A close Relationship between Carcinogenicity and Self-atom Polarizability Index of Polycyclic Aromatic Hydrocarbons and Their Metabolites

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Self-atom polarizability were calculated for 17 polycyclic aromatic hydrocarbons and their metabolites by LCAO-MO method and examined the relation with the carcinogenicity. It has been found that $\pi_{1,2,4}$, the sum of self-atom polarizability of 1, 2 and 4 positions forming *trans*-butadiene frame in a compound, agree quite well with the observed carcinogenic activity, and also, $\pi_{1,2,4}$ value increase with the metabolic activiting in agreement with the experimental facts that parent carcinogens activated with metabolism. Accordingly, we suggest that the 1, 2 and 4 positions in the carcinogenic compounds play the most important role in the process of chemical carcinogenesis, and also self-atom polarizability, as one of theoretical reactivity indices, is to be used as a measure of carcinogenic activity.

Introduction

It has been known that benzo(a)pyrene(BP) are metabolized *in vivo* to reactive intermediates that become covalently bound to cellular macromolecules. There is also evidence that this binding is a critical event in the process of carcinogenesis. Summarizing numerous results studied so far, a primary path by which BP is metabolically activated and transformed *in vivo* from precarcinogen to ultimate carcinogen is believed to consist of the states shown in Chart 1.[1]

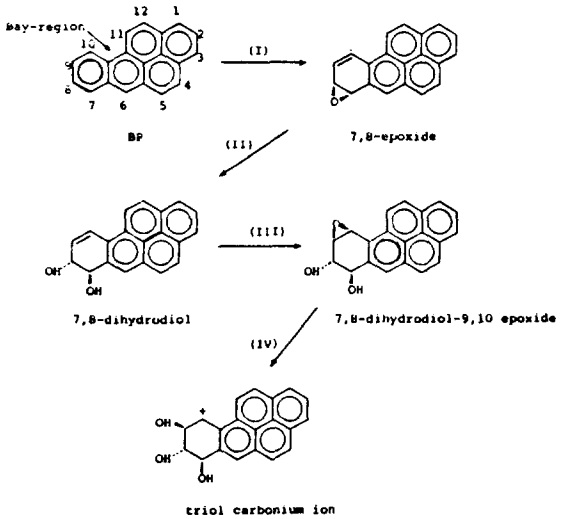
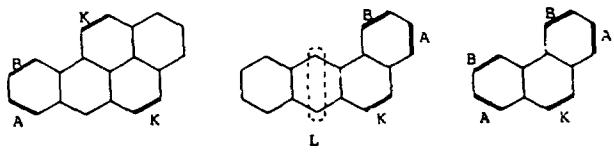


Chart 1. Metabolic steps of Benzo(a) pyrene.

In step (I) of chart 1, BP is activated *via* a cellular monooxygenase to form its 7,8-epoxide. In step (II), epoxide hydrase assists conversion of the 7,8-epoxide to the 7,8-dihydrodiol. Experimentally, the 7,8-dihydrodiol is found to be more effectively converted to mutagenic and carcinogenic metabolites than BP itself or dihydrodiols formed at other positions.[2] Saturation of the 7,8-bond activates the 9,10-bond, leading to step (III) in which the 7,8-dihydrodiol BP is transformed to the 7,8-dihydrbdiol-9,10(bay-region) epoxide. Strong support for the importance of this step has come from the experimental observation that the product BP diol-epoxides have exceptionally high carcinogenic activity. In step (IV) the 7,8-diol-9,10 epoxide BP converts spontaneously to the triol BP carbonium ion which acts as ultimate carcinogens.

One should develop a new model to explain the above facts that have gradually higher carcinogenicity with metabolic activation according to Chart 1. To do this, Jerina *et al.* have proposed the "bay-region theory" to give a theoretical explanation supporting the importance of transformation shown in Chart 1. They have shown that bay-region diol-epoxides should form carbonium ions (ultimate carcinogens) more easily than other diol-epoxides.

Recently, Smith *et al.* have reviewed in much greater detail the theoretical indices on the basis of the steps of Chart 1. They have defined two new regions other than customarily defined by the K-region and L-region, that is, A-region and B-region.[3] The A-region and B-region are the presumptive initial epoxidation site on the terminal ring of the bay-region and the site of final epoxidation on the terminal ring of the bay-region on a bond adjacent of the bay-region, respectively. (*See below*)



They have shown that formation of the A-region dihydrodiol significantly activates the B-region bond by using index I_B, which is the sum of the two atomic superdelocalizabilities, involved in B-region bond. Also, they have shown that the net π-electron charge Q_b ($Q_b = 1-q_b$, where q_b is the π-electron density) at the benzylic carbon position b of the trihydrotriol , with acts as the final metabolic species, is correlated with carcinogenicity.

Both ΔE_π, the π-energy loss in forming the dihydrodiol-epoxide from the A-region dihydrodiol (step (III) in Chart 1) and ΔE_π, the π-enegy change in forming the trihydrotriol carbonium ion from the dihydrodiolepoxide (step (IV) in Chart 1) have been shown a strong correlation with carcinogenic ac-

tivity.

As stated above Smith *et al.* used several reactivity indices in being related reactions such as those in Chart 1 to the carcinogenic activity of these compounds. Since it is accompanied by complicated calculations and confused our idea to use several reactivity indices in explaning the progress of carcinogenesis. It is necessary to explore more convenient theoretical reactivity and a new reactive region in compounds. It has been shown in our earlier reports that the electron density in the lowest unoccupied molecular orbital (LUMO), which can be regarded as a measure of electrophilicity, is a potentially useful index, and the 1, 2, and 4 positions forming *trans* butadiene form in a molecule are important region in elucidating the mechanism of carcinogenesis.[4,5]

That is, $q_{1,2,4}^{LUMO}$value the sum of LUMO electron densities of the 1, 2 and 4 positions (we called these positions the *trans* 1,2,4, region) has been shown to be commonly above 0.5 for some series of parent compounds as well as PAH's. In addition, $q_{1,2,4}^{LUMO}$value has been shown to increase gradually with metabolic activating parent compounds.

In the present paper, we have examined the properties of 17 representative PAH's and their presumptive metabolites in Chart 1 on the basis of self-atom polarizability of 1, 2 and 4 atoms in the *trans* 1, 2, 4 region.

Theory and Model

MOs Φ_μ of energy E_μ are expressed in terms of the component AOs ϕ_i by the simple Hückel molecular orbital theory:

$$\Phi_\mu = \sum_i a_{\mu i}\phi_i \tag{1}$$

Applying these MOs to the intramolecular perturbation theory,[6] we can obtain self-atom polarizability of i atom, a useful reactivity index:

$$\pi_{i,i} = 4 \sum_{\mu}^{occ} \sum_{\nu}^{unocc} \frac{a_{\mu i}^2 \cdot a_{\nu i}^2}{E_\mu - E_\nu} \tag{2}$$

Where, $\sum_{\mu}^{occ}$ implies the summation over the μ occupied orbitals; $\sum_{\nu}^{unocc}$ does the summation over the ν unoccupied orbitals.

Parameters for hetero-atom are adopted: $\alpha_O = \alpha_C + 0.6\beta$, α_C of adjacent carbon atom = $\alpha_C + 0\beta$ and $\beta_{C-O} = 0.7\beta$ for $-O-$; $\alpha_{OH} = \alpha_C + 2\beta$, α_{C-OH} of adjacent carbon atom = $\alpha_C + 0.2\beta$ and $\beta_{C-OH} = 0.6\beta$ for $-OH$.

We shall take the same model as that in the previous papers, in which the *trans* 1, 2 and 4 positions in a molecule has shown to be important region in explaining the progress of carcinogenesis. The *trans* 1, 2 and 4 positions are illustrated all compounds treated here in Chart 2.

Results and Discussion

Chart 2 designates the *trans* 1, 2 and 4 position for each compound and self-atom polarizability calculated by equation(2).

In Chart 1, formation of A-region dihydrodiol activated B-region, transforming to the 7,8-dihydrodiol-9,10 epoxide. It is necessary to give a theoretic evidence to see whether A-region dihydrodiol activated B-region. To do so, the sum of self-atom polarizabilities at two carbon atoms of B-region should be abtained:

$$\pi_{9,10} = \pi_{9,9} + \pi_{10,10} \tag{3}$$

Values of $\pi_{9,10}$ for the parent PAH's and the A-region dihydrodiol forms are summarized in Table 1. It can be seen that formation of the A-region dihydrodiol significantly activates the B-region bond, as shown by the higher value of index $\pi_{9,10}$ in the dihydrodiol than in the parent PAH without exception.

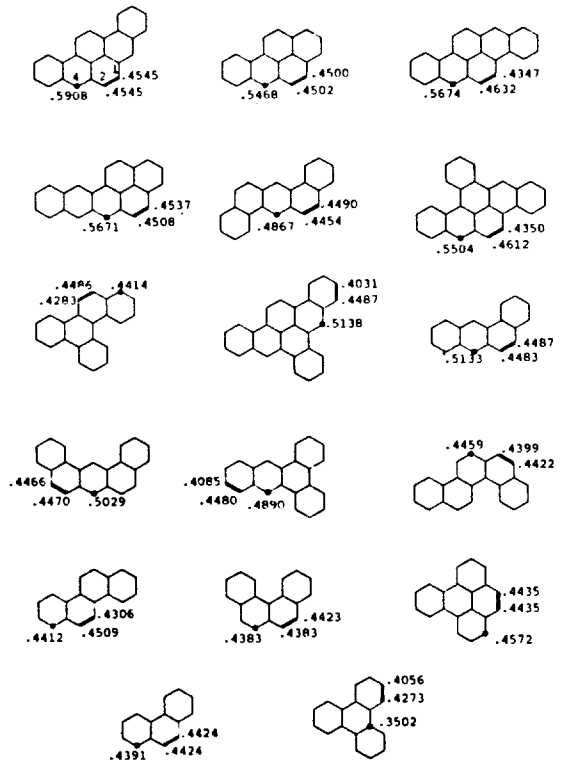


Chart 2. Self-atom polirizability($\pi_{r,r}$) of the *trans* 1,2,4 region for PAH's.

Table 1. Sum of Self-atom Polarizability at two Carbons of B-region for Parent PAH's and Dihydrodiol Forms ($\pi_{9,10}$)

Compound	$\pi_{9,10}$ ($1/\beta$)	
	Parent PAH	Diol-form
Dibenzo(a,i)pyrene	0.8481	0.8543
Benzo(a)pyrene	0.8487	0.8541
Dibenzo(a,h)pyrene	0.8516	0.8569
Naphtho(2,3-a)pyrene	0.8639	0.8692
Dibenzo(a,h)anthracene	0.8386	0.8441
Tribenzo(a,e,h)pyrene	0.8474	0.8528
Benzo(g)chrysene	0.8436	0.8491
Tribenzo(a,e,i)pyrene	0.8448	0.8501
Benzo(a)anthracene	0.8387	0.8441
Dibenzo(a,j)anthracene	0.8390	0.8445
Benzo(c)chrysene	0.8400	0.8455
Dibenzo(a,c)anthracene	0.8334	0.8390
Chrysene	0.8402	0.8457
Benzo(c)phenanthrene	0.8423	0.8478
Benzo(e)pyrene	0.8340	0.8396
Phenanthrene	0.8378	0.8433
Triphenylene	0.8328	0.8384

Table 2. Comparison of Carcinogenicity Potency and Self-atom Polarizability ($\pi_{1,2,4}$) for the *trans* 1,2,4 Region PAH's and Their Metabolites

Compound	$\pi_{1,2,4}$ (1/β)				Carcinogenicity Index[a]	
	Parent	Epoxide	Diol	Diol-epoxide	Arcos and Argus	Jerina *et al.*
Dibenzo(a,i)pyrene	1.4597	1.4902	1.4600	1.4980	74	+ + + +
Benzo(a)pyrene	1.4470	1.4561	1.4455	1.4649	73	+ + + +
Dibenzo(a,h)pyrene	1.4653	1.4723	1.4636	1.4852	70	+ + + +
Naphtho(2,3-a)pyrene	1.4716	1.4750	1.4712	1.4790	27	+ +
Dibenzo(a,h)anthracene	1.3811	1.3996	1.3813	1.4074	26	+ +
Tribenzo(a,e,h)pyrene	1.4466	1.4777	1.4469	1.4794	20	?
Benzo(g)chrysene	1.3183	1.3725	1.3067	1.3858	17	+ +
Tribenzo(a,e,i)pyrene	1.3656	1.3788	1.3657	1.3798	16	+ +
Benzo(a)anthracene	1.4103	1.4295	1.4106	1.4386	5	+
Dibenzo(a,j)anthracene	1.3965	1.4158	1.3968	1.4237	4	+
Benzo(c)chrysene	1.3280	1.3364	1.3281	1.3364	10	?
Dibenzo(a,c)anthracene	1.3455	1.3593	1.3460	1.3572	3	+
Chrysene	1.3227	1.3331	1.3229	1.3334	3	+
Benzo(c)phenanthrene	1.3188	1.3377	1.3189	1.3424	4	+
Benzo(e)pyrene	1.3443	1.3525	1.3346	1.3525	2	+
Phenanthrene	1.3240	1.3431	1.3242	1.3494	0	–
Triphenylene	1.1277	1.1329	1.1276	1.1327	0	–

[a]Reference 3.

This is consistent with the result that are already abtained by Smith *et al.* by using superdelocalizability index. We now examine self-atom polarizabilities of species at the individual stages in Chart 1 and associated *trans* 1,2,4, region.

Sums of self-atom polarizabilities at the *trans* 1, 2 and 4 positions indicated in Chart 2 are expressed as follows:

$$\pi_{1,2,4} = \pi_{1,1} + \pi_{2,2} + \pi_{4,4} \quad (4)$$

Calculations are made $\pi_{1,2,4}$ for parent compounds and their metabolites in Chart 1 according to equation(4). A comparision between $\pi_{1,2,4}$ and carcinogenic potency is shown in Table 2.

A general tendency which can be seen in Table 2 is the increase in the $\pi_{1,2,4}$ values with metabolic activating. This suggest that the carcinogenic process for these compounds involves a series of metabolic transformations that convert the relatively inert parent PAH's into highly carcinogenic metabolites. As seen in Table 2, $\pi_{1,2,4}$ values for A-region dihydrodiol is lower than that for A-region epoxide. This support Smith's result that K-region bond (this corresponds to 1 and 2 positions in Chart 2) is deactivated while B-region is activated for the formation of A-region dihydrodiol.

Also, $\pi_{1,2,4}$ values for parent compounds as well as for the corresponding dihydrodiol epoxides can be seen to correlate rather well with carcinogenic activity. As a result, it has been found that self-atom polarizability index can be used as a measure of carcinogenic activity of compounds, especially proper *trans* 1, 2 and 4 positions in a molecule are reconfirmed to be an important region in the process of carcinogenesis. We have shown elsewhere the *trans* 1,2,4 region play an important role in elucidating the mechanism of carcinogenesis.[4,5]

Conclusion

There have been proposed numerous theoretical models attempting to correlate reactivity indices from molecular orbital theory with carcinogenicity, such models proposed thus far have focused attention on properties of the parent compounds, not on carcinogenic process.

According to the present picture, the *trans* 1,2,4 region appears to act as an important one in the process of carcinogenesis, since sums of self-atom polarzability of three carbon atoms in the *trans* 1,2,4 region have been explained to increase with metabolic activation.

In other words, carcinogenicity of the parent PAH's have interpreted to increase with activating them according to the present model in agreement with experimental evidence.

In conclusion, a proper *trans* 1,2,4 region in a compound is believed to be a characteristic reactive one in carcinogenic process and so we convince that the *trans* 1,2,4 region could be greatly helpful to elucidate the mechanism of chemical carcinogenesis.

References

1. (a) A. Borgen, H. Darvey, N. Castagnoli, T.T. Crocker, R.E. Rasmussen and I.Y. Wang, *J. Med. Chem.* **16,** 502 (1973); (b) E. Boyland, *Yale J. Bio. Med.*, **20,** 321 (1948); (c) P. Daudel, M. Duquesne, P. Vigny, P.L. Grover and P. Sims, *Federation European Biochem. Soc. Letters,* **57,** 250 (1975); (d) P.B. Hulbert, *Nature,* **256,** 146 (1975); (e) A.M. Jeffrey, K.W. Jennette, S.H. Blobstein, I.B. Weinstein, F.A. Beland, R.G. Harvey, H. Kasai, I. Mivra and K. Nakanishi, *J. Am. Chem. Soc.*, **98,** 5714 (1976).
2. (a) D.M. Jerina, *Nature,* **266,** 378 (1977); (b) P. Sims, P.L. Grover, A. Swaisland, K. Pal and A. Hewer, *Nature,* **252,** 326 (1974); (c) D. M. Jerina, *J. Am. Chem. Soc.*, **99,** 2358 (1977).
3. I.A. Smith, G.D. Berger, P.G. Seybold and M.P. Serve, *Cancer Res.*, **38,** 2968 (1978).
4. B.K. Park, *J. Korean Chem. Soc.*, **24,** 225 (1980).
5. B.K. Park, M.H. Lee and S.T. Do, *Bull. Korean Chem. Soc.*, **6,** 103 (1985).
6. A. Streitwieser, Jr., *"Molecular Orbital Theory for Organic Chemists,"* John Wiley & Sons, Inc., New York, 1961.