match no. 15 pp. 251-261 1984

STRUCTURE-ACTIVITY RELATIONSHIPS IN HYDROCARBON CARCINOGENS

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ABSTRACT

The relationship between carcinogenic activity and the structure of polycyclic aromatic hydrocarbon (PAH) is discussed. The K-region or K-bond in the carbon skeleton graph of a PAH is defined in terms of the environments of its vertices. The carcinogenic activity of a hydrocarbon depends upon the symmetry and the relative position of K-bonds in the molecule.

INTRODUCTION

The search of a possible relationship between the structure of aromatic hydrocarbons and their carcinogenic activity is a topic of biological and biochemical interest. The theoretical treatments developed by Pullman[1-4] on the relation between the structure of carcinogens and their activity, suggest

that one region of high electron density[1] ,which was termed as K-region , is of essential importance in the process of carcinogenesis by aromatic hydrocarbons or their metabolites.

Pullman's calculations[1-3] by the Hückel method, and later studies by Herndon[5], correlate carcinogenic activity with a high π-electron density in the K-region. Recent studies of aromatic hydrocarbons based on graph theory[6] and SAMO (simulated ab initio molecular orbital) method[7,8], have correlated a high π-bond order in the K-region with carcinogenicity but also suggested that other factors are involved in carcinogenicity.

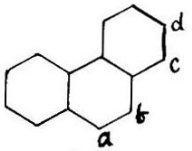
In the present communication an attempt has been made to define the K-region or K-bond in the carbon skeleton graph[9] of the polycyclic aromatic hydrocarbon (PAH). The environment of a vertex in a graph ,defined with respect to the degrees of the neighbouring vertices, has been discussed. A generalized concept of the graph centre,(which also utilizes vertex environments) and its application to polycyclic graphs, has been presented by Bonchev ,Balaban and others[10,11]. Whereas in the present investigation the author has shown that the environments of the vertices of K-bonds and the relative position of these bonds, greatly influence the carcinogenic activity of the aromatic hydrocarbons.

DEFINITIONS

Before discussing the structure-activity relation of PAH carcinogens, let us define some important terms.

1. First neighbours' degree sum (S_{i1}) : The first neighbours' degree sum of a vertex v_i (S_{i1}) in a graph is the sum of the

degrees of the nearest (first) neighbours[12]. For example in the graph I of phenanthrene, the first neighbours' degree sum of the vertex a is 5.



I

2. Vertex enviroment $\mathcal{E}_i$: The environment of a vertex v_i is defined as a sequence $\mathcal{E}_i$,

$$\mathcal{E}_i = (S_{i1}, S_{i2}, S_{i3}, \ldots)$$

where the element S_{ik} is the kth neighbours' degree sum of the vertex v_i (k= 1,2,3,...). The environment of the vertex a in I is,

$$\mathcal{E}_a = (5,8,9,9,\ldots)$$

Since only first four elements of the sequence $\mathcal{E}_i$ provide the necessary information about environment of the vertex, we shall not go beyond this number in our discussion.

3. The environment of a bond : The environment of an edge or bond (i,j) is defined in terms of the environments of the vertices v_i and v_j connecting it. The environment $\mathcal{E}_{ij}$ of the edge (i,j) is a set of sequences $\mathcal{E}_i$ and $\mathcal{E}_j$,

$$\mathcal{E}_{ij} = [(\mathcal{E}_i),(\mathcal{E}_j)]$$
$$= [(S_{i1}, S_{i2}, S_{i3},..),(S_{j1}, S_{j2}, S_{j3},..)]$$

where the elements S_{ik} and S_{jk} are the kth neighbours' degree sums of the vertices v_i and v_j respectively (k= 1,2,3,...).

In phenanthrene I the environment of the bond (a,b) is,

$$\mathcal{E}_{a,b} = [(\ 5,8,9,9,..),(\ 5,8,9,9,...)]$$

4. Symmetry of the environment of a bond : The symmetry of the environment of a bond (i,j) is defined by the nature of the elements S_{ik} and S_{jk} in the sequences $\mathcal{E}_i$ and $\mathcal{E}_j$ respectively,

If $S_{ik} = S_{jk}$ for all values of k, the bond (i,j) is said to have a symmetric environment. In this case,

$$\mathcal{E}_i \equiv \mathcal{E}_j$$

the environments of the two vertices are exactly equivalent. On the other hand if $S_{ik} \neq S_{jk}$ for any value of k, the bond (i,j) will have an asymmetric environment. The bond (a,b) of I has a symmetric environment, for

$$\mathcal{E}_a \equiv \mathcal{E}_b$$

while the bond (c,d) has an asymmetric environment,

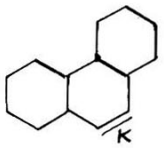
$$\mathcal{E}_{c,d} = [(\ 5,7,9,..),(\ 4,5,5,..)]$$
$$\mathcal{E}_c \neq \mathcal{E}_d$$

5. K-bond in a PAH graph : The K-bond of a PAH molecular graph is defined as a bond for which the environment $\mathcal{E}_K$ has the first neighbours' degree sums of both its ends equal to 5. Therefore ,for a K-bond,

$$S_{ik} = S_{jk} = 5 \text{ for } k=1 \quad \text{in } \mathcal{E}_K$$

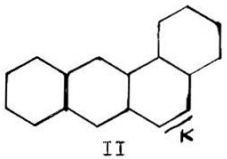
The bond (a,b) in I is a K-bond because, $S_{a1} = S_{b1} = 5$, and the bond (c,d) is not a K-bond. ($S_{c1}=5$ but $S_{d1} = 4$).

The K-bonds of some PAHs are shown below,



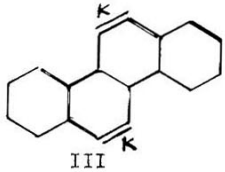
I

Phenanthrene



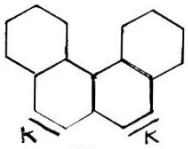
II

1,2-Benzanthracene



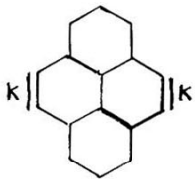
III

Chrysene



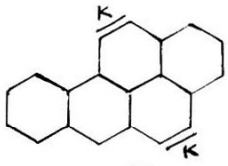
IV

3,4-Benzphenanthrene



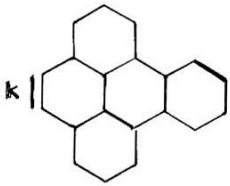
V

Pyrene



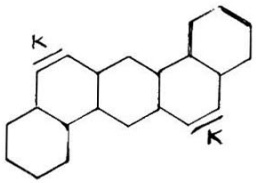
VI

3,4-Benzpyrene



VII

1,2-Benzpyrene



VIII

1,2-5,6-Dibenzanthracene

DISCUSSION

It is known[1-4] that the K-region is a bond of high π-electron density and of high π-bond order[5] plays an important role in hydrocarbon carcinogenesis. Here we consider

The topological structures of polycyclic aromatic hydrocarbons and on the basis of the symmetry of K-bonds and their relative positions in the molecules, we arrive at some important conclusions.

a) The PAHs with asymmetric K-bonds are carcinogenic and the hydrocarbons with symmetric K-bonds are non-carcinogenic[13]. The hydrocarbon , phenanthrene I has a symmetric K-bond and it is non-carcinogenic but 1,2-benzanthracene II is carcinogenic, the environment of the K-bond in II is,

$$[(\ 5,8,10,..),(\ 5,8,9,..)]$$

which is asymmetric ,for the third elements in the equences are non-equivalent. Similarly , pyrene V, and 1,2-benzpyrene VII are non-carcinogenic and 3,4-benzphenanthrene IV, 3,4-benzpyrene VI and 1,2-5,6-Dibenzanthracene VIII are carcinogenic. This is true for the hydrocarbons having one K-bond. For molecules having more than one K-bonds we have another conclusions.

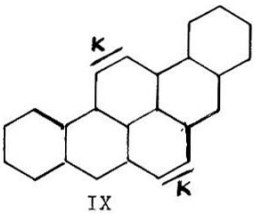
b) The PAH with two symmetric K-bonds of exactly same environments , is non-carcinogenic ,while the one having symmetric K-bonds of different environments ,is carcinogenic. Pyrene V, having two K-bond of same environments,

$[(\ 5,8,10,..),(5,8,10,...)]$ and $[(\ 5,8,10,...),(5,8,10,..)]$

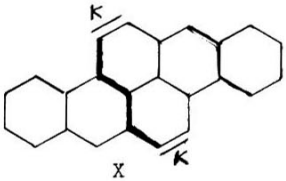
is non-carcinogenic but 3,4-9,10-dibenzpyrene IX with two K-bonds of environments,

$[(5,8,11,..),(5,8,11,..)]$ and $[(5,9,14,..),(5,9,14,..)]$

is carcinogenic.



IX

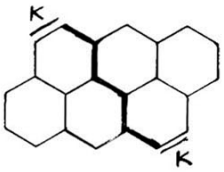


X

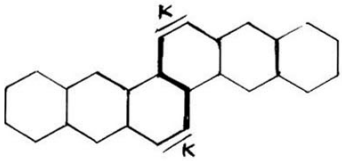
3,4-9,10-Dibenzpyrene 3,4-8,9-Dibenzpyrene

c) The PAHs of even number of cycles with two asymmetric K-bonds are carcinogenic, if the two K-bonds are separated by a chain of edges of even length(shown by bold lines in the corresponding structures) . 3,4-benzphenanthrene IV and 3,4-8,9-dibenzpyrene X, are carcinogenic[14]. They have K-bonds of asymmetric environments ,separated by chains of even lengths (2,4).

The PAHs of even number of cycles are non-carcinogenic if the two K-bonds of asymmetric environments are separated by chains of odd number of edges. For example, chrysene III, anthanthrene XI, anthra[1,2-a]anthracene XII and 1,2-7,8-dibenznaphthacene XIII , are non-carcinogenic.



XI



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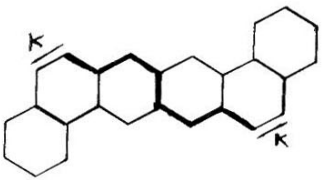
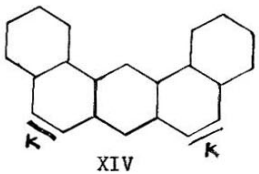


XIII



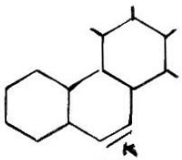
XIV

In the structures III, XI, XII, and XIII the two asymmetric K-bonds are separated by chains of edges of odd length.

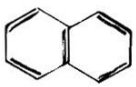
d) The hydrocarbons of odd number of cycles with two asymmetric K-bonds are carcinogenic. 3,4-benzpyrene VI, 1,2-5,6-dibenzanthracene VIII and 1,2-7,8-dibenzanthracene XIV are carcinogenic.

e) Alkyl or amino substitutions[15] in a non-carcinogenic hydrocarbon will result into a carcinogenic product if it introduces an asymmetric K-bond or a similar bond in which the environment has the first neighbours' degree sums equal to 5.

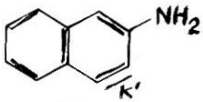
For example phenanthrene I is non-carcinogenic while 1,2,3,4-tetramethyl phenanthrene XV , is carcinogenic[16] for it has an asymmetric K-bond.



XV



XVI



XVII

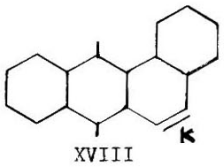
Naphthalene XVI is non-carcinogenic but 2-aminonaphthalene XVII is carcinogenic[17]. The structure XVII has a

bond with the environment, $\mathcal{E}_K$

$$[(\ 5,8,7,..),(5,6,5,..)]$$

whereas in naphtalene XVI , there is no bond of K-type.

f) The carcinogenic activity increases with increasing the asymmetry of the K-bond by substitution. 1,2-benzanthracene II is a mild carcinogen but 7,12-dimethylbenzanthracene XVIII, is a strong cancer producing substance[18].



XVIII

7,12-Dimethylbenzanthracene

The environment of the K-bond in XVIII, is

$$[(\ 5,9,9,...),(\ 5,8,10,...)]$$

which is more asymmetric than that of the same bond in II,

$$[(\ 5,8,10,...),(\ 5,8,9,...)]$$

the second elements are non equivalent in the former.

The structure-activity relationship is an important area of study both in biochemistry and medicine[19]. In a recent paper [20] we have described a correlation between the connectivity index[21] and the chemical reactivity of organic compounds. The present account is a new approach to the structure-activity relations in carcinogens , their metabolites and also other related structures[22].

Acknowledgements . The author is thankful to U.G.C. New-Delhi, for a financial support and to Dr. J.Patterson for his interest in the work.

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