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A Theoretical Approach to Relate the Reactivity Descriptors and Mulliken Charges with Carcinogenity of Some Methylated Benzo[a]Anthracene

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Abstract

Quantum chemical calculations were carried out to explain how the electronic state and reactivity indices of some methylated benzo [a] anthracenes vary with position and number of methyl substituent in molecules. The global reactivity descriptors such as ionization energy, electron affinity, molecular hardness, chemical potential and molecular philicity were estimated at ab-initio level of theory employing HF /3-21G basis set. After that these factors were correlated with the carcinogenic activity of these compounds. The result showed that two of these factors (The ionization potential (IP) and the total charge at K & L regions) can be correlated with carcinogenic activity of these compounds. On the other hand we found that methyl substitution leads to a great variation on the Mulliken charge of the carbon atoms at and near to the methyl substituents.

Keywords: Methylated benzo[a]anthracene; Theoretical study; Carcinogenity; Mulliken charges.

Introduction

The prediction of electron density at different carbon atoms and the global reactivity descriptors of certain molecule such a ionization potential(IP), electron affinity(EA), chemical hardness(η), chemical potential(μ) and molecular philicity (ω) is very important for the estimation of anticarcinogenic activities. A lot of theoretical methods have emerge to estimate these global reactivity factors [1-7]. One of the major advance application of these reactivity descriptors are the determination reactivity of some polycyclic aromatic compounds [8-10] in the binding with the DNA of the living cell. Among these factors are the reactivity of K&L regions (where K region represent the electron rich region and contain the highest molecular bond -order, while L-region represent the carbon atom which display highest valence indices) which is highly correlated [11-13] with the carcinogenic activity of these compounds. The carcinogenic activity of poly cyclic aromatic hydrocarbon (PAHs) highly varied with the presence of methyl substituent on the aromatic ring of the PAHs [14]. It is well known from the experimental data that chemical substitution, for instance methylation in the PAHs can drastically affect their carcinogenic activity [15] depending on the site of substitution and the number of substituent's.

This work is organized to estimate theoretically the effects of methyl substituent and its position on carcinogenic activity of some methylated Benz(a)anthraceneses. On the other hand the Mulliken charges of each carbon atoms belonging to the molecules under investigation were calculated, together with variation in reactivity descriptors as a result of substitution in order to highlight the effects of substitution on chemical reactivity of the compounds under investigation.

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Methods

Quantum chemical calculations were performed using GAMSS suite programs, the calculations were carried out at the Hartree – Fock energy level with 3-21G basis set. Initial geometry optimization of each molecule was carried out using molecular mechanics by the MM_2 force field [16].

The lowest energy conformers were optimized by means of semiemperical AM1 method [17]. Further optimization of geometry was under taken using HF/ 3-21G level to minimize the structure and to find an appropriate geometry and to lessen calculation time.

The HF method was also used to calculate the physical properties of the PAH compounds like electron density, HOMO, LUMO energy levels, bond order and free valance index. These properties were calculated to select active position (K & L region) and determination chemical potential, hardness and philicity for the molecules under vistigation.

HOMO & LUMO energy levels

Huckel 's molecular orbital theory is a convenient method of expressing the energy levels generated by the p- orbitals of carbon atoms. Energies will be in units of β and α where α is the coulomb integral. The energy of α can be arbitrarily standardized as zero. Then the lowest unoccupied molecular orbital (LUMO) and highest occupied molecular orbital (HOMO) can be identified.

The molecular energy level with the same energy as α is known as the nonbonding molecular orbital, the molecular energy level with a higher energy than α is known anti-bonding molecular orbital. The energy level diagram obtained is sometimes referred to as an energy level spectrum [18].

Bond order calculation

The pi- bond order is a measure of pi-electron density between carbon atoms in a compound. The number of pi- bonds can be established between the atoms. If C_i and C_k are the connecting carbon atoms, N is the number of electrons in a single orbital (1 or 2) a_{ij} and a_{ik} are the coefficients (eigenvectors) then bond orders:

$$p_{jk} = \sum N a_{ij} a_{ik} \quad \text{..... (1)}$$

The bond order thus calculated is known as a mobile bond order or the Coulson bond order [18].

The free valance index calculation

The free valance index is a measure of chemical reactivity. The measurement of the free valance index involves determination of the degree of bonding of that atoms in a molecule to adjacent atoms relative to their theoretical maximum bonding power Coulson defines the free valance index F_r as follows :

$$F_r = (N_{\text{maximum possible bonding power of ith atom}}) - \Sigma p_{ij} \quad \text{.... (2)}$$

Where Σp_{ij} is the sum of bond orders of all bonds to the ith atom including α- bonds [18].

Physical properties calculation

Quantum mechanic calculation methods provide definitions of important universal concept of molecular structure stability and reactivity [19]. An approximation for absolute hardness (η) was developed [20], as follows.

$$\eta = \frac{1}{2}(I - A) \quad \text{.....(3)}$$

where (I) is the ionization energy, (A) the electron affinity.

According to the Koopmen's theorm [21] the ionization energy and electron affinity can be expressed by the following relation:

$$I = - E_{HOMO} \qquad \text{and} \qquad A = - E_{LUMO}$$

Where HOMO is the energy of the highest occupied molecular orbital and LUMO is the energy of the lowest unoccupied molecular orbital.

A higher (or less –ve) HOMO energy corresponds to the more reactive molecule in reaction with electrophiles, while lower LUMO energy is essential for molecular reaction with nucleophiles [22]. The hardness corresponds to the gap between these two orbitals in the molecule. And it measures the resistance of a molecule to a change in their electron distribution. A number of studies shown [23-25] a good relation between the aromaticity and the hardness. i.e a small H-L energy gap has been associated with antiaromaticity and vice versa.

The global electron affinity can also be used in combination with ionization energy to calculate another global reactivity descriptor, the electronic chemical potential (μ), which can be defined [20, 26] as follows:

$$\mu = -\frac{1}{2}(I + A) = \frac{1}{2}(E_{HOMO} + E_{LUMO}) \quad \ldots\ldots(4)$$

While the global philicity index (w) can be evaluated using the electronic chemical potential (μ) and chemical hardness(η) as follow:

$$W = \frac{\mu^2}{2\eta} \quad \ldots\ldots (5)$$

The mulliken charges calculation

The Mulliken procedure is the most common population analysis technique. In population analysis, the electrons in each molecular orbital are partitioned to each atom based on the probability that the electron is in an orbital on that atom at the end of the calculation the fractional occupation for each molecular orbital is summed to get a total atomic electron population for each atom [27].

Mulliken charges arising from the Mulliken population analysis provides a mean of estimating partial atomic charges from calculations carried out by the methods of computational chemistry, particularly those based on the linear combination of atomic orbitals molecular orbital method [28,29].

Results and Discussions

The structure and carbon numbering together with the positions of K&L regions for all Benzo(a) anthracenes under investigation were depicted in Chart (1).

The mulliken charges

The Mulliken charges of each carbon atoms for optimized Geometry of each molecule under investigation were calculated and gathered in (Table 1).

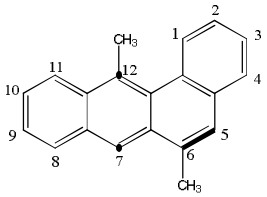
It is clear from (Table 1) that there is a large change in the Mulliken charges of the carbon atoms at which substitution occurs. These variation has pronounce effect on the reactivity of these molecules. In the previous study [30] it was found that the reactivity of K&L regions in PAHs have been used as a critical index for the carcinogenic activity of these compounds. For this reason the total Mulliken charges for the carbon atoms at these regions were calculated and tabulated in (Table 2) according to carcinogenic activity of these compounds. The relationship between the total Mulliken charges at K&L regions and the carcinogenic activity of these compounds was plotted as shown in (Fig.1).

The (Fig. 1) plot showed a good relationship between the total charges and the carcinogenic activity, with value equal to 0.7 for non-carcinogenic compounds, while the value for carcinogenic compounds is reduced to 0.5 or lower. This results offer a good index for indentifying the effect of the substituent on the carcinogenic activity of these compounds.

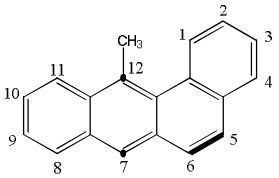
The relationship between the reactivity descriptors and carcinogenic activity

The physical properties of compounds under investigation such as ionization potential (IP), electron affinity (EA), chemical hardness(η), chemical potential and the molecular philicity were calculated and gathered in (Table 2).The Values of IP were calculated from the value HOMO energy, which is equal to the negative value of HOMO energy (21, 31). The relationship between the value of IP and the carcinogenic activity are shown in (Fig. 2).

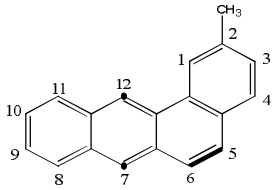
***Chart 1*. Represent the Structure with the positions of K&L regions for the compounds under investigation*[14]**



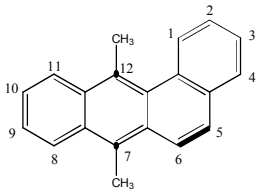
6,12-Dimethyl benzo[a] anthracene
(1) 6,12- DMBA



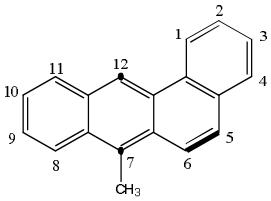
12-Methyl benzo[a]anthracene
(5) 12-MBA



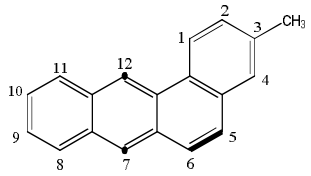
2-Methyl benzo[a]anthracene
(9) 2-MBA



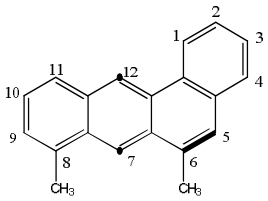
7,12-Dimethyl benzo[a] anthracene
(2) 7,12- DMBA



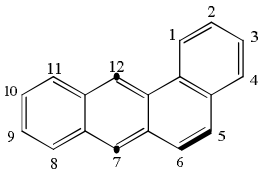
7-Methyl benzo[a]anthracene
(6) 7-MBA



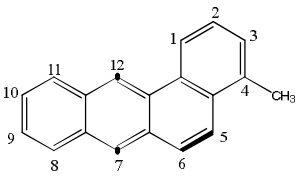
3-Methyl benzo[a]anthracene
(10) 3-MBA



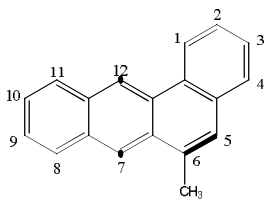
6,8-Dimethyl benzo[a] anthracene
(3) 6,8- DMBA



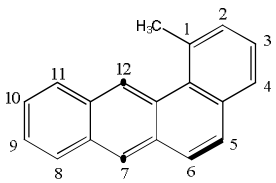
Benzo[a]anthracene
(7) BA



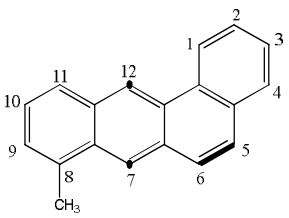
4-Methyl benzo[a]anthracene
(11) 4-MBA



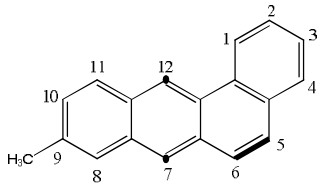
6-Methyl benzo[a]anthracene
(4) 6-MBA



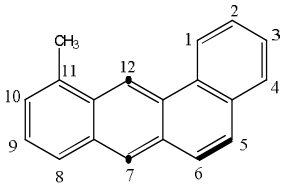
1-Methyl benzo[a]anthracene
(8) 1-MBA



8-Methyl benzo[a]anthracene
(12) 8-MBA



9-Methyl benzo[a]anthracen
(13) 9-MBA



11-Methyl benzo[a]anthracen
(14) 11-MBA

***** The bold line is the K-region & the dote is the L- region

Table 1. **The mulliken charges at all carbon atoms for the compounds.**

Comp No.	Code	C1 C2	C3 C4	C5 C6	C7 C8	C9 C10	C11 C12	C13 C14
1	6,12-DMBA	-0.2151 -0.2391	-0.2353 -0.2006	-0.1830 -0.0069	-0.1791 -0.1864	-0.2390 -0.2386	-0.1984 -0.0111	-0.5982 -0.6203
2	7,12DMBA	-0.2141 -0.2396	-0.2335 -0.1994	-0.1869 -0.1930	-0.0074 -0.1939	-0.2342 -0.2347	-0.1943 -0.0221	-0.5996 -0.6167
3	6,8DMBA	-0.2024 -0.2334	-0.2342 -0.1999	-0.1761 -0.0255	-0.1886 -0.0111	-0.2381 -0.2298	-0.1928 -0.1732	-0.5885 -0.5951
4	6MBA	-0.2031 -0.2335	-0.2348 -0.1989	-0.1858 -0.0068	-0.1759 -0.1884	-0.2385 -0.2390	-0.1861 -0.1745	-0.5935 ---
5	12-MBA	-0.2227 -0.2383	-0.2357 -0.2025	-0.1923 -0.1836	-0.1758 -0.1899	-0.2389 -0.2368	-0.1950 -0.0079	-0.6214 ---
6	7MBA	-0.2044 -0.2324	-0.2353 -0.1985	-0.1852 -0.1901	-0.0043 -0.1938	-0.2341 -0.2400	-0.1850 -0.1825	-0.5973 ---
7	BA	-0.2046 -0.2320	-0.2355 -0.1983	-0.1862 -0.1819	-0.1683 -0.1884	-0.2386 -0.2392	-0.1862 -0.1762	---
8	1-MBA	-0.0314 -0.2194	-0.2302 -0.2041	-0.1852 -0.1841	-0.1705 -0.1901	-0.2369 -0.2404	-0.1853 -0.1880	-0.6103 ---
9	2-MBA	-0.1968 -0.0687	-0.2294 -0.1909	-0.1836 -0.1851	-0.1694 -0.1893	-0.2384 -0.2397	-0.1864 -0.1764	-0.5838 ---
10	3MBA	-0.1970 -0.2255	-0.0692 -0.1922	-0.1870 -0.1813	-0.1679 -0.1886	-0.2392 -0.2390	-0.1871 -0.1781	-0.5861 ---
11	4-MBA	-0.2123 -0.2235	-0.2305 -0.0249	-0.1928 -0.1776	-0.1694 -0.1888	-0.2384 -0.2396	-0.1860 -0.1753	-0.5946 ---
12	8-MBA	-0.2047 -0.2320	-0.2358 -0.1981	-0.1872 -0.1791	-0.1791 -0.0281	-0.2301 -0.2303	-0.1942 -0.1745	-0.5893 ---
13	9-MBA	-0.2051 -0.2318	-0.2361 -0.1980	-0.1861 -0.1825	-0.1710 -0.1898	-0.0689 -0.2254	-0.1796 -0.1747	-0.2051 -0.2318
14	11MBA	-0.2062 -0.2317	-0.2361 -0.1981	-0.1863 -0.1822	-0.1667 -0.1953	-0.2298 -0.2371	-0.0117 -0.1845	-0.2062 -0.2317

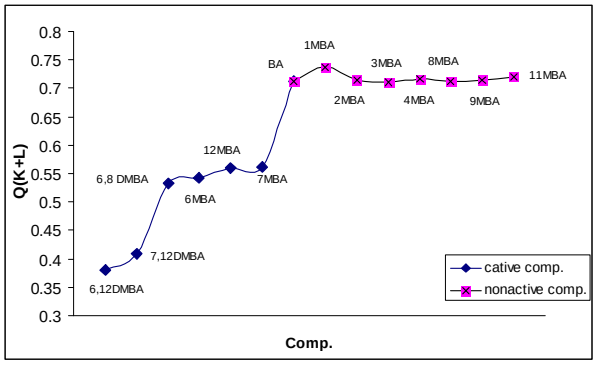


Figure 1. **The relationship between the total charge and the carcinogenic activity.**

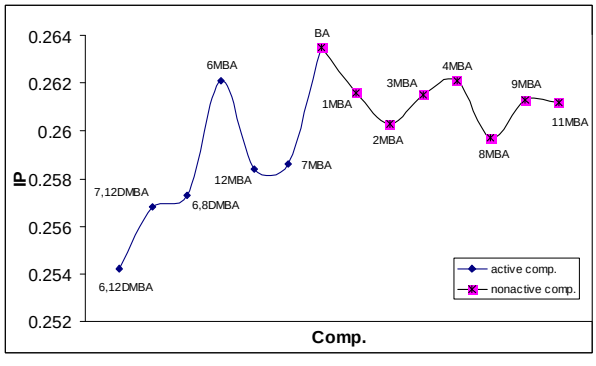


Figure 2. **The relation between IP and carcinogenic activity.**

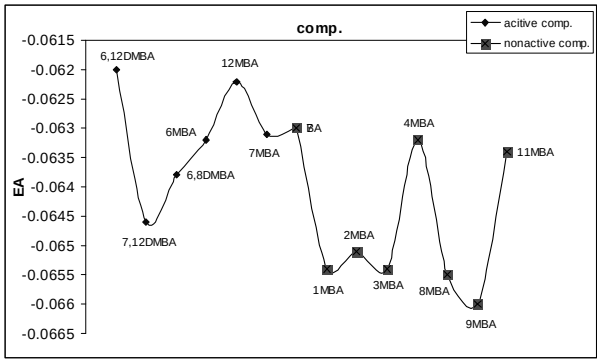


Figure 3. **The relation between EA and the carcinogenic activity.**

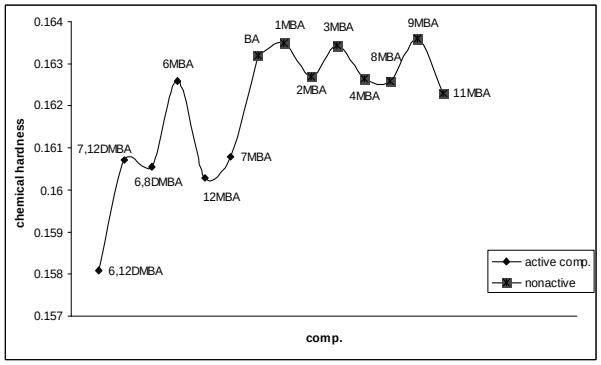


Figure 4. **The relation between the hardness and carcinogenic activity.**

The values of chemical hardness were calculated using equation 3 and tabulated in (Table 2). The relation between the hardness and carcinogenic activity is shown in (Fig. 4), which shows that an increase in the hardness leads to a decrease in the carcinogenic activity.

The values for chemical potential were calculated according to equation 4 and tabulated in (Table 2). The relationship between the chemical potential and carcinogenic activity of these compounds is shown in (Fig. 5).

Table 2. **Physical properties and carcinogenic activity for investigation compounds.**

Sr. No	Code	Ionization Potential	Electron Affinity	Chemical Hardness	Chemical Potential	Philicity	(K+L) Mull Charge	$\mp$ C.A(14)
		I.P	E.A	η	μ	W x 10^{-2}	Q_m	
1	6,12-DMBA	0.2542	-0.062	0.1581	-0.0961	2.92	0.3802	++++
2	7,12-DMBA	0.2568	-0.0646	0.1607	-0.0961	2.873	0.4084	++++
3	6,8-DMBA	0.2573	-0.0638	0.16055	-0.09675	2.915	0.5334	+++
4	6-MBA	0.2621	-0.0632	0.1626	-0.0994	3.04	0.543	++
5	12-MBA	0.2584	-0.0622	0.1603	-0.0981	3	0.5596	++
6	7-MBA	0.2586	-0.0631	0.1608	-0.0977	2.97	0.5621	++
7	**BA**	**0.2635**	**-0.063**	**0.1632**	**-0.1002**	**3.078**	**0.7126**	$\pm$
8	1-MBA	0.2616	-0.0654	0.1635	-0.098	2.937	0.7378	-
9	2-MBA	0.2603	-0.0651	0.1627	-0.0976	2.927	0.7145	-
10	3-MBA	0.2615	-0.0654	0.16345	-0.09805	2.9408	0.7094	-
11	4-MBA	0.2621	-0.0632	0.16265	-0.09945	3.04	0.7152	-
12	8-MBA	0.2597	-0.0655	0.1626	-0.0971	2.899	0.7126	-
13	9-MBA	0.2613	-0.066	0.1636	-0.0976	2.913	0.7143	-
14	11-MBA	0.2612	-0.0634	0.1623	-0.0989	3.013	0.7197	-

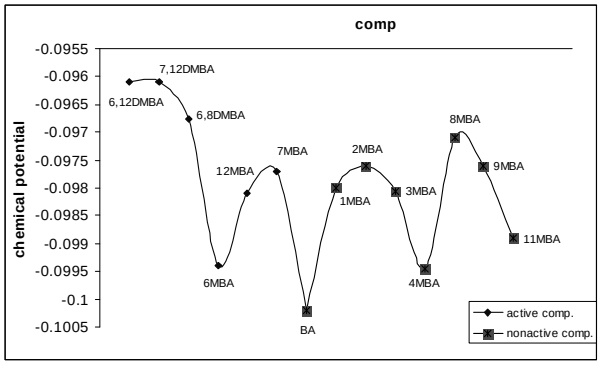


Figure 5. **The relation between chemical potential and carcinogenic activity.**

A perusal of (Fig. 5) reveals that the relation between the chemical potential and carcinogenic activity is very weak.

The values of molecular phillicity were calculated according to the equation 5.

The values of molecular philicity for all compounds under investigation were tabulated in (Table 2). The relationship between these values and carcinogenic activity is shown in (Fig. 6). This plot shows that the phillicity has no relationship with carcinogenic activity of these compounds.

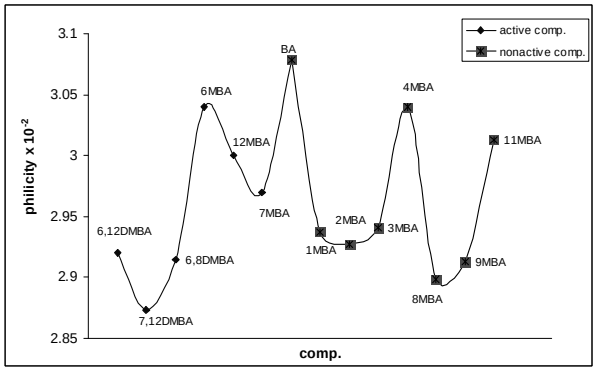


Figure 6. **The relationship between the phillicity and carcinogenic activity.**

Conclusions

1- The methyl substitution of benzo(a)anthracene can lead to a variation of Mullikin charge of the whole atoms in molecules specially the atoms at and near to the substituent.

2- Only the total Mulliken charges variation at K&L regions have a pronounce effects on carcinogenic activity.

3- Two factors (the IP energy and the total Mulliken charges at the two regions K&L) are the most important factors can used to highlight the variations in carcinogenic activity due to the change in the position of methyl substituent.

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