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On the relationship between electronic structure and carcinogenic activity in substituted Benz[*a*]anthracene derivatives

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ABSTRACT

A quantum chemical study was carried out to find relationships between the carcinogenic potency, quantified by the Iball and Berenblum indices, and the electronic structure of a group of substituted benz[a]anthracene derivatives. The electronic structure was calculated within Density Functional Theory at the mPW1PW91/LanL2DZ level with full geometry optimization. We obtained statistically significant relationships for both indices. The most important local atomic reactivity index appearing in both equations corresponds to the hardness of a carbon atom not bearing hydrogen. This result is important because some theories about carcinogenicity (K-L regions theory and bay-region theory) do not include this atom.

Keywords: Benz[a]anthracene, carcinogenic activity, polycyclic aromatic hydrocarbons, PAHs, QSAR, Iball, Berenblum.

INTRODUCTION

Cancer is the name given to a group of related diseases. In all forms of cancer, some of the body's cells begin to divide without stopping and spread into adjacent tissues. The earliest known descriptions of cancer appear in seven Egyptian papyri. One of them, called the Edwin Smith papyrus, describes eight cases of tumors or ulcers of the breast that were removed by cauterization. The George Ebers papyrus lists pharmacological, mechanical and magical treatments. The origin of the word cancer is credited to Hippocrates (460-370 BCE). He used the word *karkinos* (Greek for crab) and carcinoma since a tumor looked like a crab. Galenno (130-200 AD) used the word *oncos* to describe tumors. Up to the XVI century the theory that cancer was produced by an excess of black bile continued to prevail. After the theories and works of Wilhelm Fabry, Francois de la Boe Sylvius, Nicolaes Tulp and Gaspare Aselli, the surgeon Percivall Pott discovered the first cause of cancer when he noted that the cancer of the scrotum was a common disease amongst chimney sweeps. Today we rely in the surgery-drugs-radiation troika to combat this disease. Among chemicals possessing carcinogenic and mutagenic effects we find several polycyclic aromatic hydrocarbons (PAHs, organic compounds comprising only carbon and hydrogen and composed of several aromatic rings). Strictly speaking, the class is defined as lacking branching substituents on the ring structures. PAHs occur naturally in coal, crude oil, and gasoline and also exist in products such as coal-tar pitch, creosote and asphalt. Forest fires and volcanoes produce PAHs naturally. From a chemical point of view PAHs are systems with delocalized π electrons. The first theory for the action mechanism of carcinogenic compounds was suggested during the Third Reich by Otto Schmidt, an engineer working in the *Interessen-Gemeinschaft Farbenindustrie Aktien Gesellschaft* (IG Farben) [1-4]. He considering that, being the lowest energy of photons producing cancer artificially

about 3.4 eV, the mechanism of the mutation should involve similar energies. This energy is low and will affect only the weakly bonded π electrons. At Schmidt's time, PAHs constituted the most part of carcinogenic agents. In 1946, Raymond Daudel improved this suggestion by stating that "*la mutation est sans doute la conséquence d'une ou de plusiers réactions successives à des excitations des constituants de la cellule et qui mettent en jeu des électrons faiblement liés*" [5]. The first attempt to correlate electronic structure with carcinogenic activity in unsubstituted PAHs was proposed by the Pullmans and is known as the K-L regions theory (see Fig. 1). This theory holds that carcinogenicity is related to the existence of a reactive K region (with a high π electron density) and an unreactive region (L) in unsubstituted PAHs [6-15].

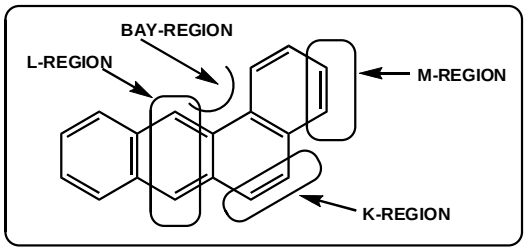

Figure 1. K, L, M and bay regions of benz[a]anthracene

This theory ruled the field until the years 60s. The term M-region (Fig. 1) was employed to designate sites such as the 3,4 positions of benz[a]anthracene where it was supposed that metabolism to oxidized products take place selectively. As metabolism happens at very diverse molecular sites, this term was abandoned. Jerina et al. proposed that a bay region could play an important role in chemical carcinogenesis [16-18]. The term bay refers to the region between two angularly fused aromatic rings (Fig 1). This theory proposes that "*diol epoxides on benzo-rings of PAHs will have the highest chemical reactivity and presumably biological activity when the epoxide group forms part of a bay-region of the hydrocarbon*" [16]. A fjord region (region surrounded by four aromatic rings) has also been suggested.

Regarding the K-L regions theory, in 1969 Pullman resumed the way in which this research was carried out by stating that "*il s'agit, en primer lieu, de trouver des règles de sélection qui permettraient de distinguer, parmi tous les hydrocarbures précités* [a list of 38 hydrocarbons composed by one to six fused aromatic rings], *les neuf molécules actives*" [19]. We feel that this way of analyzing the question of the carcinogenic activity of PAHs has several pitfalls. The first one is that the original set of PAHs was incomplete: today we know that there are several PAHs composed by six fused aromatic rings that present carcinogenic activity. The second one is that in the original set there are several PAHs that were considered to be non-carcinogenic when in fact they are. This last consideration could be associated to the fact that for the several rules stated for carcinogenic activity, a number of exceptions exist. And, with the passage of time, more and more exception rules appeared. The reasons why this theory lasted so long are not clear. **A more logical approach is to analyze a set of active molecules to find possible explanations for their carcinogenic activity. Only after the full picture is known it would be possible to understand why some molecules are inactive**.

To carry out correct quantitative structure-activity (QSAR) studies, it is mandatory that the set of molecules fulfill at least two criteria: the existence of a trustworthy index measuring the carcinogenic activity and a set of experimental data obtained in almost the same experimental conditions. Regarding the quantification of the carcinogenic activity, at least two numerical indices have been proposed to compute it. Iball introduced the *carcinogenic index* (Iball index, I) defined as the percentage of tumors divided by the average latent period in days [20]. Berenblum created a system of twelve *carcinogenic grades* (G index). For strong carcinogens, G is defined as G=16-6.5(log W), where W is the latency period in weeks [21]. For very weak carcinogens, G is defined as G=12-6.5 log(2w), were w represents the time of appearance of the first tumor in weeks. Badger made a very clever analysis of the Iball and G indices [22]. He noted that the I index eliminates the animals which die before to be affected for the carcinogen. In the case of Berenblum's twelve grades, Badger considers that it *is apt to give a greater resemblance of accuracy than is justified*. Regarding the experimental data of carcinogenic compounds, the way to apply the carcinogen (inhalation, intratracheal, insufflation, intra-nasal, subcutaneous, intravenous, etc.), the quantity of compound used and the species (rats, pigs, rabbits, hamsters, mice, guinea pigs, dogs, etc., of the same strain or type) must be the

same. In this way the limitation of the data will come only from the inaccuracies inherent in all biological essays [22, 23].

In this article we present the results of the application of a formal structure-activity method to the analysis of the relationship between electronic structure and carcinogenic potency in a group of substituted benz[a]anthracene derivatives. We did not discuss the vast theoretical literature about the relationships between electronic structure and carcinogenic potency because we expect first to apply the same method used here to groups of substituted and unsubstituted PAHs and other molecular systems to accumulate more quantitative data. Nevertheless, we have noticed that several papers can be classified as statistical *divertimenti*: statistical analysis is employed as the "*orchestra director*" instead as the "*slave*".

MATERIALS AND METHODS

Methods, models and calculations

Selection of the experimental data

Within the aforementioned constraints, we have selected for this study the carcinogenic data of a group of substituted benz[a]anthracene derivatives from two publications [24, 25]. In both papers the sarcoma induction was carried out in the Long-Evans rat strain, about 25 days old, with i.m. injection in a hind leg with 0.5 ml of oil containing 2.5 mg of the compound. Rats were sacrificed on day 270 unless sarcomas were detected (in one paper the authors did not mention the rat strain explicitly. Considering that the experiments were carried out in the same place, we have accepted that the rat strain was the same). The Iball and Berenblum indices were calculated from the experimental data on sarcoma. Figure 2 and Table 1 show the molecules.

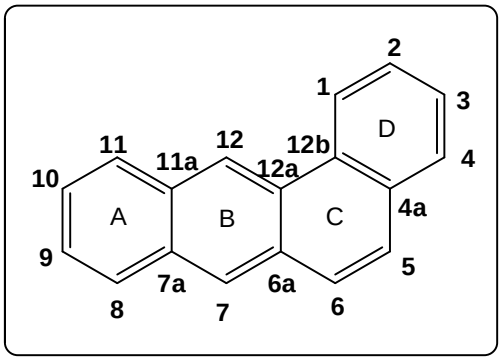

Figure 2. Benz[a]anthracene derivatives numbering

Calculations.

Starting from the statistical-mechanical definition of the equilibrium constant, a formal relationship between the equilibrium constant of a small molecule-site system and local atomic reactivity indices of the small molecule was developed time ago [26-32]. This relationship was extended few years ago to any biological activity [32]. Each atom is described by the following twelve local atomic reactivity indices: net charge (Q), total atomic electrophilic superdelocalizability (S^E), total atomic nucleophilic superdelocalizability (S^N), Fukui indices of the three highest occupied local MOs, Fukui indices of the three lowest vacant local MOs, electrophilic superdelocalizabilities of the three highest occupied local MOs, nucleophilic superdelocalizabilities of the three lowest vacant local MOs, local atomic electronic chemical potential (μ), local atomic hardness (η), local atomic softness (s), maximal amount of charge that an atom may receive (Q^{max}) and local atomic electrophilicity (ω). The orientational parameter (OP) of the substituent was added to this set (the OPs are originated from the rotational partition function [26]). We refer the reader to the literature. The hypothesis that the model developed only for equilibrium constants could be also applied to *any* biological activity has been tested against several different molecular systems and biological activities with success ([33-42] and references therein).

Geometries were fully optimized within Density Functional Theory with the Perdew-Wang exchange as modified by Adamo and Barone combined with PW91 correlation (mPW1PW91) functional together with a LanL2DZ basis set (for first row atoms this basis set is the same than Dunning/Huzinaga's valence double-zeta basis set). The Gaussian

set of programs was employed [43]. Linear multiple regression analysis was performed using as dependent variable the carcinogenic potency and as independent variables all the local atomic reactivity indices of atoms 1-12b of Fig. 1, plus the orientational parameters of the R_6-R_{10} and R_{12} substituents. The Statistica software was employed [44]. The values of the orientational parameters were taken from the literature [45, 46].

Table 1. Benz[a]anthracene derivatives and carcinogenic potency

Mol.	Name	log(I)	log(G)
1	7-Methyl-BA	1.97	0.93
2	6-Methyl-BA	1.84	0.87
3	8-Methyl-BA	1.50	0.82
4	12-Methyl-BA	3.54	0.82
5	7-Ethyl-BA	0.35	0.83
6	7-Methoxy-BA	0.46	0.80
7	12-Ethyl-BA	0.23	0.77
8	6,7-Dimethyl-BA	1.98	0.92
9	6,8-Dimethyl-BA	1.95	0.91
10	6,12-Dimethyl-BA	2.10	0.96
11	7,8-Dimethyl-BA	1.98	0.92
12	7,12-Dimethyl-BA	2.06	0.95
13	8,12-Dimethyl-BA	2.04	0.94
14	9,10-Dimethyl-BA	0.84	0.83
15	7-Methoxy-12-Methyl-BA	2.07	0.95
16	7-Ethoxy-12-methyl-BA	2.05	0.94
17	7,12-Dimethoxy-BA	1.67	0.85
18	7-Hydroxymethyl-12-methyl-BA	1.19	0.85
19	7-Formyl-12-methyl-BA	1.99	0.93
20	6,7,8-Trimethyl-BA	2.02	0.93
21	6,7,12-Trimethyl-BA	1.94	0.91
22	6,8,12-Trimethyl-BA	2.04	0.94
23	7,8,12-Trimethyl-BA	2.08	0.95
24	7-Et-12-Me-BA	2.08	0.95
25	7-Propyl-12-Me-BA	1.65	0.86
26	7-Me-12-Et-BA	1.52	0.84

RESULTS

For the set considered here the numerical values of both indices are highly correlated: $r^2(G,I)=0.95$. Therefore, we expect to obtain quite similar results. For the Berenblum index we obtained the following equation:

$$\log(G)=1.80-0.26\eta_{12a}-0.59S_{11}^{E}(HOMO-1)^{*}-0.003\varphi_9 \quad (1)$$

with n=24, R=0.91, R^2=0.82, adj-R^2=0.79, F(3,20)=30.22 ($p<0.000001$) and a standard error of estimate of 0.04. No outliers were detected and no residuals fall outside the $\pm 2\sigma$ limits. Here, η_{12a} is the local atomic hardness of atom 12a, $S_{11}^{E}(HOMO-1)^{*}$ is the electrophilic superdelocalizability of the highest occupied MO localized on atom 11 and φ_9 is the orientational parameter of the substituent at position 9. Tables 2 and 3 show the beta coefficients, the results of the t-test for significance of coefficients and the matrix of squared correlation coefficients for the variables of Eq. 1. There are no significant internal correlations between independent variables (Table 3). Figure 3 displays the plot of observed *vs.* calculated values.

Table 2. Beta coefficients and t-test for significance of coefficients in Eq. 1

Variable	Beta	t(20)	p-level
η_{12a}	-0.73	-7.66	<0.000001
$S_{11}^{E}(HOMO-1)^{*}$	-0.38	-3.47	<0.002
φ_9	-0.24	-2.16	<0.04

Table 3. Matrix of squared correlation coefficients for the variables in Eq. 1

	η_{12a}	S_{11}^{E}(HOMO-1)*	φ_9
η_{12a}	1.00		
S_{11}^{E}(HOMO-1)*	0.00	1.00	
φ_9	0.00	0.24	1.00

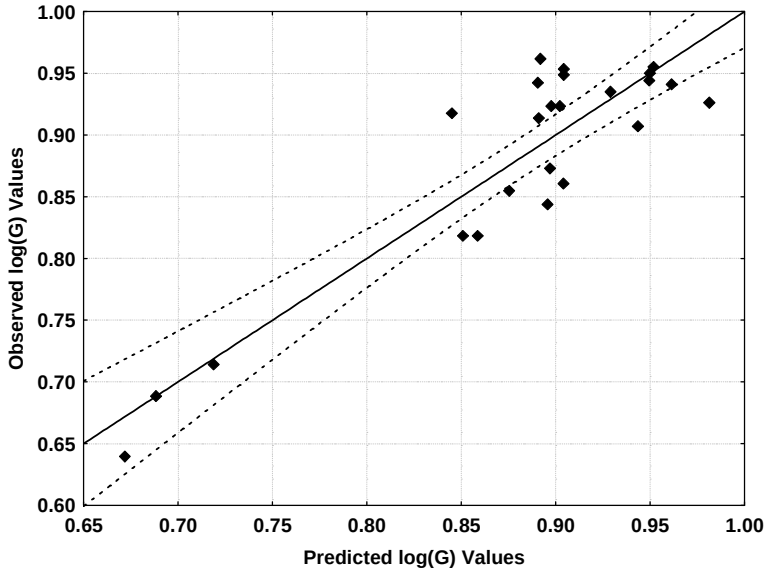

Fig. 3. Graphical representation of observed *vs*. estimated values (Eq. 1). Dashed lines denote the 95% confidence interval

The associated statistical parameters of Eq. 1 indicate that this equation is statistically significant and that the variation of the numerical values of a group of three local atomic reactivity indices of atoms of the common skeleton explains about 79% of the variation of the carcinogenic potency.

For the Iball index we obtained the following equation:

$$\log(I)=6.14-1.22\eta_{12a}-2.87S_{11}^{E}(HOMO-1)^{*}-4.05F_{5}(HOMO-2)^{*} \quad (2)$$

with n=24, R=0.90, R^2=0.81, adj-R^2=0.78, F(3,20)=27.54 ($p<0.000001$) and a standard error of estimate of 0.20. No outliers were detected and no residuals fall outside the ±2σ limits. Here, η_{12a} is the local atomic hardness of atom 12a, $S_{11}^{E}(HOMO-1)^{*}$ is the electrophilic superdelocalizability of the highest occupied MO localized on atom 11 and F_5(HOMO-2)* is the Fukui index (electron population) of the third highest local MO localized on atom 5. Tables 4 and 5 show the beta coefficients, the results of the t-test for significance of coefficients and the matrix of squared correlation coefficients for the variables of Eq. 2. There are no significant internal correlations between independent variables (Table 5). Figure 4 displays the plot of observed *vs.* calculated values.

Table 4. Beta coefficients and t-test for significance of coefficients in Eq. 2

Variable	Beta	t(20)	p-level
η_{12a}	-0.72	-7.28	<0.000001
S_{11}^{E}(HOMO-1)*	-0.39	-3.60	<0.002
F_5(HOMO-2)*	-0.25	-2.23	<0.03

Table 5. Matrix of squared correlation coefficients for the variables in Eq. 2

	η_{12a}	S_{11}^{E}(HOMO-1)*	F_5(HOMO-2)*
η_{12a}	1.00		
S_{11}^{E}(HOMO-1)*	0.00	1.00	
F_5(HOMO-2)*	0.00	0.14	1.00

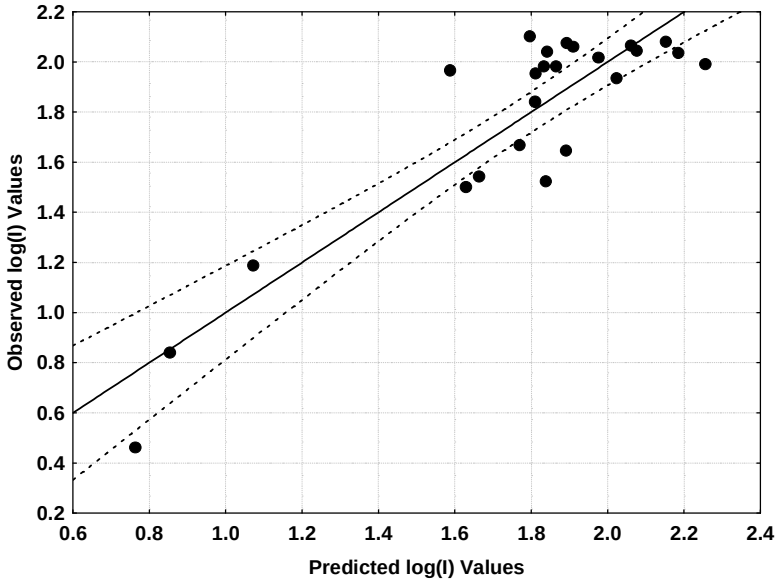

Fig. 4. Graphical representation of observed *vs*. estimated values (Eq. 2). Dashed lines denote the 95% confidence interval

The associated statistical parameters of Eq. 2 indicate that this equation is statistically significant and that the variation of the numerical values of a group of three local atomic reactivity indices of atoms of the common skeleton explains about 78% of the variation of the carcinogenic potency.

Local Molecular Orbitals.

Table 6 displays the local molecular orbital structure of atoms appearing in Eqs. 1 and 2 (Reading: molecule's number (HOMO)/ (HOMO-2)*, (HOMO-1)*, (HOMO)*- (LUMO)*, (LUMO+1)*, (LUMO+2)*).

Table 6. Local molecular orbital structure of atoms 5,12b and 11

	Atom 5	Atom 12b	Atom 11
1 (64)	61π63π64π-65π66π68π	61π63π64π-65π66π68π	62π63π64π-65π66π67π
2 (64)	61π63π64π-65π66π68π	61π63π64π-65π66π68π	62π63π64π-65π66π67π
3 (64)	61π63π64π-65π66π68π	61π63π64π-65π66π68π	62π63π64π-65π66π67π
4 (64)	61π63π64π-65π66π68π	61π63π64π-65π66π68π	62π63π64π-65π66π67π
5 (68)	65π67π68π-69π70π72π	65π67π68π-69π70π72π	66π67π68π-69π70π71π
6 (68)	65π67π68π-69π70π72π	63π65π67π-69π70π72π	66π67π68π-69π70π71π
7 (68)	65π67π68π-69π70π72π	65π67π68π-69π70π72π	66π67π68π-69π70π71π
8 (68)	65π67π68π-69π70π72π	65π67π68π-69π70π72π	66π67π68π-69π71π72π
9 (68)	65π67π68π-69π70π72π	65π67π68π-69π70π72π	66π67π68π-69π71π72π
10 (68)	65π67π68π-69π70π72π	65π67π68π-69π70π72π	66π67π68π-69π70π71π
11 (68)	65π67π68π-69π70π72π	65π67π68π-69π70π72π	66π67π68π-69π70π71π
12 (68)	65π67π68π-69π70π72π	65π67π68π-69π70π72π	66π67π68π-69π70π71π
13 (68)	65π67π68π-69π70π72π	65π67π68π-69π70π72π	66π67π68π-69π70π71π
14 (68)	64π67π68π-69π70π72π	65π67π68π-69π70π72π	66π67π68π-69π70π71π
15 (72)	69π71π72π-73π74π76π	69π71π72π-73π74π76π	70π71π72π-73π74π75π
16 (76)	73π75π76π-77π78π80π	73π75π76π-77π78π80π	74π75π76π-77π78π79π
17 (76)	72π75π76π-77π78π80π	72π75π76π-77π78π80π	74π75π76π-77π78π79π
18 (72)	66σ71π72π-73π74π76π	68π71π72π-74π76π77π	70π71π72π-73π74π75π
19 (71)	67π70π71π-72π73π76π	69σ70π71π-72π73π76π	68π70π71π-72π73π74π
20 (72)	69π71π72π-73π74π76π	69π71π72π-73π74π76π	70π71π72π-73π75π76π

21 (72)	69π71π72π-73π74π76π	69π71π72π-73π74π76π	70π71π72π-73π74π75π
22 (72)	69π71π72π-73π74π76π	69π71π72π-73π74π76π	70π71π72π-73π74π75π
23 (72)	69π71π72π-73π74π76π	68π71π72π-73π74π76π	70π71π72π-73π74π75π
24 (72)	69π71π72π-73π74π76π	69π71π72π-73π74π76π	70π71π72π-73π74π75π
25 (76)	73π75π76π-77π78π80π	73π75π76π-77π78π80π	74π75π76π-77π78π79π
26 (72)	69π71π72π-73π74π76π	69π71π72π-73π74π76π	70π71π72π-73π74π75π

DISCUSSION

Figures 3 and 4 show that several points fall relatively far from the 95% confidence interval. The first explanation is the possibility that other atoms than 1-12b directly act in the process. A second explanation is related to the mean latent period employed in the calculation of the Iball and Berenblum indices. It is possible that during this time, one or more molecules produce one or more active metabolites contributing to the appearance of sarcomas. The fact that Eqs. 1 and 2 explain only about 78-79% of the variation of the carcinogenic potency confirm the possible existence of a factor that we are not taking into account. Therefore, more results from other systems are needed to clarify this point. Our results show that, within the approximations employed to build the theoretical model, the results obtained show that there is a direct dependence between the variation of the carcinogenic potency and the variation of the values of a set or reactivity indices.

The beta values and the *t*-test results (Tables 2-5) show that the most important variable in Eqs. 1 and 2 is the local atomic hardness of atom 12a (Fig. 2). For atom p, the energy gap between the $HOMO_p$* and $LUMO_p$* is equal to the local atomic η_p and it is always a positive number. This fact and the sign associated to this index in Eqs. 1 and 2 indicate that a small numerical value is related with a high carcinogenic activity. In other words, a soft atom is desired at position 12b. This, in turn, indicates that this atom seems to be participating in an electron transfer reaction (an additional option is that atom 12a participates in a rearrangement process, but there is no experimental evidence supporting this). As far as we know, this is the first time that formal evidence involving a carbon atom of this kind in carcinogenesis is found. This atom is part of a bay (see Fig. 1). Eqs. 1 and 2 show that a high carcinoginecity is associated with a high value of the electrophilic superdelocalizability of the second highest occupied MO localized on atom 11 (Fig. 2). Table 6 shows that the first three highest occupied local MOs of atom 11 have a π nature. Then, we suggest that atom 11 is interacting with an electron-deficient center. Note that atom 11 do not belong to any of the regions showed in Fig. 1. Eq. 1 includes the orientational parameter of the R_9 substituent (Fig. 2). A high carcinogenicity is associated with a small value for this index. On the other hand, Table 2 shows that the associated t value is not too high. Nevertheless, and for future studies, some words are necessary. If this OP really contributes significantly, the most suitable substituents can be hydrogen, methyl or ethyl. Eq. 2 includes F_5(HOMO-2)*, the electron population of the third highest occupied MO localized on atom 5. A high carcinogenicity is associated with a small value for this index. Table 6 shows that the energy of $(HOMO-2)_5^*$, of π nature in all molecules but one (molecule 18, Table 6), is lower than the third highest occupied MO of the corresponding molecule. Given the low t value associated with this index (Table 4) we shall only suggest that this atom could be involved in an interaction with empty MOs. Note that this atom is in the Pullmans' K-region. Figure 5 shows the corresponding partial 2D pharmacophore.

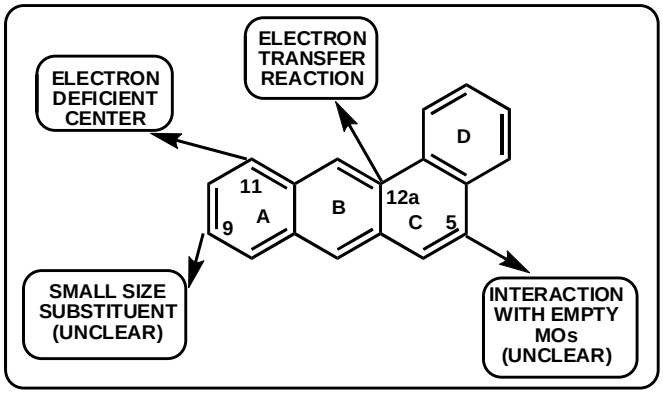

Figure 5. Partial 2D pharmacophore for the carcinogenic potency of benz[a]anthracene derivatives

In conclusion we have found, for the first time, a formal quantitative relationship between the variation of the carcinogenic potency and the variation of the values of a set of local atomic reactivity indices in a group of benz[a]anthracene derivatives. The next step in this research is finding similar relationships for a set created with PAHs with different numbers of rings.

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