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CORRELATION OF AN ELECTRONIC REACTIVITY INDEX WITH CARCINOGENICITY IN POLYCYCLIC AROMATIC HYDROCARBONS

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Summary. Recent experimental studies indicate that one step in the transformation of polycyclic aromatic hydrocarbon precarcinogens to ultimate carcinogens involves oxidation of a dihydrodiol intermediate to a dihydrodiol epoxide. This step is examined for 25 compounds using a molecular orbital reactivity index, and a strong correlation with carcinogenic activity is found.

Considerable strides have been made recently in understanding the metabolic stages by which polycyclic aromatic hydrocarbons (PAHs) are "activated" and transformed in vivo to mutagenic and carcinogenic end products.[1-10,18] A variety of experimental studies suggests that a principal pathway leading from the original compounds to highly carcinogenic products involves transformations of the form:

Parent hydrocarbon → an epoxide intermediate → a dihydrodiol intermediate → dihydrodiol epoxide → bay region carbonium ion

In some cases presumptive intermediates have been synthesized and shown to be more active than the parent PAHs.[8,9] Involvement of "bay region"[11] carbonium ions has been indicated in recent work [5-9], and it is apparently these strong electrophiles which act as ultimate carcinogens[4], attacking some critical cellular material such as DNA.

Most approaches to PAH carcinogenicity using molecular orbital theory have focused on properties of the parent hydrocarbon. The best known example is the theory of the Pullmans,[12] which relates carcinogenicity to a reactive K region and an unreactive L region, as determined by an index based on a combination of localization energies. Mainster and Memory [13,14] have shown that similar results can be achieved using a simpler index, which is a sum of atomic superdelocalizabilities for the region of interest. The superdelocalizability[15] S_r of atom r is defined as

$$S_r = 2\sum_i \frac{C_{ir}^2}{m_i}$$

where C_{ir} is the coefficient of atom r in MO i, m_i comes from the MO energy $\epsilon_i = \alpha + m_i\beta$, and

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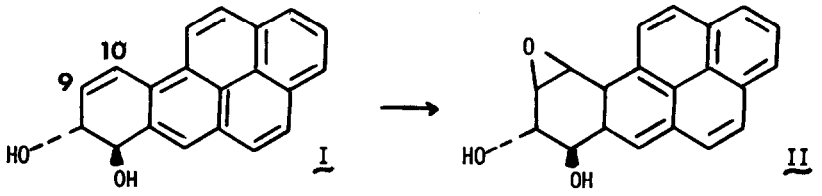
the sum is over all occupied molecular orbitals. In a few cases attention has focused on properties of the ultimate carcinogen carbonium ions [6,7,16]. The recent theory of Jerina and Lehr[6,7] has yielded very suggestive results and drawn attention to the importance of "bay region" carbonium ions.

Here we direct attention to the step involving conversion of the dihydrodiol to the dihydrodiol epoxide, shown below for the well-studied carcinogen benzo(a)pyrene (BP). Formation of the dihydrodiol I causes the nearby 9,10 region bond to become highly activated, thereby preparing it for epoxidation. Potential reactivity at this latter bond can be



represented using a superdelocalizability index of the type employed by Mainster and Memory [13,14]. We shall call this index I_B', the subscript B referring to the bond adjacent to the bay region and the prime indicating the dihydrodiol intermediate. (Note that from the simple π molecular orbital theory viewpoint taken here the initial epoxide and the corresponding dihydrodiol are equivalent.) We have calculated the index I_B' for the 25 compounds examined by Jerina et al.[6,7], and compared the results with the carcinogenic potencies of these compounds. The results are listed in Table 1.

It is apparent that a good correspondence exists between the index I_B' and carcinogenic activity in these compounds, of the same order of accuracy as the Pullman K and L theory [12,13] and the alternative bay region carbonium ion approach [6,7]. Correspondence, of course, does not necessarily imply causation. None-the-less, the results would appear to lend theoretical support to the idea that the specific metabolic transformation under consideration is important for carcinogenic activity in these compounds. (Experimentally, it has been found that I and its analog in benzo(a)anthracene are substantially more carcinogenic/mutagenic than their parent hydrocarbons[8,9].) We suggest that in future studies of carcinogenicity by PAH compounds all stages of metabolic transformation be considered using appropriate indices. Elsewhere[17], we demonstrate that the index I_B' helps to provide a satisfactory explanation for variations in carcinogenic activity of the monomethyl derivatives of chrysene, a system that has heretofore defied explanation. We are also preparing a comprehensive examination of reactivity indices suitable for use in the above framework.

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Table 1. Relationship between the Superdelocalizability Index I_B' and Carcinogenic Activity[a]

Compound	I_B'	Carcinogenic Activity[b]
Dibenzo(a,i)pyrene	2.407	++++
Dibenzo(a,h)pyrene	2.390	++++
Benzo(a)tetracene	2.375	-[c]
Tribenzo(a,e,i)pyrene	2.361	++
Benzo(a)pyrene	2.358	++++
Dibenzo(a,l)pyrene	2.353	++++
Dibenzo(a,e)pyrene	2.335	+++
Benzo(a)anthracene	2.333	+[d]
Dibenzo(a,h)anthracene	2.318	++
Benzo(g)chrysene	2.309	++
Dibenzo(a,c)anthracene	2.308	+
Dibenzo(a,j)anthracene	2.307	+
Hexacene	2.303	?
Benzo(e)pyrene	2.301	+
Triphenylene	2.275	-
Pentacene	2.275	-
Naphtho(2,3-b)pyrene	2.274	++
Picene	2.273	-
Phenanthrene	2.272	-
Benzo(b)chrysene	2.264	-
Chrysene	2.261	+
Tetracene	2.242	-
Benzo(c)phenanthrene	2.238	+
Anthracene	2.205	-
Naphthalene	2.177	-

a. In a number of compounds more than one dihydrodiol epoxide can be formed; in such cases the highest I_B' value has been selected.

b. See ref 7; also J.C. Arcos and M.F. Argus, Adv. Cancer Res. 11, 305 (1968), W. Herndon, Trans. N.Y. Acad Sci. 36, 200 (1974).

c. Has two reactive L regions.

d. Reactive L region; see ref. 13.

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11. A "bay region" is a concave exterior region of a PAH bordered by three benzene rings, at least one of which is a terminal ring. The simplest example is the region between carbons 4 and 5 of phenanthrene.

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