been furnished as authentic standards for studies aimed at determining the relative importance of the three pathways of PAH activation and carcinogenesis in human cancer. These investigations were carried out as part of a program project supported by NIH grant (P01-CA-092537).