Study of the Relation Between the Theoretical Descriptors Derived From Ab-initio Calculations with the Carcinogenity of Some Poly Aromatic Hydrocarbons

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الخلاصة:

تضمن البحث دراسة ووصف الفعالية لـبعض المركبـات الهيدروكربونيـة متعـددة الحلقات (PAHs) من خلال حساب الطاقة الايونية، الصلادة، مـستويات الطاقـة الجزيئيـة إضافة إلى الكثافة الالكترونية لكل ذرة من ذرات المركبات متعددة الحلقات حيث تـم تطبيـق احد طرق الحسابات الأساسية (Ab-initio level) من نوع هارتري- فوك والمنجـزة عنـد مستوى نظري (3-21G) .

أظهرت النتائج ان اهم العوامل المؤثرة على العلاقة بين قوة تـأثير هـذه المركبـات كمسببات للأمراض السرطانية هي الكثافة الالكترونية العالية لذرة الكربون في المواقع الفعالة أولاً، إضافة الى عامل الصلادة ثانيا حيث تم استخدام الكثافة الالكترونية كمؤشر لقوة الترابط بين مركبات (PAHs) مع مادة (DNA) للخلايا الحية عن طريق عملية الايض حيث تشمل العملية تكوين مركب دايول ايبوكسيد ثم مركب ايون البنزيليك الموجب وعن طريق فتح حلقة الايبوكسيد التي يتم إضافتها الى الجانب الباحث عن النواة في مادة (DNA) ومن خلال هـذه العملية يظهر تأثير هذه المركبات المسرطنة على الخلايا الحية مع اختلاف تراكيبها.

Abstract:

The various types of descriptors such as ionization energy, molecular hardness, electrophilicity, frontier molecular orbital energies together with electron densities of each atom for the optimized geometries of the molecule of different polyaromatic hydrocarbons (PAHs) were estimated by employing on ab-initio method expressed by Hartree – Fock (HF) model performed at the (3-21G) level of theory.

After that these theoretical parametrs were related to the activity carcinogenity of these compounds as carcinogenic agents. The results showed that two factors can be related to carcinogenity of these compounds; the first one is the carbon atoms of low electron densities (i.e the position of electrophilic atoms), the second is the hardness of these compounds.

We have also used electron density to highlight the possible strengths of interactions of PAHs with DNA of living cells. On the bases that the main metabolic pathway for activation of these compounds involves formation of bay-region diol epoxide, then, the benzylic carbocations generated from these electrophilic diol epoxide by opening of the epoxide ring are capable of forming covalent adducts with the nucleophilic site in DNA which represent the main factors of carcinogenity of these compounds since adduct is accepted as a critical step in the mechanism by which (PAHs) can cause a genetic mutation resulting inductions of cancer.

Key words: carcinogenity, PAHs, Ab-initio calculations

Introduction

Poly aromatic hydrocarbons (PAHs) are a class of planner molecules, abundant in urban environment which can induce chemical carcinogenesis. Their carcinogenic power varies in a large range, from very strong carcinogens to inactive ones. Models suggesting a link between the carcinogenic activities of aromatic compounds and electronic properties date back at least to 70 years ago, belongs to the pioneering work published by Schmidt (1). Since that a numerous theories have been proposed (2,3) attempting to correlate electronic indices estimated by using molecular orbital theory with carcinogenic activity. A successful theoretical correlation of this nature is extremely important in chemistry and medicine due to the following reasons:

A) Provides an important view for the chemical mechanism.
B) When the results are perfect, they could provide a rapid and simple screening procedure to replace the time-consuming and expensive animal experiments now required for testing of potential of carcinogens.
C) The results might be used to design an effective antitumer agents.

Most theoretical models proposed for carcinogenity have focused on electronic properties of aromatic hydrocarbons, yielding in many cases quite interesting and suggestive results(4-6). However, during the past years a considerable expansion has been carried out on theoretical calculation of reactivity indices of PAHs.

It was demonstrated (7,8) that the HF / 3-21G is one of the most reliable methods for calculation of geometries and energies of PAHs. The

optimized geometries and calculated electron density parameter of some aromatic hydrocarbons were estimated in order to determine their reactivity in electrophilic substitution and Diels-Alder reaction (9-11).

The concepts of chemical potential (μ), electronegativity (w) and hardness (η) are collectively(12-17) known as global reactivity descriptor, have systemized the study in this area. The principle of maximum hardness (PMH) (18), relating the relative stability of a system to a larger value of hardness has been tested by employing semi- empirical as well as ab-initio quantum chemical calculations (19). Local reactivity descriptors such as Fukui function (FF) and local softness, relating change in electron density to the number of electron and chemical potential respectively have been used to determine the site reactivity of system (20-21). Electrophilicity and nucleophilicity (FFs) have been used as indicators for measuring the reactivity toward different reagents of these compounds (22).

In this work, we presented a study of the reactivity of a number of descriptors for some PAHs in order to highlight the donor- acceptor sites on some PAHs and estimate their capability as carcinogenic factor; since it is well known that the main metabolic pathway of these compounds depends on their capability to form covalent adducts with the nucleophilic sites in DNA and RNA of the living cell leading to alteration in their structure and behaviour as genetic materials (23).

Calculations

Quantum chemical calculations were performed using GAMSS (General atomic and molecular structure system) suite programs.

Initial geometry optimization for each molecule of the poly aromatic hydrocarbons compounds was carried out using molecular mechanics (MM2)(24), then the lowest energy conformers were optimized by means of semiempirical Austain Model 1 (AM1) method (25).

Further optimization of geometry was undertaken using Hartree-Fock level (HF) with the (3-21G) basis set level of theory in order to minimize structure and find an appropriate geometry.

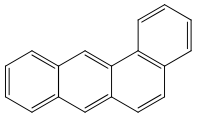
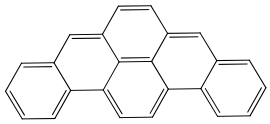
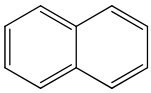
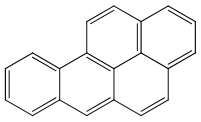
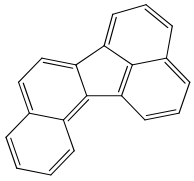
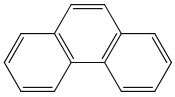
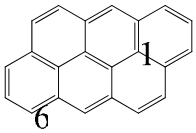
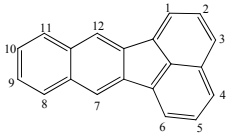
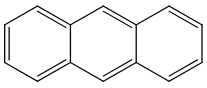
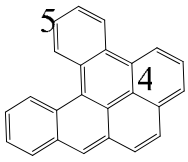
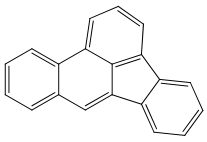
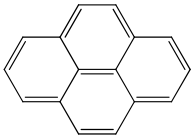
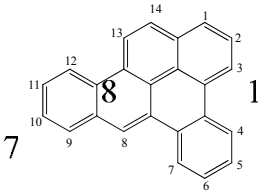
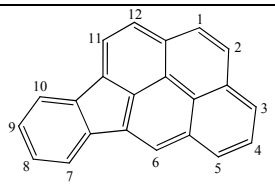
Some physical properties can be calculated with section of GAMSS input. The required data such as Mulliken charges of all atoms and energy levels (HOMO & LUMO) obtained in output. The energies will be in units β relative to α from this HOMO and LUMO can be identified (26).

Result and Discussion

The structure of some poly aromatic hydrocarbons PAHs, together with the numbering active carbon atom in the molecules are shown in

chart (I). Some of these compounds are reasonably anticipated to be human carcinogens based on sufficient evidences obtained from tests carried out on animals experiment (27).

Chart (1) : Structure of Poly Aromatic Hydrocarbons Compounds and their Carbon Number

 Benzene(1)	 Benzo[a]anthracene (6)	 Dibenzo[a,i]pyrene (11)
 Naphthalene(2)	 Benzo[a]pyrene (7)	 benzo[J]fluoranthene(12)
 Phenanthrene (3)	 Naphtha-tetraphene(8)	 benzo[k]fluoranthene (13)
 Anthracene (4)	 Dibenzo[a,l]pyrene (9)	 Benzo[b]fluorathene(14)
 Pyrene (5)	 Dibenzo[a,e]pyrene (10)	 Indeno[1,2,3-cd]pyrene (15)

The Mulliken charges, at the reactive carbon atoms in molecules under investigation together with reactivity descriptors are calculated for the optimized geometries of these compounds. The Mulliken charges at all reactive carbon of these carcinogenic compounds are calculated using ab-initio HF/3-21G method and gathered in Table (1), according to numbering shown in chart No(1).

Table (1): The Mulliken Charges at all Carbon in PAHs*

Comp. no.	C1 C2	C3 C4	C5 C6	C7 C8	C9 C10	C11 C12	C13 C14
1	-0.2392 -0.2392	-0.2392 -0.2392	-0.2392 -0.2392	---	---	---	---
2	-0.1950 -0.2386	-0.2386 -0.1950	-0.1950 -0.2386	-0.2386 -0.1950	---	---	---
3	-0.1956 -0.2368	-0.2327 -0.2039	-0.2039 -0.2327	-0.2368 -0.1956	-0.1875 -0.1875	---	---
4	-0.1860 -0.2403	-0.2404 -0.1861	-0.1860 -0.2403	-0.2404 -0.1861	-0.1713 -0.1713	---	---
5	-0.2081 -0.2273	-0.2081 -0.1822	-0.1822 -0.2081	-0.2273 -0.2081	-0.1822 -0.1822	---	---
6	-0.2046 -0.2320	-0.2355 -0.1983	-0.1862 -0.1819	-0.1683 -0.1884	-0.2386 -0.2392	-0.1862 -0.1762	---
7	-0.2022 -0.2264	-0.2139 -0.1802	-0.1763 -0.1718	-0.1877 -0.2378	-0.2338 -0.1952	-0.1890 -0.1790	---
8	-0.1966 -0.2264	-0.2163 -0.1787	-0.1743 -0.1692	-0.1966 -0.2264	-0.2163 -0.1787	-0.1743 -0.1692	---
9	-0.2096 -0.2211	-0.2114 -0.1818	-0.1779 -0.1625	-0.1831 -0.2399	-0.2356 -0.2058	-0.2094 -0.2373	-0.2294 -0.1971
10	-0.1988 -0.2222	-0.2166 -0.1983	-0.2300 -0.2301	-0.1973 -0.1750	-0.1854 -0.2372	-0.2328 -0.1950	-0.1885 -0.1778
11	-0.1758 -0.1758	-0.1725 -0.1900	-0.2364 -0.2334	-0.1966 -0.1868	-0.1868 -0.1966	-0.2334 -0.2364	-0.1900 -0.1725
12	-0.2475 -0.2253	-0.1940 -0.1942	-0.2260 -0.2507	-0.2052 -0.2343	-0.2394 -0.1861	-0.1844 -0.2179	---
13	-0.2516 -0.2219	-0.1985 -0.1985	-0.2219 -0.2516	-0.2010 -0.1948	-0.2387 -0.2387	-0.1948 -0.2010	---
14	-0.2047 -0.1936	-0.2387 -0.2303	-0.2033 -0.2052	-0.2187 -0.2470	-0.2329 -0.2288	-0.2312 -0.2290	---
15	-0.1799 -0.1792	-0.2024 -0.2306	-0.2010 -0.2010	-0.2298 -0.2329	-0.2273 -0.2364	-0.2254 -0.1987	---

These results reveal that the electron density are homogeneous at different carbon atoms of symmetric molecules such as benzene.

The homogenity decreases as the symmetry of these molecules decreases, producing different types of atoms. These differences in electron density increase the reactivity of atoms toward the electrophilic and nucleophilic substitution reaction. It is well known that, aromatic compounds undergo electrophilic or nucleophilic substitution reactions (aromatic substitution) more easily than to addition reaction. In other words they exhibit tendency to retain their π- electron delocalization with resonance stabilization energy unchanged. So that the highly charged atom has a tendency to accept electrophilic reagent such as positions No. (2&7) in phenanthrene and No.(8&9) in benzo[a]pyrene (8). While position No.(10&11) in phenanthrene and position No.(6) in benzo[a] pyrene have the capability to accepted nucleophilic reagents. i.e these positions tend to react with nucleophilic sites of the DNA in the living cells. These results give a preliminary indication of the capability of these compound to bind with DNA of the cell, performing the first step in carcinogenity of these compounds.

Global Physical Properties

Quantum mechanic calculation methods provide definitions of important universal concept of molecular structure stability and reactivity (28). An approximation for absolute hardness (η) was developed (17), as follows.

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

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

According to the Koopmen's theorm [29] the ionization energy and electron affinity can be expressed by the following relation:

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

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

The higher HOMO energy corresponds to the more reactive molecule in reaction with electrophiles, while lower LUMO energy is essential for molecular reaction with nucleophiles (30). The hardness corresponds to the gab between these two orbitals in the molecule. On the other hand the hardness measures the resistance of molecules to change in their electron distribution. A number of studies shown [31-33] 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 hardness, ionization potential and electron affinity of these compounds were calculated and listed in Table (2).

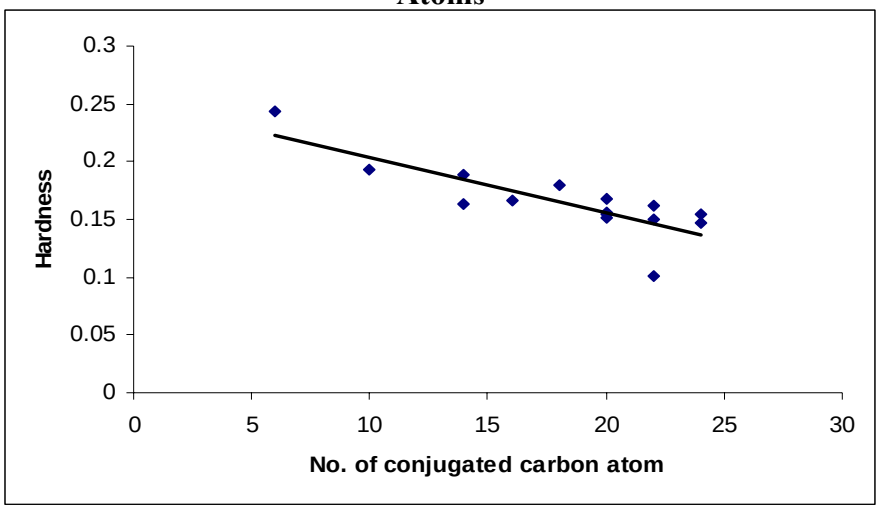
Table (2): Some Physical Properties of Poly Aromatic Compounds

Compounds no.	No. of conjugated carbon atom	Ionization Potential I.P	Electron Affinity E.A	Chemical hardness η
1	6	0.3381	-0.1478	0.2429
2	10	0.2903	-0.0903	0.1929
3	14	0.2860	-0.0919	0.1889
4	14	0.2623	-0.0650	0.1636
5	16	0.2659	-0.0681	0.1670
6	18	0.2635	-0.0635	0.1632
7	20	0.2531	-0.0553	0.1542
8	22	0.2369	-0.0338	0.1015
9	20	0.2524	-0.0498	0.1511
10	24	0.2549	-0.0535	0.1542
11	24	0.2469	-0.0473	0.1471
12	20	0.2704	-0.0400	0.1552
13	22	0.2679	-0.0553	0.1616
14	20	0.2835	-0.0536	0.1685
15	22	0.2617	-0.0369	0.1493

IP= ionization potential = - HOMO, E.A= electron affinity = - LUMO

The relation between the hardness and number of conjugated carbon atoms are shown in Figure (I), which reveals clearly that, the hardness of these compounds decreases as the number of carbon atoms increase.

Figure (1): The Relation Between Hardness and Number of Conjugated Carbon Atoms



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 (17) as follows:

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

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

$$W = \frac{\mu^2}{2\eta} \quad \text{---- (3)}$$

Table (3) summarized the values of chemical potential (μ) and global philicity (w), for the compounds under investigation.

Table (3): The Values of Chemical Potential and Global Philicity

Compounds no.	No. of conjugated carbon atom	Chemical potential μ	Philicity W
1	6	-9.515×10^{-2}	1.86×10^{-2}
2	10	-9.730×10^{-2}	2.45×10^{-2}
3	14	-9.705×10^{-2}	2.49×10^{-2}
4	14	-9.865×10^{-2}	2.97×10^{-2}
5	16	-9.889×10^{-2}	2.93×10^{-2}
6	18	-10.025×10^{-2}	3.07×10^{-2}
7	20	-9.890×10^{-2}	3.17×10^{-2}
8	22	-13.53×10^{-2}	7.93×10^{-2}
9	20	-10.13×10^{-2}	3.39×10^{-2}
10	24	-10.07×10^{-2}	3.28×10^{-2}
11	24	-9.980×10^{-2}	3.38×10^{-2}
12	20	-11.52×10^{-2}	4.27×10^{-2}
13	22	-10.63×10^{-2}	3.49×10^{-2}
14	20	-11.49×10^{-2}	3.91×10^{-2}
15	22	-11.24×10^{-2}	4.23×10^{-2}

Figures (2) and (3) represent the relation between (μ) and (w) with number of carbon atoms in molecules. The value of (μ) decreases as the carbon number increases with large deviation from linearity. On the other hand the value of (w) increases as the number of carbon atom increase. The above relationships are all showed a very low values of R^2 indicating that, the global reactivity factors are not the only factors can be used to visualize the reactivity and carcinogenity of these compounds, so that we thought that local reactivity at some positions in these compounds may play an important role in reactivity and carcinogenity of these compound.

Figure (2): The Relation Between Chemical Potential (μ) and Number of Conjugated Carbon Atoms

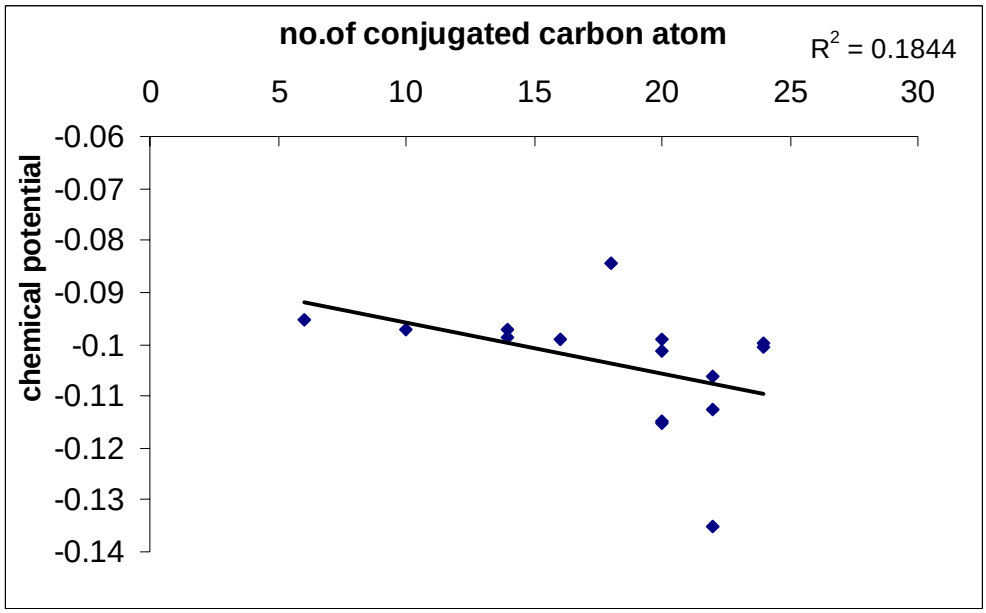
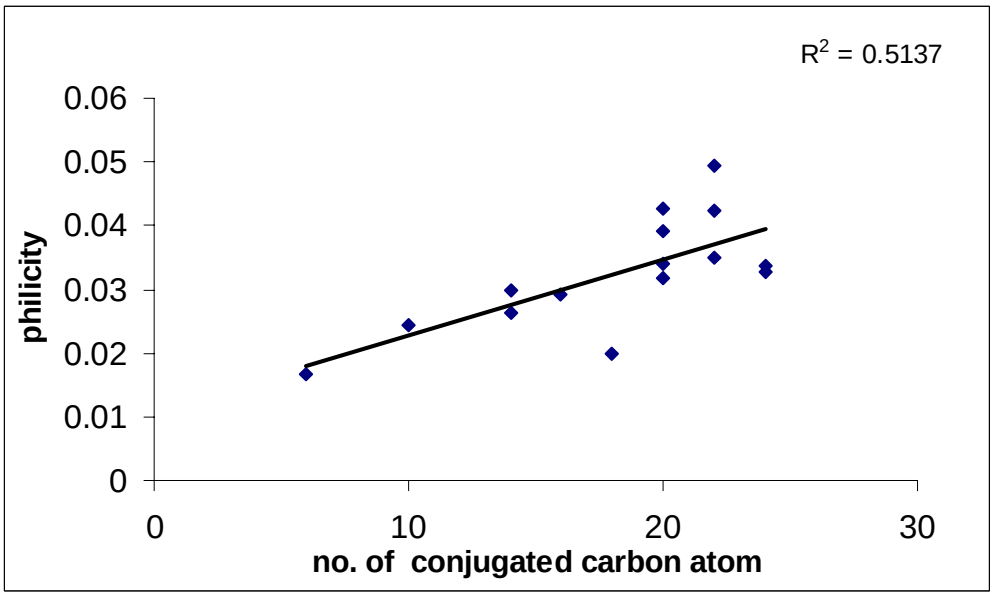


Figure (3): The Relation Between Global Philicity (w) and Number of Conjugated Carbon Atoms



Carcinogenicity

The L and K- region theory represent the first successful attempt to explain the carcinogenicity of poly aromatic hydrocarbons where the K-region is defined as the electron-rich region and containing the highest molecular π- bond order while the L- region consist of two para carbon atoms which display the highest free valance indices. Moreover Boyland and Kooymans pointed out that the presence of K-region alone it seems difficult to explain the mechanism of carcinogenesis (5, 34). The presence of K- region is an essential condition for carcinogensis and required the presence of inactive L- region as a supplementary condition. This implies the mutual dependence between the two regions L and K (35). This result showed the importance of the presence of trans butadiene conformation in PAHs for the carcinogenity of these compound. These positions 1 and 2 correspond to the two atoms of K-region and the other carbon atom (position 4) correspond to L-region. Chart number (2) shows the position of K- region for these compound together with trans position (position 4).

It is well known that the carcinogenity of these compound depends on their capability to form covalent bond with nucleophilic sites of the DNA. For this reason electrophilicity (f^+) position of these compound were theoretically calculated as shown in following equation

$$f^+ = q_a\,(N+1) - q_a(N) \qquad \text{---- (4)}$$

which q_a (N+1) and q_a(N) stand for the Mulliken charges on (a) atom of the anion and neutral molecule respectively. The result of these calculation are gathered in Table (4).

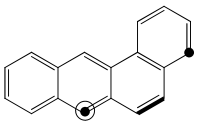
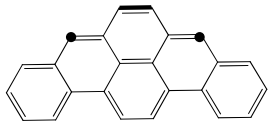
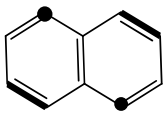
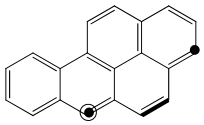
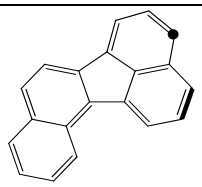
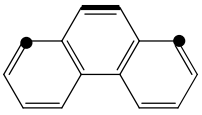
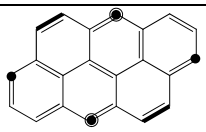
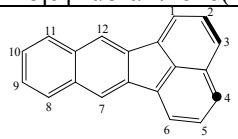
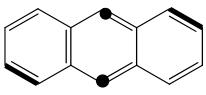
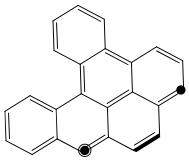
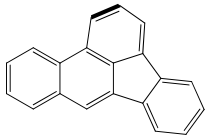
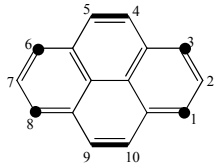
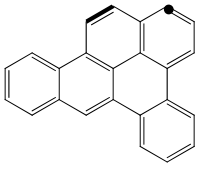
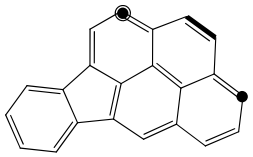
Table (4) shows that the non-carcinogenic compounds have values of ($\boldsymbol{f^+}$) less than 0.17 for trans position while all carcinogenic compounds have value greater than 0.17 which implies that the **($\boldsymbol{f^+}$)** factors are most important factors in determining the carcinogenity of these compound. These results are in agreement with the result reported by Park (36), where the sum of π- electron densities in the LUMO for the two carbon at K-region (position 1,2) together with position 4 in L-region represent a good index for carcinogenicity of some series of PAHs compounds.

Table (4): The Electrophilicity (f^+) Values for Trans Position (Position 4) to K-region

Compounds No.	f^+(4-position)	f^+(K-region)	Carcinogenity(37)
1	C1= 0.0705	---	-
2	C8 = 0.116643	C1=0.117407 C2=0.09082	-
3	C1& C6 = 0.12719	C9&C10=0.134878	-
4	C10 = 0.132676	C1=0.134818 C2=0.107131	-
5	C3&C6= 0.166008	C4&C5=0.139367	-
6	C7 = 0.193075	C5=0.142721 C6=0.139039	+

7	C6= 0.22520	C4=0.146466 C5=0.144184	+++
8	C6&C12=0.233685	C4=0.147250 C5=0.145977	+
9	C3= 0.177332	C4=0.151361 C5=0.148572	+
10	C1= 0.173988	C13= C14=0.165431	+
11	C3&C8= 0.227341	C5=0.158584 C6=0.101942	+
12	C3= 0.22362	C4=0.167411 C5=0.105920	+
13	C4= 0.161552	C2=0.102191 C3=0.16214	+
14	---	C6=0.170523 C7=0.110546	+
15	C3= 0.188813	C1=0.141187 C2=0.152877	+

Chart (2): The position of K- region for PAHs together with trans position to K-region (position 4)*

 Benzene(1)	 Benzo[a]anthracene (6)	 Dibenzo[a,i]pyrene(11)
 Naphthalene(2)	 Benzo[a]pyrene (7)	 benzo[J]fluoranthene(12)
 Phenanthrene (3)	 Naphtha-tetraphene(8)	 benzo[k]fluoranthene (13)
 Anthracene (4)	 Dibenzo[a,l]pyrene (9)	 Benzo[b]fluorathene(14)
 Pyrene (5)	 Dibenzo[a,e]pyrene (10)	 Indeno[1,2,3-cd]pyrene(15)

* K-region are represented by the bold lines.
The trans positions to K-region, represented as bold dots.

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