

On the Problem of the Connection between the Electronic Structure of Polynuclear Aromatic Hydrocarbons and Their Carcinogenic Effect

J. KOUTECKÝ AND R. ZAHRADNÍK

(*Institute of Physical Chemistry, Czechoslovak Academy of Sciences, and Institute of Industrial Hygiene and Occupational Diseases, Prague 2, Czechoslovakia*)

SUMMARY

On the basis of exact values of atomic localization energies and ortho-localization energies, the validity of the theory of A. Pullman and B. Pullman was investigated concerning the relation between the electronic structure and carcinogenic effect of aromatic hydrocarbons. The application of exact values of localization energies has led to almost the same results as obtained by the Pullmans. By means of exact superdelocalizabilities, a criticism of the theory of the relation between carcinogenic effect and electronic structure suggested by Nagata, Fukui, Yonezawa, and Tagashira was undertaken. The sums of atomic localization energies, exact superdelocalizabilities, and self-polarizabilities of the atoms of this region can be defined as new indices of the reactivity of the K-region, since they offer the same statements on the reactivity as the combined indices introduced by A. Pullman and B. Pullman. Special advantages for rapid orientation are presented by the application of indices based upon the easily obtainable superdelocalizabilities.

In the post-war years several theories have been suggested concerning the relation between the electronic structure of polycyclic aromatic hydrocarbons and their derivatives, on the one hand, and their carcinogenic effect, on the other hand. In the majority of these theories the carcinogenic effect is related to the reactivity of the K-region and L-region of these compounds (29). Formerly static indices were used to characterize the reactivity of the K-region (cf. Coulson's report [10]). In more recent investigations the ortho- or para-localization energy has been used to estimate the rate constants (7, 12) of the formation of a protein complex with the K-region or L-region of the hydrocarbon (18, 36, 37), or the reactivity of these regions has been expressed by combined dynamic indices (28-30). In both these theories the considerable reactivity of the K-region and the small reactivity of the L-region, insofar as this region exists, are simultaneously considered as a necessary and sufficient condition of the carcinogenic effect. Chalvet and Daudel (6) calculated the localization energy of hydrocarbons, interest-

ing from the viewpoint of carcinogenic effect, with regard to hyperconjugation, using the parameters of Muller and co-workers (25). Chalvet and Moser (8) used as an index of carcinogenic effect the difference between the highest occupied and the lowest unoccupied level of the pertinent hypothetical complex. A model of the complex of a hydrocarbon and a cell acceptor was also used by Pullman and Baudet (32), who characterized the linkage of the hydrocarbon to the cell acceptor by parameters used for quinonoid systems. The reactivity of the K-region was also estimated by means of parameters connected with the removal of the orbital of the bond pertaining to this region (1).

Another explanation of the role of a carbon atom of the mesoanthracene type (subsidiary carcinogenophore) in the initiation of a carcinogenic process was suggested by Nagata, Fukui, and co-workers (26), whose concept has been recently criticized by Pullman (31). Nagata *et al.* used as a reactivity index the frontier-electron density for the approximate superdelocalizability (16).

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Setting out from the Szent-Györgyi concept of the semiconductivity of proteins (15, 35) which was experimentally proved (5), Mason (22-24) suggested a theory of initiation of carcinogenic processes, based upon the theory that the electron is transferred from the protein to the hydrocarbon. In addition to some unclear points in the basis formulation (cf. the general discussion [14]), it seems unsatisfactory that in this theory the application of the approximation of the MO-LCAO

3,4,9,10-dibenzpyrene and inactive 1,2-benzpyrene (9, 30).

As is evident from the above brief survey, the theories of carcinogenic effect can be divided into two groups. Into the first group we may place the theories considering as the criterion of carcinogenic effect the reactivity of a certain part of the hydrocarbon, and into the second group theories considering magnitudes decisive for an easy transfer of the electron between the hydrocarbon and the biological substrate.

In the present work are analyzed on the basis of exactly calculated indices the theory of A. Pullman and B. Pullman and the theory of the Japanese authors, which both belong to the first group. In the hitherto published works indices were calculated, characterizing the carcinogenic effect in the framework of both theories by means of approximate magnitudes. The combined indices of A. Pullman and B. Pullman (29)¹ are calculated by means of an estimate (27) of Wheland's localization energy from the reactivity number (13) and by means of an estimate of the ortho-localization energy according to Brown's empirical rule for the calculation of the annelation energy (3, 4). Nagata, Fukui, and co-workers (26) characterize the reactivity of the K-region by the sum of the approximate superdelocalizabilities, and the reactivity of the "subsidiary carcinogenophore" by the pertinent superdelocalizability.

METHODS USED

The atomic localization energies, accurate and approximate superdelocalizabilities, self-polarizabilities, and free valences have been critically surveyed and supplemented in a recent paper (20) for a number of important polycyclic aromatic hydrocarbons (Chart 1).

For the calculation of the combined indices of A. Pullman and B. Pullman it was also necessary to supplement some accurate values of ortho-localization energies. The calculation was carried out according to the relation (19),

$$L_{jj}L_{kk} - |L_{jk}|^2 = 0, \quad (1)$$

¹ The Pullman index for the K-region is defined as the sum of the ortho-localization energy of the bond between the atoms forming the K-region and the smaller atom localization energy of these two atoms. Similarly, the index for the L-region is defined as the sum of the para-localization energy of two atoms belonging to the position of meso-anthracene type and the smaller atom localization energy of these atoms. Atom localization energy is defined as the difference between the π -electron energy of the parent hydrocarbon and the π -electron energy of the torso remaining after the removing of the p_z orbital of the carbon atom which reactivity is considered. The ortho- and para-localization energies are defined analogously, but the torso is formed with the putting out of p_z orbitals of two atoms belonging to the ortho- and para-positions, respectively.

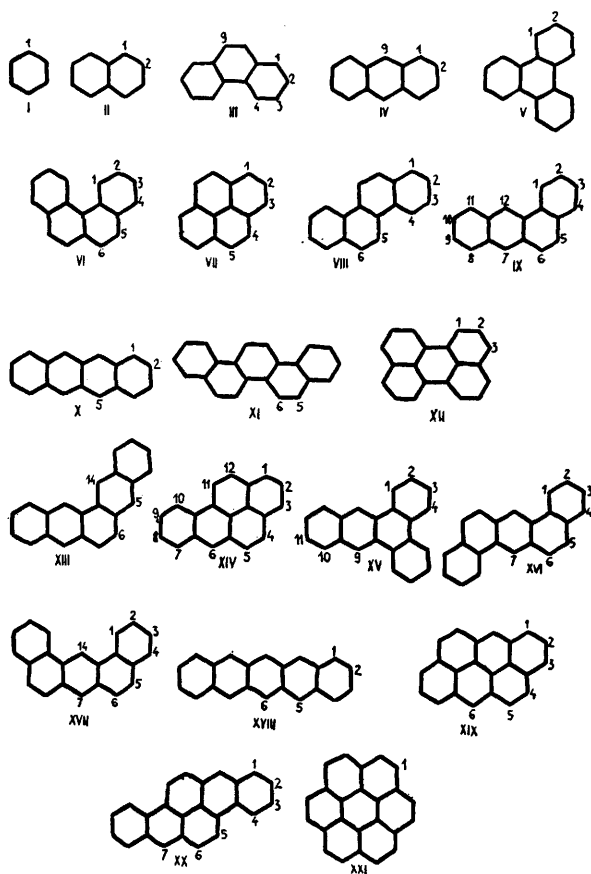


CHART 1.—Various polycyclic aromatic hydrocarbons considered in this paper.

method given by Hückel and Wheland leads in some cases to differing theoretical predictions. At the same time it seems that it is not the matter of minor changes caused by another approximation, but that the Mason criterion itself is extremely sensitive to the approximation used. Therefore, the agreement between the prediction and the carcinogenic activity found experimentally should not be overestimated. This does not mean that the concept of the importance of electron transfer in chemical carcinogenesis is wrong. Moreover, we have found that the criterion suggested by Mason does not apply to carcinogenic 1,2,3,4- and

where

$$L_{jk} = \sum_{m=1}^N \frac{c_{mj} \bar{c}_{mk}}{W - E_m}, \quad (2)$$

except when, by the removal of the carbon atoms of the K-region from the conjugation, no hydrocarbon is formed. This latter situation has already been treated elsewhere by the MO-LCAO method. The subscripts j, k denote the orbitals taken out of conjugation in the calculation of the ortho-localization energy; c_{mj} denotes the coefficient for the j -th atomic orbital in the molecular orbital, whose energy is E_m . N is the number of atoms in the molecule, and W the sought orbital energy of the molecule formed by taking out the j -th and k -th orbitals.

If the disconnection of two orbitals from the conjugation leads to a hydrocarbon consisting of two aromatic parts connected by one bond ("polyphenyl type"), it is more advantageous to calculate the orbital energy of this system by attaching these partial systems to each other. The orbital energy of the composed system can then be calculated according to equation (14) in the cited work (20).

The results of these calculations together with data taken from the literature are summarized in Table 1. The first of the mentioned methods was employed to ascertain the π -electron energy of 2,3-benzchrysene (XXII) (30.8389 β), and the second method for the determination of the π -electron energy of 2-phenylphenanthrene (XXIII) (27.9356 β) and 3-phenylphenanthrene (XXIV) (27.8333 β).²

² The energies pertaining to the individual molecular orbitals of the compounds (XXII-XXIV) are at the disposal of the authors.

RE-EXAMINATION OF THE THEORY OF A. PULLMAN AND B. PULLMAN

The combined indices, calculated according to these authors by means of exact values of localization energies, are compared with estimations of these indices (29) in Table 2. It is evident that the application of exact values involves in principle

TABLE 1
ORTHO-LOCALIZATION A_o AND PARA-LOCALIZATION A_p ENERGIES OF POLYCYCLIC AROMATIC ALTERNATE HYDROCARBONS

Substance	Position	A_o^*	Position	A_p^*
I	1-2	1.528		
II	1-2	1.259 (19)		
III	9-10	1.065 (19)		
IV	1-2	1.21 (34)	9-10	3.314 (11)
V				
VI	5-6	1.10 (29)		
VII	4-5	1.056 (19)		
VIII	5-6	1.12 (29)		
IX	5-6	1.03 (29)	7-12	3.419 (11)
X	1-2	1.19 (33)	5-12	3.249 (11)
XI	5-6	1.106		
XII				
XIII	6-7	1.013 (2)	5-14	3.449 (11)
XIV	4-5	1.034 (11)		
	11-12	1.122 (11)		
XV			9-14	3.494 (11)
XVI	5-6	1.044	7-14	3.514 (11)
XVII	5-6	1.046	7-14	3.513 (11)
XVIII			6-13	3.178 (11)
XIX	4-5	1.028 (11)		
XX	5-6	1.089		
XXI	1-2	1.147 (11)		

* Ortho-localization energy, A_o , is defined as the difference between the π -electron energy of the parent hydrocarbon and the π -electron of the torso remaining after the removing of two carbon p_z orbitals in ortho-position. The para-localization energy, A_p , is defined analogously for a pair of carbon p_z orbitals in para-position.

TABLE 2
COMPARISON OF EXACT VALUES OF COMBINED REACTIVITY INDICES WITH THEIR ESTIMATES GIVEN BY A. PULLMAN AND B. PULLMAN

SUBSTANCE	K-REGION		L-REGION		CARCINOGENIC ACTIVITY (29)
	Exact value	Estimate (28)	Exact value	Estimate (28)	
XX	3.26	3.17			++++
XIX	3.27	3.23			++++
XVI	3.30	3.30	5.64	5.69	++
XVII	3.31	3.31	5.60	5.66	+
VI	3.40	3.41			+
IX	3.29	3.29	5.47	5.53	μ
XIX	3.26	3.20			
XIII	3.25	3.23	5.50	5.56	
VII	3.33	3.33			
III	3.36	3.37			
XI	3.36	3.37			
VIII	3.37	3.38			
XXI	3.45				

no change in the findings of the mentioned authors. The critical value of the combined indices for the L-region, however, must be reduced to 5.60β when exact values are used, whereas the critical value of the index for the K-region remains unchanged (3.31β). Although it was shown (20) that the dependence of the reactivity number on the atomic localization energy is not so exact as to permit an accurate estimate of the atomic localization energy by means of the reactivity number, this dependence is nevertheless divided into partial dependences for certain classes of positions in the hydrocarbon which are very close. Since the positions considered for the calculation of the combined index in the K-region belong to the same class, and even subclass (cf. [20]), and, similarly, the positions considered in the

the considerable approximations on which the employed method of calculating quantum-mechanical magnitudes is based.

CRITICISM OF THE THEORY OF NAGATA, FUKUI, AND CO-WORKERS

Table 3 presents a comparison of the values of the combined indices of A. Pullman and B. Pullman with the sums of the reactivity indices of carbon atoms in the K-region for the hydrocarbons treated in our preceding work (20). As is evident, the characterization of the K-region by the sum of accurate superdelocalizabilities of the pertinent carbon atoms leads to approximately the same order of the K-regions in the individual hydrocarbons as the combined Pullman index. It is also obvious that the high reactivity of the L-

TABLE 3
CHARACTERISTICS OF THE REACTIVITY OF THE K-REGION

Index*	Order†	($i_n - i_l$) (of resp. units)
According to A. and B. Pullman		
S	XIII < XX < XIX < XIV < IX < XVI < XVII < VII < XI < III < VIII < VI < XXI	0.200
A	XX > XIX > XIII > XIV > IX > XVI > XVII > VII > XI > VIII > III > XXI > VI	0.199
π_{ii}	XIII < XIX < XX < XIV < IX < XVI < XVII < VII < XI < VIII < III < XXI < VI	0.156
F	XIII > XIX > XIV > XX = XVII > IX > XVI > VII > III > XI > VIII > VI = XXI	0.098
	XIII > IX > XIV > XIX > XVI = XVII > XX = VII = III > VI = XI > XXI > VIII	0.019

* The sum of superdelocalizabilities, S ; atomic localization energies, A ; self polarizabilities, π_{ii} ; and free valences, F , of atoms belonging to the K-region.

† In cases where the difference of two consecutive indices is less than or equal to ± 0.002 of the respective units, the symbol \leq is used.

calculation of the index of the L-region belong all into another single class, the procedure employed by A. Pullman and B. Pullman did not result in a change of the order of the reactivities of the individual compared positions. 3,4-Benzphenanthrene and 1,2-benzanthracene thus appear again as noncarcinogenic and anthanthrene as carcinogenic, contrary to experimentally ascertained facts. For this reason, it seems especially important to study more thoroughly the causes of the anomalous behavior of these compounds in the framework of this theory (cf. [29]).

There has been criticism (17, 21) that the differences between the indices for carcinogenic and noncarcinogenic substances are very small. With the use of exact values, these differences have further diminished; the maximum deviation from the critical value of the criterion for the K-region in a carcinogenic substance is -0.05β . It is a problem requiring detailed study whether such small differences are significant with regard to

region must be considered as an obstacle in the initiation of the carcinogenic process. In the explanation by Nagata and co-workers (26) difficulties are encountered mainly in the case of pentaphene. This circumstance was in principle already pointed out by Chalvet and Daudel (6), who showed that the accurately calculated localization energies lead, for the model of Muller, Pickett, and Mulliken (25), to approximately the same order of estimates of the reactivity of the K-region as the ortho-localization energy.

Nagata, Fukui, and co-workers employed approximate superdelocalizabilities. It was shown, however, that the correlation between the approximate superdelocalizability and the exact superdelocalizability is not very close and that there exist, especially in cases important from the viewpoint of carcinogenic effect, considerable deviations from the continuous course of the interdependence of these two magnitudes. It is interesting that Nagata and co-workers, when dis-

cussing the carcinogenic effect, use in some cases a higher approximation of the superdelocalizabilities, whereby, however, the data given by them become heterogeneous.

CHARACTERIZATION OF THE K-REGION BY SUM INDICES

The parallel courses of the various reactivity indices depending on the atomic localization energy show that the characterization of the atoms of the same class of hydrocarbons by means of different reactivity indices leads to approximately the same order of the reactivities of the individual atoms. This circumstance induced us to characterize the reactivity of the K-region by the sum of the reactivity indices of the individual atoms (Table 3). Such a procedure, however, has already been customary in using the free valence (10) but has not been employed in the cases of localization energy and superdelocalizability.

Approximately the same order as given by the Pullman index is not only obtained by the sum of the superdelocalizabilities but also by the sum of atomic localization energy. A similar order is also attained by using the self-polarizabilities and free valences, but the results are distorted owing to the very small differences between the individual values. The orders following from these two indices are in this and similar cases not in agreement, and it is therefore natural that the application of free valences was discarded. It would be possible, of course, to achieve by more accurate calculations a more exact determination of the order according to these indices, but the question arises whether the simplifying assumptions on which the calculation is based would not here exert an especially disturbing influence. The application of the ortho-localization energy as characteristic of the K-region leads to the prediction of carcinogenic inefficiency of 3,4,8,9-dibenzpyrene (29): $\text{XIII} < \text{XIX} \leq \text{IX} < \text{XIV} \leq \text{XVI} \leq \text{XVII} < \text{VII} < \text{III} < \text{XX} < \text{VI} < \text{XI} < \text{VIII} < \text{XXI}$.

CONCLUSION

Three new combined indices have been introduced to characterize the K-region, based upon the atomic localization energies, superdelocalizabilities, and self-polarizabilities. From an analysis presented in this work it is obvious that, similar to the reactivity indices of alternate hydrocarbons (20), the composed indices characterizing the reactivity of the bonds of these hydrocarbons also afford in principle corresponding statements on the reactivity. We see the importance of this statement not in the possibility

of introducing new indices for the prediction of carcinogenic activity, but in the proof of non-specificity of the properties of Pullman indices.

To characterize the K-region and similarly also the L-region, it is possible to use any of these indices—the combined Pullman index, the sum of accurate superdelocalizabilities, and the sum of atomic localization energies appearing equally suitable. For a rapid estimate of the carcinogenic effect, the exact superdelocalizability is convenient. An advantage of the combined Pullman indices is that unreal K-regions, i.e., ortho-position with minimum ortho-localization energy, appear as quite nonreactive.

The character of all indices seems to support the prediction that the indices of the free molecule will be parallel to the indices characterizing the complex formed by an aromatic hydrocarbon and a group in the protein molecule (cf. [20]). The circumstance that, by the introduction of accurate values of localization energies, the concept of A. Pullman and B. Pullman has in principle been confirmed, leads further to the conclusion that it is of special importance to proceed in the theoretical and experimental verification of the predictions established by these authors.

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J. Koutecký and R. Zahradník

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