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CHEMICAL REARRANGEMENT OF PHENOL-EPOXIDE METABOLITES OF POLYCYCLIC AROMATIC HYDROCARBONS TO QUINONE-METHIDES

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SUMMARY: Evidence for the involvement of triol-epoxide and phenol-epoxide metabolites in the metabolic activation of polycyclic hydrocarbons is accumulating. It is proposed that the phenolic OH-groups present in such epoxides will activate the epoxide moieties and permit their rearrangement to quinone-methides. These quinone-methides are highly reactive, potentially-isolable chemical entities with strong alkylating activity. In one resonance form they are resonance-stabilized carbonium ions. Only epoxides that also possess phenolic OH-groups in certain positions will form quinone-methides: these appear to include 9-hydroxybenzo[a] pyrene 4,5-oxide and the triol-epoxides 9-hydroxy-trans-1,2-dihydro-1,2-dihydroxychrysene 3,4-oxide and 2-hydroxy-trans-9,10-dihydro-9,10-dihydroxybenzo[a]pyrene 7,8-oxide.

The polycyclic aromatic hydrocarbons require metabolic activation in order to exert their carcinogenic effects and diol-epoxide metabolites appear to be the principal species responsible for the binding of these environmental carcinogens to DNA (1,2). The stereochemical features of diol-epoxide isomers and their role in the formation of a carbonium ion as the reactive intermediate have also been recognized (3) and studies on the configurational relationship of the diol-epoxide moiety to the remaining aromatic rings led to the 'bay-region' hypothesis (4). The widespread applicability of metabolic routes leading to diol-epoxides, the existence of stereoisomers with differing reactivities, and the general ability of diol-epoxides to react covalently with DNA are now well recognized (5).

Studies in one of our laboratories on the metabolism of chrysene and on the covalent binding of metabolites to DNA have provided the first evidence (6) for the formation of a triol-epoxide, 9-hydroxy-trans-1,2-dihydro-1,2-dihydroxychrysene 3,4-oxide (I, Fig. 1). This triol-epoxide appears to be

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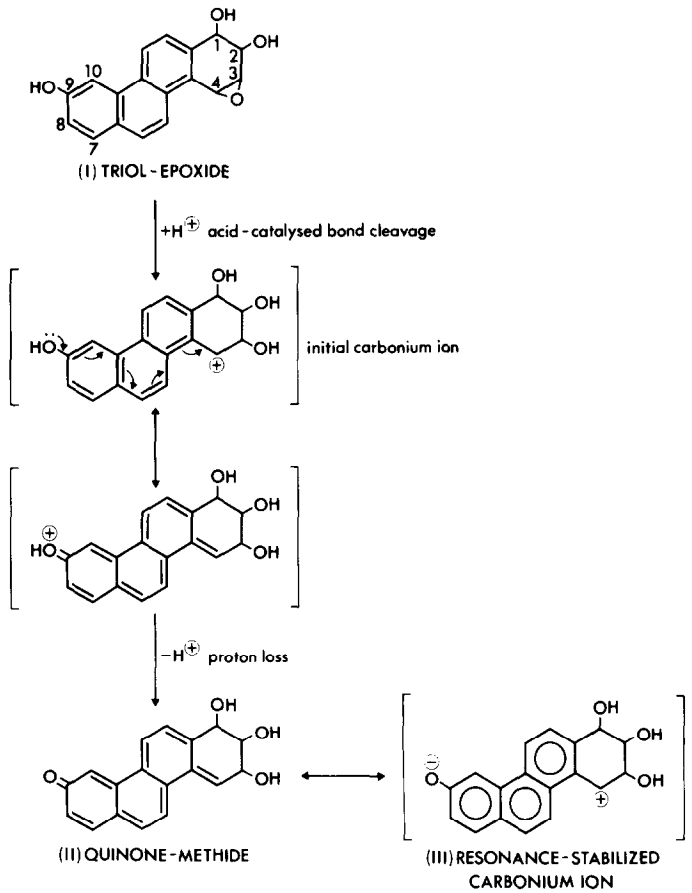

Figure 1. Rearrangement of chrysene triol-epoxide (I) to form a quinone-methide (II).

formed as an intermediate in the metabolic activation of chrysene since chromatographic comparisons have shown that a hydrocarbon-deoxyribonucleoside adduct that is present in hydrolysates of DNA isolated from mouse skin that has been treated with chrysene is identical to adducts formed when either trans-1,2-dihydro-1,2-dihydroxychrysene or 3-hydroxychrysene are incubated in a rat-liver microsomal system in the presence of DNA (6). (Because of the structural symmetry of chrysene, the 3- and 9-positions are equivalent). This triol-epoxide metabolite (I, Fig. 1), which contains a vicinal diol-epoxide moiety and a distant phenolic OH-group, bears some structural resemblance to 9-hydroxybenzo[a]pyrene 4,5-oxide (IV, Fig. 2) which, in some biological situations, is involved in the metabolic activation of benzo[a]pyrene (7,8). The purpose of this communication is to describe the role of phenolic OH-groups in

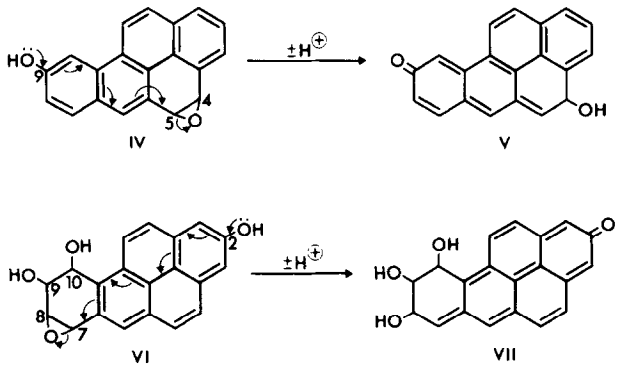

Figure 2. Quinone-methides (V) and (VII) formed by chemical rearrangement of 9-hydroxybenzo[a]pyrene 4,5-oxide (IV) and 2-hydroxy-trans-9,10-dihydro-9,10-dihydroxybenzo[a]pyrene 7,8-oxide (VI).

enhancing the chemical reactivity of hydrocarbon epoxides. The phenolic OH-groups will stabilize the reaction transition states by donating electronic charge to the incipient carbonium ions, thereby enhancing chemical reaction rates. They may also stabilize the resulting carbonium ions to such an extent that new and distinct chemical species, quinone-methides, may be postulated. The quinone-methide (II), formed by chemical rearrangement of chrysene triol-epoxide (I) is, in fact, identical to the resonance-stabilized carbonium ion (III) although the uncharged quinone-methide structure is the preferred representation (Fig. 1). Although highly reactive, such hydrocarbon quinone-methides may be sufficiently stable to be isolated as distinct chemical entities.

Other quinone-methides are known to exist as discrete entities (9,10) and quinone-methide intermediates have been suggested previously as the alkylating species responsible for the binding to DNA of the drugs adriamycin (11) and mitomycin C (12). They are also designed to be the reactive species formed in the bioreductive class of alkylating drugs (11,13). Thus our postulate of the formation of polycyclic hydrocarbon quinone-methides has established precedents. Figure 1 depicts how the quinone-methide structure arises from the chrysene triol-epoxide by epoxide bond cleavage, which is initiated by proton attack and enhanced by the ability of the phenolic oxygen atom to contribute electronic charge, and which is then followed by proton loss.

Although the phenolic OH-group at the 9-position of chrysene triol-epoxide (I) will allow formation of a quinone-methide, not all phenols are chemically

capable of resonance-stabilizing a carbonium ion. In chrysene, the positions at which phenolic OH-groups will stabilize a carbonium ion at the 4-position are 6-, 7-, 9- and 11-; phenols at other positions cannot form quinone-methides from a 1,2-diol-3,4-epoxide structure. The 3-hydroxychrysene precursor has been found to be mutagenic to S. typhimurium TA 98 in a microsome-mediated assay (H. Marquardt, personal communication) but the biological activities of other chrysene phenols have not been investigated in detail yet.

With regard to the possible role of quinone-methides in the activation of polycyclic hydrocarbons other than chrysene, there are a variety of situations in which they may be formed.

As mentioned above, the phenol 9-hydroxybenzo[a]pyrene is thought, in some instances, to be an intermediate metabolite in the metabolic activation of benzo[a]pyrene. This phenol is believed to yield the 'K-region' 4,5-oxide (IV) and hydrocarbon-deoxyribonucleosides with the required physico-chemical characteristics have been isolated (7,8,14). In this case, a quinone-methide (V) can also be formed by rearrangement of the epoxide (IV) (see Fig. 2), a compound whose synthesis is proving difficult (15), probably because of its high reactivity and its ready rearrangement to the quinone-methide (V).

When other phenols derived from benzo[a]pyrene were tested for carcinogenicity, the 2-phenol (but not the 1-phenol or the 3-phenol) showed strong activity (16). In order to obtain a quinone-methide from the 2-phenol and for the deoxyribonucleoside-adduct derived from this phenol to have the pyrene-like fluorescence described (17), we predict that the putative triol-epoxide metabolite must have the structure (VI) shown in Figure 2. Its quinone-methide has structure (VII). It is of interest that (VI) is a derivative of a non 'bay-region' 9,10-diol-7,8-epoxide and this is in contrast to the 'bay-region' 7,8-diol-9,10-epoxide moiety that is normally produced metabolically from the parent hydrocarbon (2). Thus 2-hydroxybenzo[a]pyrene is likely to be metabolized to a diol-epoxide that is different from that formed from benzo[a] pyrene itself.

There is a possibility that triol-epoxides and related quinone-methides might be involved in the metabolic activation of other polycyclic hydrocarbons: the adducts thought to arise from reaction of a chrysene triol-epoxide with DNA (6) elute in the same region of the Sephadex LH20 column elution profile as do diol-epoxide adducts and a variety of adducts derived from polycyclic hydrocarbons other than chrysene have been detected using Sephadex LH20 column chromatography but have not been identified. The chromatographic characteristics of some of these unidentified adducts are consistent with their being triol-epoxide adducts.

It also seems possible that reactive species analogous to quinone-methides are also formed in the metabolic activation of other classes of chemical carcinogens. Thus a quinimine-methide (a carbonium ion stabilized by an amino group in conjugation with it) has been suggested as the alkylating species that is formed from the carcinogenic, anti-schistosomal drug hycanthone (18, 19). A quinimine-methide probably also arises by decomposition of the sulfate ester of N-hydroxy-N-acetylaminofluorene. We suggest that quinimine-methides may also be formed metabolically from certain nitro-substituted polycyclic aromatic hydrocarbons where reduction of the nitro-group to the amino group is followed by distant epoxide formation. Chemically, quinone-methides and quinimine-methides are alkylating species which will react with moderately 'soft' nucleophilic groups on DNA.

We believe that quinone-methides may be involved in the metabolic activation of a variety of chemical carcinogens. They may therefore prove to be an important type of ultimate carcinogenic metabolite whose further study would prove worthwhile.

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