ON THE STRUCTURE OF METABOLITES OF CARCINOGENIC HYDROCARBONS*

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A considerable number of studies have been made in relation to the metabolism of carcinogenic hydrocarbons. Through these experiments the metabolic products of some of the polycyclic hydrocarbons have been isolated. It is a remarkable fact that in rats and mice the polycyclic hydrocarbons give rise to phenols in which the hydroxyl groups occupy the positions different from the points at which the oxidation would take place in a test tube. That is, 3: 4-benzpyrene is converted to 8-hydroxy-3: 4-benzpyrene (1, 2), 1: 2-benzanthracene to 4'-hydroxy-1: 2-benzanthracene (3), chrysene to 1-hydroxy-chrysene (4), and 1: 2: 5: 6-dibenzanthracene to 4', 8'-dihydroxy-1: 2: 5: 6-dibenzanthracene (7, 12, 18, 19). In order to explain the mechanism of such a metabolic oxidation various models have been postulated by many authors. No satisfactory explanation has been given, however.

Some of the present authors have introduced the frontier electron method (15, 16, 17) as one of the quantum-mechanical treatment of chemical reactivity. In the previous paper (20) the frontier electron method was put into application to the carcinogenic problem and an intimate correlation was pointed out between the carcinogenic activities and the frontier electron distributions in aromatic hydrocarbons. Furthermore, it is applied in the present paper to the problem of metabolism of carcinogenic hydrocarbons, in the search for an explanation of the structure of metabolites.

RESULT AND DISCUSSION

Fieser (9, 14) and Weigert (23) assumed that the carcinogen (for example 3: 4-benzpyrene) in rats and mice would be converted to 8: 9-dihydroxy-8: 9-dihydro-3: 4-benzpyrene by the addition of hydrogen peroxide and then transformed to 8-hydroxy-3: 4 benzpyrene by loss of water. On the other hand, Pullman (21, 22) postulated that the carcinogen (for example 1: 2-benzanthracene) would combine

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with tissue at K-region and 3': 4'-epoxide would be formed intermediately since that position of this tissue-carcinogen conjugate was found to be reactive to an electrophilic reagent. By enzymatic hydrolysis the epoxide would be converted to its trans-diol and then to 4'-hydroxy-1: 2-benzanthracene by dehydration. In these two theories the diol has been considered as the precursor of phenol. Boyland and Wiltshire (6, 8), however, have recently stressed that the processes of phenol formation and diol formation are separate and independent of each other. In this connection the above-stated theories might deservedly be reconsidered.

Daudel (10, 11) postulated that the carcinogen, taking 1: 2-benzanthracene as an example, would combine with tissue at K-region and in this tissue-carcinogen conjugate 4' position would be most reactive, so that oxidation would take place at that position and 4'-hydroxy-1: 2-benzanthracene would be formed. In that paper, however, the calculation was carried out only for the cases of benzene and naphthalene and no quantitative treatment was made for other polycyclic hydrocarbons. Pullman and Baudet (21) pointed out that according to their calculation based on Daudel's model the position which should be theoretically most reactive is not coincident with the position of attack in experiment.

The present authors postulate a model for metabolism of polycyclic aromatic hydrocarbons and will show how the structure of the metabolites formed is explained according to this model. The carcinogen, for example 3: 4-benzpyrene,

\[ 
\begin{align*}
\text{(I)} & \quad \text{+ Y} \quad \text{\rightarrow (II)} \quad \text{+ OH} \\
\text{Y} & \quad \text{H}
\end{align*}
\]

Chart I.-A model of metabolic oxidation of carcinogenic hydrocarbons. Black spot in (I) indicates the position which is most reactive to electrophilic reagents. (Y) represents a certain kind of enzyme which here acts as an electrophilic reagent.

\[ 
\begin{align*}
3:4\text{-BENZPYRENE} & \quad \text{+ Y} \quad \text{\rightarrow (II)} \quad \text{+ OH} \\
(20\pi-\text{ELECTRONS IN 21\pi-ORBITALS}) & \quad \text{Y} \quad \text{H}
\end{align*}
\]

Chart II.-A theoretical interpretation of the electronic structure of carcinogen-enzyme conjugate ((II) in Chart I). The mode of \(\pi\)-conjugation is shown schematically by dotted lines.
would interact with some group, possibly with an enzyme (Y) forming a weak bond at the most reactive 5 position, as shown in Chart I. The electronic structure of this conjugate might be entirely different from that of the original hydrocarbon and is assumed to be in the calculation equivalent to such a model as shown in Chart II. There the most reactive meso-position is attacked by the enzyme, which is here considered as an electrophilic reagent, and the π-electrons are delocalized from the aromatic nucleus to the pseudo-π-orbitals (15, 20) through the loose bond which might be formed between the hydrocarbon and the enzyme. Thus, these pseudo-orbitals act as π-electron acceptors, and the degree of the electron migration can be varied by the value of exchange integral between meso-carbon and the pseudo-orbital. Calculated results show that in this case the qualitative prediction of the position of reaction is not so seriously affected by the value of exchange integral. The present authors consider the conjugation stated above to be very small and take the limit where the exchange integral tends to zero. The Coulomb integral of the pseudo-orbitals is taken as \( \alpha + a\beta \) (20) where \( a \) may be arbitrary so long as \( a \geq 1 \). The frontier electron distribution (20) is calculated according to this model. The results of calculation show that 8 position (indicated by a black spot in (II)) is to be most reactive to a radical reagent in the case of 3, 4-benzpyrene. Accordingly the substitution by OH radical

![Chart III.](image)

*Chart III.* The frontier electron distribution of carcinogen-enzyme conjugates. Numerical values indicate the frontier electron density at each position in the conjugate, and the position where the density is markedly large is shown by a black spot.
would take place at that position, resulting in the formation of 8-hydroxy-3:4 benzpyrene. The positions of hydroxyl group in other metabolites are explained in the same way. The calculated results of the electronic structure of the carcinogen-enzyme conjugates are shown in Chart III. The numerical values represent the frontier electron density for a radical substitution at each carbon atom, and the larger the value is, the more reactive is that position.

From Chart III it is clearly understood that the metabolic oxidation takes place at 8 position in 3:4-benzpyrene and at 4' position in 1:2-benzanthracene. In 1:2:5:6-dibenzanthracene, the frontier electron densities at 4' and 8' positions are a little smaller than the values at 1' and 5' positions where the attack of metabolic oxidation has not been reported. This may be attributed to the steric hindrance there. As for chrysene, the values of frontier electron density at 12 and 1 positions are large and almost equal to each other. Therefore, the expected structures are 12- and 1-hydroxy-chrysenes among which only 1-hydroxy-chrysenes has already been found as a metabolite. Thus, a nearly satisfactory explanation has been given as to the structure of metabolites of polycyclic hydrocarbons.

In Table I, the value of frontier electron density at the principal carcinogenophore (20) of each original hydrocarbons is compared with that of its metabolite. For the original hydrocarbons these values have previously been reported (20) and the values for metabolites are calculated in the same manner. In the course of calculation the Coulomb integral at OH substituent is put equal to $\alpha$ (16, 20). It is seen in Table I that the value of frontier electron density at the principal carcinogenophore decreases remarkably when the hydrocarbon is metabolized.

<table>
<thead>
<tr>
<th>Original Hydrocarbons</th>
<th>The Value of Frontier-Electron Density at Carcinogenophore</th>
</tr>
</thead>
<tbody>
<tr>
<td>3:4-Benzpyrene</td>
<td>0.3025</td>
</tr>
<tr>
<td>1:2-Benzanthracene</td>
<td>0.3435</td>
</tr>
<tr>
<td>1:2:5:6-Dibenzanthracene</td>
<td>0.3714</td>
</tr>
<tr>
<td>Chrysene</td>
<td>0.4100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Metabolites</th>
<th>The Value of Frontier-Electron Density at Carcinogenophore</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-OH-3:4-Benzpyrene</td>
<td>0.1593</td>
</tr>
<tr>
<td>4'-OH-1:2-Benzanthracene</td>
<td>0.2138</td>
</tr>
<tr>
<td>4', 8'-OH-1:2:5:6-Dibenzanthracene</td>
<td>0.2471</td>
</tr>
<tr>
<td>1-OH-Chrysene</td>
<td>0.3728</td>
</tr>
</tbody>
</table>
This result coincides with the well-known fact that the carcinogenicity of polycyclic hydrocarbons is lost or otherwise considerably weakened by the metabolic oxidation. Hence, it may be said that the metabolic oxidation is considered as a process of detoxication. Such a consideration has already been made by Fieser (9) and Dobriner et. al. (13).

If a somewhat speculative discussion is here permitted, the following will be added. There seems to be almost no doubt about the fact that the principal carcinogenophore plays the main role in the course of carcinogenesis. On the other hand, the chemists do not hesitate to recognize that in ordinary chemical reactions the most reactive position is not the principal carcinogenophore but the meso-position in such condensed aromatic hydrocarbons. In the tissue there might exist electrophilic reagents of various sorts and there is no reason to believe that the meso-position is attacked by none of them. It is the opinion of the present authors that the very reaction which is due to the chemical reactivity of meso-position is the combination of carcinogen with tissue at that point, which causes the detoxication, and, moreover, some of the carcinogen molecules which do not come into contact with detoxicating reagents would be subjected to a chemical combination with a certain kind of protein at the principal carcinogenophore, which might become the cause of tumor production.

**Summary**

1. Frontier electron method, one of the quantum-mechanical treatment of chemical reactivity, is applied to the problem of metabolism of carcinogenic polycyclic hydrocarbons and a nearly satisfactory explanation is given as to the well-known fact that the metabolic oxidation of these hydrocarbons takes place at the position different from the point at which oxidation occurs in a test tube.

2. The frontier electron densities at the principal carcinogenophore of the metabolites such as 8-hydroxy-3:4-benzpyrene, 4'-hydroxy-1:2-benzanthracene, 1-hydroxy-chrysene and 4', 8'-dihydroxy-1:2:5:6-dibenzanthracene are obtained. They are much smaller than the values of the original hydrocarbons. This coincides with the experimental result that the carcinogenic activity of polycyclic hydrocarbons is lost or otherwise considerably weakened by metabolic oxidation.

**References**


6) Boyland, E. Different Types of Carcinogenesis and Their Possible Modes of Action; A Review. Cancer Research, 12, 77-84, 1952.


21) Pullman, B., et Baudet, J. Sur le métabolisme des hydrocarbures cancérigènes. Comp-
発癌性炭化水素の代謝産物の構造について

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1. 発癌性芳香族炭化水素の代謝産物は、通常の化学反応における反応様式からは、ほとんど予測できない構造を有している。すなわち、酸化をうけた位置が、通常の試験管内酸化実験で期待される反応位置と一致する傾向に相当している。この事実を説明するために、いろいろの理論が提唱されたが、いずれも不十分なもので、発癌性炭化水素のすべてについて共通に説明を与える理論は見当らない。

著者らは、さきに芳香族炭化水素の化学反応性を説明する理論として、フロンティア電子法を提示し、これによって非置換芳香族炭化水素の発癌性についても満足な説明を与えることができたが、さらにこれら炭化水素の代謝過程にたいしてある仮定を置くことにより、8-オキシン-3,4-ベンツビシン、4'-オキシン-1, 2-ベンツアンスラセン、1-オキシクリレン、4', 8'-ジオキシン-1, 2, 5, 6-ジベンツアンスラセンなど、いままでに構造の決定されているフェノール性代謝産物のすべてについて、その生成の理由をほぼ満足に説明することができた。

2. これら代謝産物の主発癌物（発癌反応における反応位置と考えられる）のフロンティア電子密度は、もとの化合物のそれにくらべていじろしく低下していることがわたった。これは、発癌性化合物が代謝産物に変化すると、発癌性は失われるか、あるいはいじろしく低下するという実験事実と一致する。このことから、従来一、二の研究者によって考えられていたように、発癌性化合物の代謝を一つの解毒過程と考えた。 (文部省科学研究費による)