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A Density Functional Theory analysis of the relationships between the Badger index measuring carcinogenicity and the electronic structure of a series of substituted Benz[a]anthracene derivatives, with a suggestion for a modified carcinogenicity index

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Abstract We carried out a quantum-chemical analysis of the relationships between the electronic structure of several substituted benz[a]anthracene derivatives and Badger's qualitative scale for grading skin and subcutaneous tissue carcinogenic activity. We obtained statistically significant results for the Badger index used for carcinogenicity in the skin but not for the subcutaneous tissue. A new carbon atom was detected as being important in the carcinogenic process. We defined a new carcinogenic index based on the earliest day of death of tumor-bearing mice. The use of this new index provided better results than Badger's. A carbon atom, never detected previously, appeared in the equation relating structure with carcinogenic potency. The results presented here, together the ones of a previous paper, allow to begin to understand why concepts such as K-L regions, bay region and M-region never were fully satisfactory.

Keywords QSAR, cancer, carcinogenesis, KPG model, benz[a]anthracene, Badger, chemical reactivity

Introduction

The search for obtaining *formal* relationships between electronic structure and carcinogenic activity began around 1946[1-53]. Up to year 2015 no research group succeeded in this task. During year 2016, and employing a physically-based method[54] to link the electronic structure of a group of benz[a]anthracene derivatives with Iball's carcinogenic index and Beremblum's carcinogenic grades, we finally obtained the first formal quantitative results[55]. Iball and Beremblum's indices have a numerical scale. On the other hand, there is a third index proposed by Badger for grading the carcinogenic potency. This qualitative or semi-quantitative scale was defined as follows: ++++ signifies very marked carcinogenic activity (CA), +++ signifies CA, ++ signifies moderate CA, + signifies slight CA and 0 denotes an inactive molecule. Badger says that the error of this scale is *at least* one + symbol. This scale has been used until recent times. The problem is that, to employ Badger's scale in a formal QSAR study, we need to associate it with a numerical scale. This problem needs to be addressed and solved because Badger's scale is still the only way in which carcinogenic activity is reported in some papers.

In this paper we present the results of two quantum-chemical analyses of the relationships between the electronic structure of several carcinogenic substituted benz[a]anthracene derivatives and Badger's scale. These results prompted us to propose a modified Badger index that is presented and analyzed here. The studies are presented consecutively for the sake of clarity.

Models, Methods and Calculations

Starting from the statistical-mechanical definition of the equilibrium constant, a strict relationship between the biological activity and a set of local atomic reactivity indices was developed time ago (the KPG model, [54]). Each atom is described at least by the following 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[56], 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), the maximal amount of charge that an atom may receive (Q^{max}) and local atomic electrophilicity (ω). When needed, the orientational parameters (OP) of the substituents were added to this set [57-59]. We refer the reader to the numerous papers published on the model [60-64], specially to Ref. [54] in which a full detailed description of the method is presented. The hypothesis that the model developed only for receptor affinity constants can be applied to any biological activity has been tested in several different molecular systems and biological activities with complete success ([65-81]and references therein). In one case, my collaborators and I were able to predict the hallucinogenic properties of a molecule and in another case we were able to show that the experimental data was erroneous [82, 83]. Therefore we shall discuss here only the resulting equations. All molecular geometries were fully optimized within the Density Functional Theory with the mPW1PW91 functional and a LanL2DZ basis set. The Gaussian suite of programs was employed [84]. All linear multiple regression analyses (LMRA) were performed using as dependent variable the carcinogenic potency and as independent variables all the local atomic reactivity indices of the atoms composing a common skeleton plus the orientational parameters when needed. The Statistica software was employed [85]. The values of the orientational parameters were taken from the literature [57, 58] or calculated with the Steric software written in our Unit [59]

Part A. Studies with the original Badger index.

A1. Molecules selected for the original set of Badger values.

The transformation of Badger's scale into a numerical one was made as follows. First, we cannot associate + with the number 1 because Badger suggested that the error of his scale could be at least one +. As we work with logarithms this is not a safe approach. Moreover, we found in more recent literature that the symbol 0/+ was introduced for carcinogenic activity. These two facts led us to employ the following rules for avoiding problems in future studies: to the symbol + we assigned the value 3, to the symbol ++ the value 4 and so on.We inspect the literature to create a set of molecules with the Badger index. The final set is shown in Fig. 1 and Table 1. Table 1 also shows the value of the Badger index for skin and subcutaneous tissue.These values were taken from several Tables of Ref. [86].

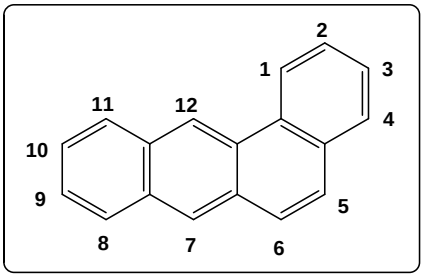

Figure 1: Substituted benz[a]anthracene derivatives

Table 1: Substituted benz[a]anthracene derivatives and carcinogenic activity.

Mol.	Name	Badger (B) Skin	log(B) Skin	Badger (B') Subcutaneous	log(B') Subcut.
1	5-methyl-BA	+	0.48	++	0.60
2	6-methyl-BA	+	0.48	++	0.60
3	7-methyl-BA	+++	0.70	++++	0.78
4	8-methyl-BA	++	0.60	++	0.60
5	9-methyl-BA	+	0.48	nd	--

6	10-methyl-BA	+	0.48	+	0.48
7	11-methyl-BA	+	0.48	nd	--
8	12-methyl-BA	++	0.60	+++	0.70
9	6,7-dimethyl	nd	--	++	0.60
10	6,12-dimethyl-BA	nd	--	+++	0.70
11	7,8-dimethyl-BA	nd	--	++++	0.78
12	7,11-dimethyl-BA	nd	--	+++	0.70
13	7,12-dimethyl-BA	nd	--	+++	0.70
14	8,9-dimethyl-BA	+++	0.70	nd	--
15	8,12-dimethyl-BA	nd	--	++++	0.78
16	9,10-dimethyl-BA	+	0.48	nd	--
17	7,8,12-trimethyl-BA	++++	0.78	+++	0.70
18	7,9,12-trimethyl-BA	++++	0.78	++	0.60
19	7,8,9,12-tetramethyl-BA	+++	0.70	+	0.48
20	8-ethyl-BA	++	0.60	nd	--
21	8-n-propyl-BA	++	0.60	nd	--
22	8-iso-propyl-BA	++	0.60	+	0.48
23	8-n-butyl-BA	++	0.60	nd	--
24	8-n-amyl-BA	++	0.60	nd	--
25	8-n-hexyl-BA	+	0.48	nd	--
26	8-n-heptyl-BA	+	0.48	nd	--
27	7-ethyl-BA	nd	--	+++	0.70
28	7-CH_2CN-BA	nd	--	+	0.48
29	7-CH2OH-BA	++	0.60	+++	0.70
30	7-CH_2OCOCH_3-BA	++	0.60	+++	0.70
31	7-$CH_2OCH_2CH_3$-BA	+	0.48	nd	--
32	7-CH_2COOCH_3-BA	nd	--	+	0.48
33	7-OCH_3-BA	nd	--	++	0.60
34	7-NH_2-BA	nd	--	+	0.48
35	7-CN-BA	+	0.48	++	0.60
36	7-NCO-BA	nd	--	+	0.48
37	7-CHO-BA	nd	--	++	0.60

A2. Results for the original Badger index.

The atoms composing the common skeleton used in this part of the study are shown in Fig. 2. For LMRA we employed all the local atomic reactivity indices of these atoms plus the orientational parameters of the substituents attached to some of them (R_5 to R_{12} of Table 1).

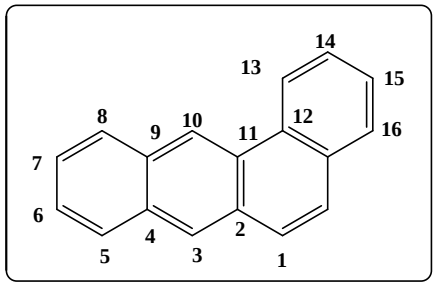

Figure 2: Common skeleton numbering

A.2.1. Results for the skin carcinogenic activity.

The best equation obtained is:

$$\log(B) = 0.56 - 0.65S_2^E(HOMO-2)^* + 0.11S_3^E(HOMO-2)^* + 0.27S_3^E - \\ -0.00005\varphi_{R8} + 0.34S_{10}^N(LUMO)^* \quad (1)$$

with n=24, R=0.95, R^2= 0.90, adjusted R^2= 0.88, F(5,18)=34.224 (p<0.000001) and a standard error of estimate of 0.03. Here, S_2^E(HOMO-2)* is the electrophilic superdelocalizability of the third highest occupied MO localized on atom 2, S_3^2(HOMO-2)* is the electrophilic superdelocalizability of the third highest occupied MO localized on atom 3, S_3^E is the total atomic electrophilic superdelocalizability of atom 3, φ_{R8} is the orientational parameter of the substituent attached to atom 5 in Fig. 2 (atom 8 in Fig. 1) and S_{10}^N(LUMO)* is the nucleophilic superdelocalizability of the lowest empty MO localized on atom 10. All atom numbering refers to Fig. 2. 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 3: Beta coefficients and t-test for significance of coefficients in Eq. 1.

Variable	Beta	t(18)	p-level
S_2^E(HOMO-2)*	-0.64	-7.62	<0.000001
S_3^2(HOMO-2)*	0.76	8.09	<0.000001
S_3^E	0.35	4.23	<0.0005
φ_{R8}	-0.37	-4.24	<0.0005
S_{10}^N(LUMO)*	0.23	2.74	<0.01

Table 4: Matrix of squared correlation coefficients for the variables in Eq. 1.

	S_2^E(HOMO-2)*	S_3^2(HOMO-2)*	S_3^E	φ_{R8}
S_3^2(HOMO-2)*	0.13	1.00		
S_3^E	0.16	0.03	1.00	
φ_{R8}	0.07	0.30	0.01	1.00
S_{10}^N(LUMO)*	0.04	0.18	0.08	0.12

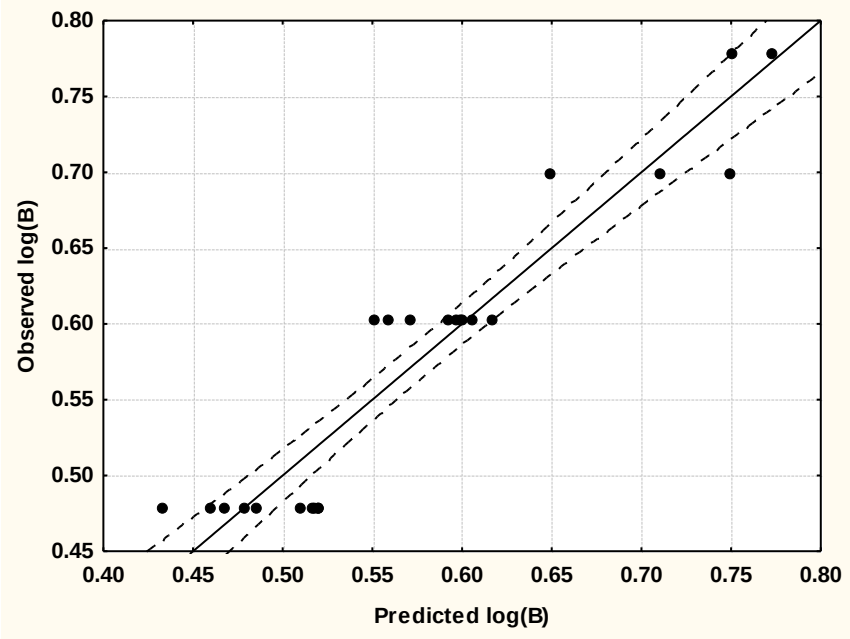

Figure 3: Plot of predicted vs. observed carcinogenic potency (skin, Eq. 1).Dashed lines denote the 95% confidence interval.

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 five local atomic reactivity indices of atoms of the common skeleton plus one orientational effect of the substituent explains about 88% of the variation of the carcinogenic potency. Figure 3 shows that there is a good correlation of observed *versus* calculated values. Most points are inside the 95% confidence interval but also there are some points located quite far from it.

A.2.2. Results for the subcutaneous carcinogenic activity.

We applied all techniques we used in our previous studies but no statistically significant relationship could be obtained. Only for the effects of providing information we show in Fig. 4 the plot of predicted vs. observed carcinogenic potency for the best equation.

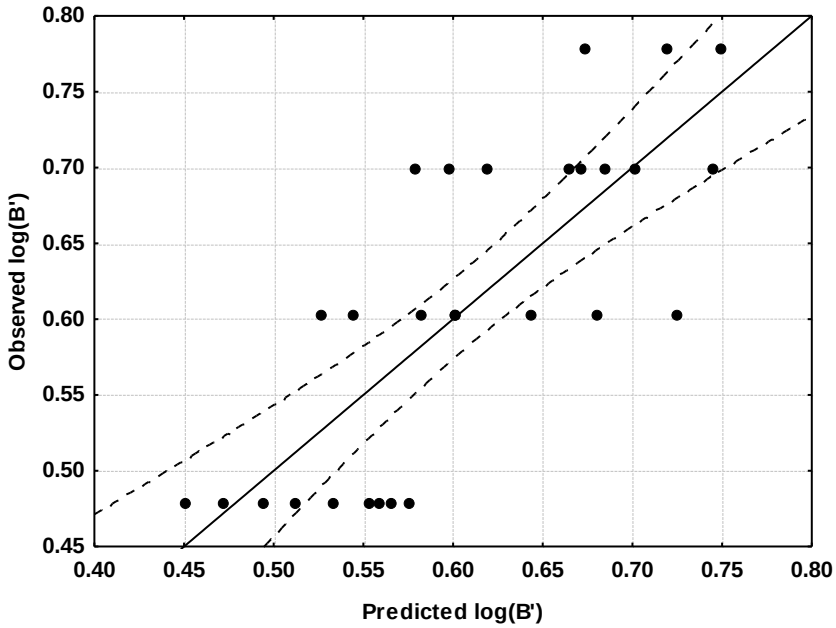

Figure 4: Plot of predicted vs. observed carcinogenic potency (subcutaneous tissue).Dashed lines denote the 95% confidence interval

We can see that the best equation obtained produced very bad results.

A.3. Local Molecular Orbitals.

Table 5 shows the local MO structure of atoms 2, 3 and 10 (see Fig. 2). Nomenclature: Molecule (HOMO) / (HOMO-2)* (HOMO-1)* (HOMO)* - (LUMO)* (LUMO+1)* (LUMO+2)*.

Table 5: Local Molecular Orbitals of atoms 2, 3 and 10 (Eq. 1).

Molecule	Atom 2	Atom 3	Atom 10
1(64)	62π63π64π-65π66π67π	59π60π64π-65π69π70π	62π63π64π-65π66π67π
2(64)	62π63π64π-65π66π67π	60π62π64π-65π69π71π	62π63π64π-65π66π67π
3(64)	62π63π64π-65π66π67π	58σ60π64π-65π69π71π	62π63π64π-65π66π67π
4(64)	62π63π64π-65π66π67π	58σ60π64π-65π67π69π	61π63π64π-65π66π67π
5(64)	62π63π64π-65π66π67π	59π60π64π-65π69π71π	62π63π64π-65π66π67π
6(64)	62π63π64π-65π66π67π	59π60π64π-65π68π69π	62π63π64π-65π66π67π
7(64)	62π63π64π-65π66π67π	59π60π64π-65π67π69π	61π63π64π-65π66π67π
8(64)	62π63π64π-65π66π67π	59π60π64π-65π69π70π	62π63π64π-65π66π67π
9(68)	66π67π68π-69π70π71π	64π66π68π-69π73π75π	66π67π68π-69π70π71π
10(68)	66π67π68π-69π70π71π	64π66π68π-69π73π74π	66π67π68π-69π70π72π
11(68)	66π67π68π-69π70π71π	62σ64π68π-69π73π75π	65π67π68π-69π70π71π
12(68)	66π67π68π-69π70π71π	64π65π68π-69π71π73π	65π67π68π-69π70π71π
13(68)	66π67π68π-69π70π71π	63π64π68π-69π73π75π	66π67π68π-69π70π72π

14(68)	66π67π68π-69π70π71π	62σ64π68π-69π71π73π	65π67π68π-69π70π71π
15(68)	66π67π68π-69π70π71π	63π64π68π-69π71π73π	65π67π68π-69π70π71π
16(68)	66π67π68π-69π70π71π	63π64π68π-69π73π74π	66π67π68π-69π70π71π
17(72)	70π71π72π-73π74π75π	68π69π72π-73π77π79π	69π71π72π-73π74π75π
18(72)	70π71π72π-73π74π75π	67π68π72π-73π77π79π	70π71π72π-73π74π75π
19(76)	74π75π76π-77π78π79π	72π73π76π-77π81π83π	73π75π76π-77π78π79π
20(68)	66π67π68π-69π70π71π	62σ64π68π-69π71π73π	65π67π68π-69π70π71π
21(72)	70π71π72π-73π74π75π	66σ68π72π-73π75π77π	69π71π72π-73π74π75π
22(72)	70π71π72π-73π74π75π	66σ68π72π-73π75π77π	69π71π72π-73π74π75π
23(76)	74π75π76π-77π78π79π	70π72π76π-77π79π81π	73π75π76π-77π78π79π
24(80)	78π79π80π-81π82π83π	74σ76π80π-81π83π85π	77π79π80π-81π82π83π
25(84)	82π83π84π-85π86π87π	79σ80π84π-85π87π89π	81π83π84π-85π86π87π
26(88)	86π87π88π-89π90π91π	83σ84π88π-89π91π93π	85π87π88π-89π90π91π
27(68)	66π67π68π-69π70π71π	62σ64π68π-69π73π75π	66π67π68π-69π70π71π
28(70)	68π69π70π-71π72π73π	64σ66π70π-71π75π77π	68π69π70π-71π72π73π
29(68)	66π67π68π-69π70π71π	65σ66π68π-69π72π73π	66π67π68π-69π70π71π
30(79)	77π78π79π-80π81π82π	74π75π79π-80π83σ85π	76π78π79π-80π81π82π
31(76)	74π75π76π-77π78π79π	70σ71π76π-77π79π81π	73π75π76π-77π78π79π
32(75)	73π74π75π-76π77π78π	71σ73π75π-76π78σ81π	73π74π75π-76π77π80π
33(68)	66π67π68π-69π70π71π	63π64σ68π-69π73π76π	66π67π68π-69π70π71π
34(64)	62π63π64π-65π66π67π	57σ58π64π-65π69π70π	60π63π64π-65π66π67π
35(66)	64π65π66π-67π68π69π	60σ62π66π-67π70π71π	64π65π66π-67π68π69π
36(70)	68π69π70π-71π72π73π	66π67π70π-71π74π75π	68π69π70π-71π72π73π
37(67)	65σ66π67π-68π69π70π	64π65σ67π-68π73π74π	64π66π67π-68π69π71π

A.4. Discussion of Part A Results.

The first fact to comment on is the origin of the experimental results Badger used to build his Tables used in Part A [86]. An extensive search and full analysis of Badger's papers and the data he employeddid not allow us to deduce the logics he used to build his scale. For the very bad results obtained for the carcinogenic potency in subcutaneous tissues, we have three provisional explanations. The first one is that Badger's original scale is wrong in some case. Another possibility is that our change from a qualitative scale to a quantitative one was not correct. This option could be ruled out based on our results on skin. The third one is related to the fact that in subcutaneous tissue the action mechanism of the molecules is not the same. We think that the first explanation is the most probable one.

Regarding the results on skin, Eq. 1 and Table 3show that the importance of variables is S_3^2(HOMO-2)*> S_2^E(HOMO-2)*>> φ_{R8}> S_3^E> S_{10}^N(LUMO)*. The examination of the coefficients of the variables of Eq. 1 and knowing that a higher Badger index corresponds to a higher carcinogenic activity, allow tosuggest that a high activity is associated with high (negative) values of S_2^E(HOMO-2)*, small (negative) values of S_3^2(HOMO-2)* and S_3^E, small values for φ_{R8} (position 5 in Fig. 2) and high (positive) values for S_{10}^N(LUMO)*.Atom 2 is a carbon without hydrogen atoms bonded to it. Table 5 shows that the three highest occupied local MOs and the three lowest empty local MOs have a π nature. These six local MOs coincide with the molecular MOs. The fact that a high carcinogenic activity is associated with high (negative) values of S_2^E(HOMO-2)* strongly suggests that this atom is interacting with its first three occupied local MOs with an electron-deficient site. This is important because it is the second time that an unsaturated carbon atom, not found in any other previous study, is detected as participating in the carcinogenic activity. Last year and in this Unit, a structure-carcinogenic activity (sarcoma induction) analysis of several substituted benz[a]anthracene derivatives showed that atom 11 of Fig. 2 seems to be involved in the process [55]. Note that in that study quantitative scales to measure carcinogenic potency were employed.Atom 3 is a carbon atom (Fig. 2, see atom 7 in Fig. 1). A high carcinogenic activity is associated with small (negative) values of S_3^E and S_3^E(HOMO-2)* (both indices are not correlated, Table 4). Table 5 shows that $(HOMO-2)_3^*$ and $(HOMO-1)_3^*$ are of π or σ in some molecules, while $(HOMO)_3^E$ has a π nature in all molecules. Considering that the best way to obtain small negative values for these indices is by making more negative the MO energies, we suggest that this atom is interacting with a rich-electron center and acting probably as an electron acceptor. Atom 10 is a carbon atom (Fig. 2,

see atom 12 in Fig. 1). Table 5 shows that the three highest occupied local MOs and the three lowest empty local MOs have a π nature, and that they coincide with the molecule's MOs. A high carcinogenic activity is associated with high (positive) values for S_{10}^{N}(LUMO)*. As these values are obtained by lowering the MO energy and making it more reactive, we suggest that this atom is interacting with an electron-rich center and acting probably as an electron acceptor. Small values for φ_{R8} (position 5 in Fig. 2) are associated with high carcinogenic activity. This suggests that hydrogen or methyl substituents are suitable. All the suggestions are displayed in the partial 2D pharmacophore of Fig. 5.

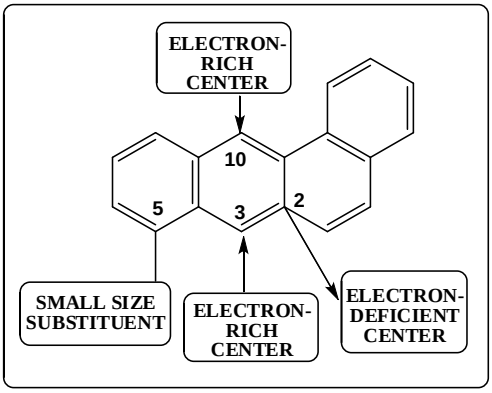

Figure 5: Partial 2D pharmacophore for carcinogenic potency

Part B. Studies with a new carcinogenicity index.

B1. The new index.

The unsatisfactory results obtained for the relationship betweensubcutaneous carcinogenic activity and electronic structure with the Badger scale pushed us into the task of creating a modified scale. Our goal is twofold. The first one is to analyze the quality of the results obtained using a modified scale built on logical and known foundations. The second one could be perfectly called "the big prize", which consists in carrying out the study of the activity of many molecules with very different number of aromatic rings. We proceeded as follows. *We hypothesized that the carcinogenic activity is well represented by the earliest day of death of tumor-bearing mice* (D). Using this data we defined the following rules:

0-100 D = +++++
101-150 D = ++++
151-200 D = +++
201-250 D = ++
251-299 D = +
D larger than 300 = 0/-

Next, we made the following associations:+++++=7, ++++=6, +++=5, ++=4, +=3, 0/-=2. Our scale is quite similar to Beremblum's one, but he used the latency period in weeks or the time of appearance of the first tumor.

B2. Molecules selected for part B.

We selected a small group of substituted benz[a]anthracene derivatives showing carcinogenic activity on the skin of mice (papilloma and epithelioma) [87, 88]. The molecules are displayed in Figure 6 and Table 6.

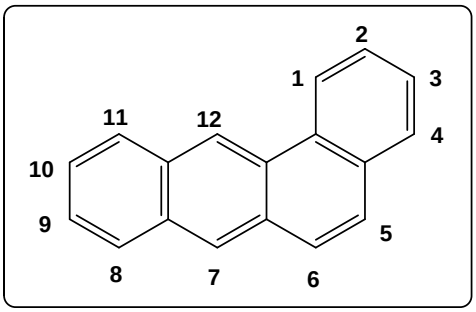

Figure 6: Selected molecules

Table 6: Substituted benz[a]anthracene derivatives and the new index (E).

Mol.	Name	A	E	log(E)
1	5-methyl	0/-	2	0.30
2	7-methyl	++++	6	0.78
3	10-methyl	0/-	2	0.30
4	11-methyl	0/-	2	0.30
5	12-methyl	+	3	0.48
6	7,12-dimethyl	+++++	7	0.85
7	7,9,12-trimethyl	++++	6	0.78
8	7,8,9,12-tetramethyl	+++++	7	0.85
9	8-iso-propyl	0/-	2	0.30
10	8-n-butyl	0/-	2	0.30
11	8-n-amyl	++	4	0.60
12	8-n-hexyl	0/-	2	0.30
13	8-n-heptyl	0/-	2	0.30
14	7-CH_2OH	++	4	0.60
15	7-CH_2OCOCH_3	++	4	0.60
16	7-CN	0/-	2	0.30

B3. Results for the new index.

The common skeleton numbering is shown in the following figure.

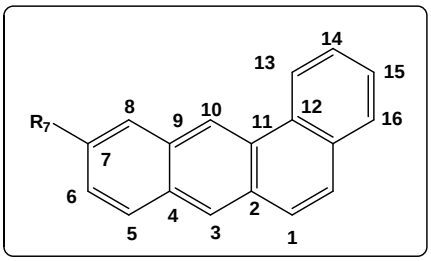

Figure 7: Common skeleton numbering

The best equation obtained is the following:

$$\log(E) = -7.18 - 0.96S_2^E + 0.72S_9^N(LUMO)^* - 0.003\varphi_7 \quad (2)$$

with n= 15, R= 0.99, R^2= 0.98, adjusted R^2= 0.97, F(3,11)=164.51 ($p<0.000001$) and a standard error of estimate of 0.04. Here, S_2^E is the electrophilic superdelocalizability of atom 2, $S_9^N(LUMO)^*$ is thenucleophilic superdelocalizability of the highest local MO localized on atom 9 and φ_7 is the orientational parameter of the R_7 substituent.All atom numbering refers to Fig. 7. Tables 7 and 8 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 4). Figure 8 displays the plot of observed *vs.* calculated values.

Table 7: Beta coefficients and t-test for significance of coefficients in Eq. 2.

Variable	Beta	t(11)	p-level
S_2^E	-1.07	-21.37	0.000001
S_9^N(LUMO)*	0.33	6.49	0.00005
φ_7	-0.15	-2.99	0.01

Table 8: Matrix of squared correlation coefficients for the variables in Eq. 2.

	S_2^E	S_9^N(LUMO)*	φ_7
S_2^E	1		
S_9^N(LUMO)*	0.19	1	
φ_7	0.03	0.07	1

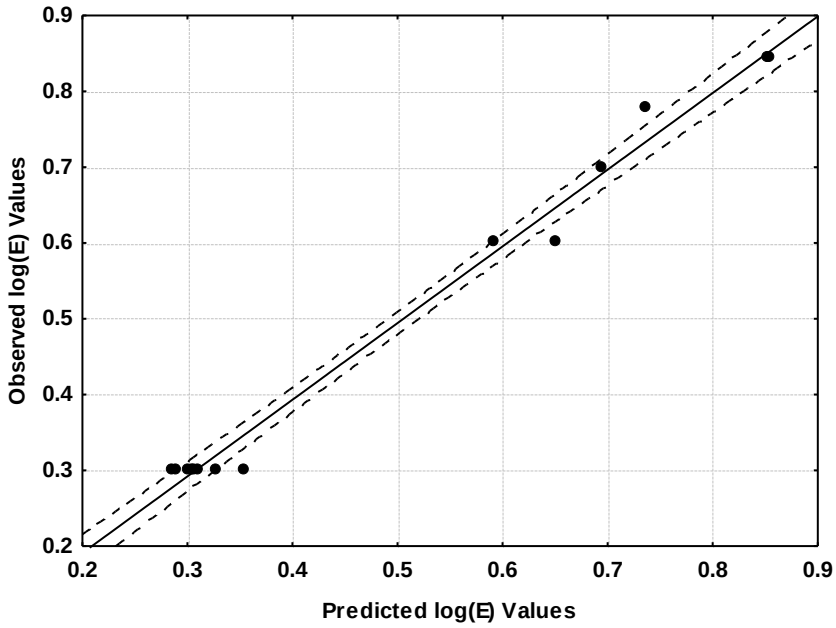

Figure 8: Plot of predicted vs. observed carcinogenic potency (Eq. 2). Dashed lines denote the 95% confidence interval

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 97% of the variation of the carcinogenic activity. Figure 8, spanning about 0.5 orders of magnitude, shows that there is a good correlation of observed *versus* calculated values and that almost all points are inside the 95% confidence interval.

B.4. Discussion of Part B results.

Table 3 shows that the importance of variables is $S_2^E >> S_9^N$(LUMO)* $> \varphi_7$.The examination of the coefficients of the variables of Eq. 2 and knowing that a higher modified index corresponds to a higher carcinogenic activity, allow to suggest that a high activity is associated with high (negative) values for S_2^E, high positive values for S_9^N(LUMO)* and small values for the orientational parameter of the R_7 substituent.High negative values for S_2^E are associated

with high carcinogenic activity. Higher negative values are obtained by shifting upwards the energies of the occupied MOs. As the local HOMO is the dominant term in the electrophilic superdelocalizability definition (if there is HOMO degeneracy the contribution is greater), we require then a more reactive MO. This suggests that atom 2 is interacting with an electron-deficient center, probably donating electrons to it. Interestingly, in part A of this study (see above and also Ref. [55]) the same atom appears to be significant in the corresponding equation. As this is the third time that this atom appears, we hold that this fact proves its importance in the carcinogenic activity.High positive values for S_9^N(LUMO)* are associated with high carcinogenic activity (Fig. 7). This MO has a π nature in all molecules. High positive values are obtained by shifting downwards the energy of $(LUMO)_9^*$. As this makes this MO more reactive, we suggest that atom 9 is interacting with an electron-rich center through at least its first empty local MO. Atom 9 has not hydrogen atoms bonded to it, and this is the first time that it appears to be significant. No previous QSAR study pointed to it. Small values of the orientational parameter of the R_7 substituent (φ_7) are associated with high activity. Therefore, a hydrogen atom is preferred over a methyl group.All the suggestions are displayed in the partial 2D pharmacophore of Fig. 9.

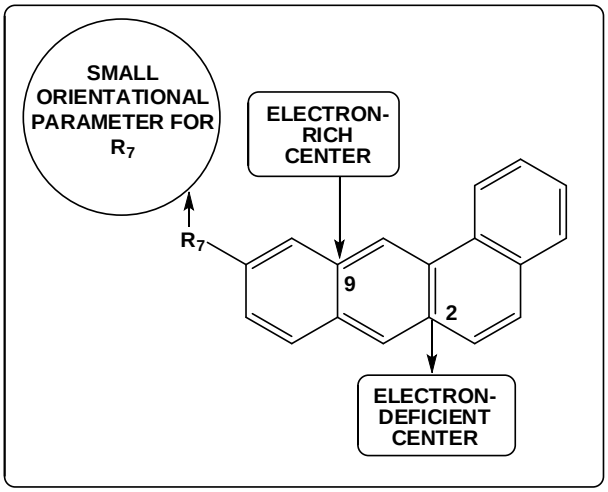

Figure 9: Partial 2D pharmacophore for carcinogenic potency

The previous result and the ones presented here point to the fact that the carcinogenic activity is not only regulated by the carbon atoms with a hydrogen atom or other substituents attached to them, but also by carbon atoms without substituents. This fact can be explained by suggesting that these compounds are placing themselves in such a way that many carbon atoms, with or without hydrogen atoms bond to them, interact simultaneously with the site through their π electron system. *If this suggestion is true, then suggestions such as K-L regions, bay region and M-region are notoriously incomplete*.

Conclusions

In conclusion, we have obtained relevant relationships between the carcinogenic potency and the electronic structure of some benz[a]anthracene derivatives. New carbon atoms that seem to participate in the carcinogenic activitywere detected were detected that were not considered in K-L regions, bay region and M-region models.

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