Cumhuriyet Science Journal
CSJ

e-ISSN: 2587-246X
ISSN: 2587-2680

Cumhuriyet Sci. J., Vol.38-4, Supplement (2017) 138-155

A Computational Study of 1-Substituted Methyl 9-Methyl-9H-Pyrido[3,4-*b*]indole-3-Carboxylate: Quantum Chemical Descriptors, FMO and NBO Analysis

Mustafa ELIK*, Goncagul SERDAROGLU

Department of Mathematics and Science Education, Cumhuriyet University, Sivas / TURKEY

Received: 19.11.2017; Accepted: 06.12.2017 *http://dx.doi.org/10.17776/csj.356185*

Abstract: This work dealt with the investigation of the methyl 9H-pyrido[3,4-b]indole-3-carboxylate (Basic compound) and its C1-substituted derivatives to search for the best substituent group that enhances the chemical reactivity behavior of the Basic compound. In this context, DFT (Density Functional Theory) calculations were performed at B3LYP level of theory at three basis sets, also in 10 different solvents because the chemical behavior strongly depends on the solvent media. This study revealed that the anthracene-9-yl substitution on the C1-position of the Basic compound has increased the chemical reactivity of the Basic compound more than those of the other substituent groups. Also, the results were supported by the NBO analysis: the highest electron delocalization for the structure A was found out π C19-C20→ p_v C42-C43 with the interaction energy of the 50.98 kcalmol-1, due to the anthracene-9-yl substitution on the C1-position of the Basic compound makes the electron delocalization on the substituted compound enhances, at 6-311++g**basis set in the water phase.

***Keywords*:** Quantum chemical descriptors, substituent effect, NBO, FMO analysis

1- Sübstitüeli Metal-9-Metil-9H-Pirido [3,4-*b*]indol-3-Karboksilat Üzerine Hesaplamalı Kimya Çalışması: Kuantum Kimyasal Belirleyiciler, FMO ve NBO Analizi

Özet: Bu çalışma metil 9H-pirido [3,4-b] indol-3-karboksilat (Temel bileşik) ve bu bileşiğin C1-substitüeli türevlerinin incelenmesi ile Temel bileşiğin kimyasal tepkime davranışını arttıran en iyi substitüe grubu belirlemek ile ilgilenmiştir. Bu bağlamda DFT (Yoğunluk Fonksiyonel Teori) hesaplamaları 3 temel set ve kimyasal aktivite davranışı çözücü ortamına bağlı olduğundan dolayı 10 farklı çözücü ortamında yapılmıştır. Bu çalışma, Temel bileşiğin C1-konumundaki antrasen-9-il substitüe grubunun, diğer sübstitüe gruplarınınkinden daha fazla Temel bileşiğin kimyasal reaktivitesini arttırdığını ortaya koymuştur. Ayrıca, sonuçlar NBO analizi ile desteklenmiştir: 6-311++g(d,p) temel seti ile su fazında, Temel bileşiğin C1 konumunda antrasen-9-il substitüe grubu bulunduğunda elektron delokalizasyonu arttığından dolayı, A bileşiğinin en büyük elektron delokalizasyonu π C19-C20→ p_v C42-C43 elektronik geçişi için 50.98 kcalmol^{-1} olarak bulunmuştur.

Anahtar Kelimeler: Kuantum kimyasal tanımlayıcılar, bağlı grup etkisi, NBO, FMO analizi

* Corresponding author. *Email address:* *melik@cumhuriyet.edu.tr*

1. INTRODUCTION

Beta Carboline (βC) with the structural unit (9-hydro-pyrido (3,4-*b*) indole) is a prototype molecule being the planar polycyclic system and its derivatives are natural-occurring in many medicinal plants as well as are produced from the marine organism and the human tissues as secondary metabolism. [1-3] Because of their polycyclic structure, they act on different receptor sites such as Benzodiazepine Receptor (BzR), imidazoline and serotonin receptors in CNS (Central Nervous System) [4-6], and therefore they have invaluable importance in terms of the pharmaceutical.

In the literature, there is much research of βC and of its derivatives about their actions on several receptor sites and/or about their biochemical/biophysical properties which is important to illuminate the causes of the challenging diseases, like cancer and AIDS. Because of the anticancer and anti-HIV activities, novel βC derivatives are synthesized and continue to be increasingly synthesized. [7-10] Also, the cytotoxicity is important to be determining the good anti-cancer agents as well as for investigating the drug/agent used in the many other diseases. For this reason, the scientists have led to study the cytotoxic activity of the βCs. [11-13] In the past, it had been suggested by Cao R. et al. that the type of the substituent group and its location on the βC nucleus, especially the position 1- and position 9-, are very important to improve the cytotoxic potency of the βCs. [11] Also, Chen Z. and co-workers have synthesized the novel βC derivatives as the potent antitumor agents to determine the structural requirements of them and to evaluate the structure-activity relationship. They have shown that the cytotoxic potency of each derivative depends on both the length of the substituent group as well as the position of the substituent group of βCs. [13] On the other hand, the photochemical/ photophysical properties [14-17] of the βCs have also commonly investigated by scientist because the cytotoxic activity is affected by light. Until now, the acid-base equilibria of the βCs have been widely studied due to it is vital to elucidate the photo tautomerism and H-bonding interaction affecting the photochemical/photophysical properties of the βCs. Reyman and co-workers [18] have suggested that the proton-transfer reactions strongly depends on the solvent-compound and on the solvent-cage interaction resulting in the change of the fluorescence Dynamics due to the increase in the charge density of pyridine nitrogen (the stronger base) in the ground state, and vice versa for pyrrole nitrogen (stronger acid). In another work, Biondic MC and Erra-Balsells R [19] had determined the pKa of the βC derivatives by spectrophotometric methods to evaluate the acid-base equilibrium in the ground and in the excited states of the βCs; they had proposed that the partially hydrogenated βCs were more basicity than the full aromatic pyridinic ring. Guan H and et al. [20] had also synthesized the novel 1,3,9-trisubstituted βCs derivatives as the photosensitizers. Accordingly, they had confirmed that the nitrogen atom in position-2 could contribute to the photophysical properties of the compound more than the alkyl or aryl group in position -9.

Although these compounds have been extensively studied on from their synthesis to the photochemical properties of them, the physical and chemical reasons of underlying their current effects have not been adequately illuminated. Nowadays the computational tools have got increasingly used to explain the mechanism of action of the pharmaceutical important compounds, but the current computational works are limited [4-5, 17, 21-22], and even Molecular Orbital calculations for the **Basic** compound have not been found in the literature. The only computational study was performed to explain the photophysical properties of the **Basic** compound. [22]

Mainly, this work aims to determine the comprehensive the quantum chemical parameters of studied molecules how substituent group influenced the efficiency of the **Basic** structure, not only in the gas-phase but in the 10 solvents as well. The first, the solvation free energy and the dipole moments of the studied molecules were calculated to determine the chemical stability behavior of the

studied compounds. Second, Natural Bond Orbital (NBO) analysis was carried out to determine the possible intramolecular interactions such as the hyperconjugation, resonance, electron delocalization resulting in the chemical stability of the compounds. After that, the Frontier Molecular Orbital (FMO) analysis was performed to show the nucleophilic or electrophilic attack centers. Last, the quantum chemistry parameters such as electrophilicity, the capability of charge transfer, electronic chemical potential, the Energy Gap obtained from HOMO and LUMO energies were calculated to determine which substituent group influenced the efficiency of the **Basic** structure.

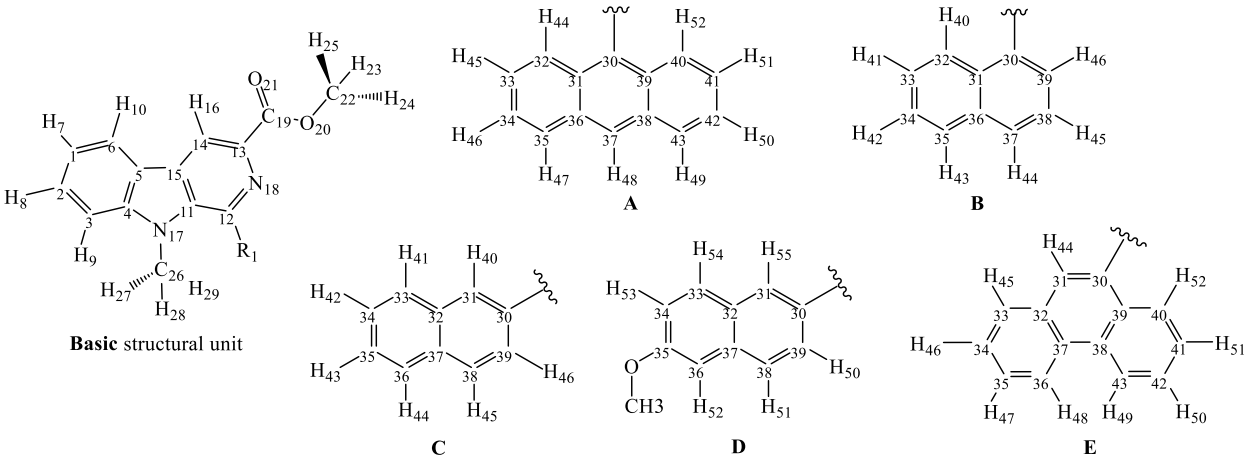

Figure 1. The methyl 9H-pyrido[3,4-b]indole-3-carboxylate (**Basic** compound) and its substituent groups as **A** (anthracen-9-yl)**, B** (naphthalene-1-yl)**, C** (naphthalene-2-yl)**, D** (6-methoxynaphthalene-2-yl)**, E** (phenanthrene-9-yl).

2. COMPUTATIONAL METHOD

In this study, the methyl 9H-pyrido[3,4-b]indole-3-carboxylate (**Basic**) and its derivatives depicted in Figure 1 were optimized at 6-31G(d,p) basis set in the gas phase. In this study, all methyl 9H-pyrido[3,4-b]indole-3-carboxylate derivatives depicted in Figure 1 were optimized at 6-31G(d,p) basis set in the gas phase. Then the stable structures in the gas phase were used as a starting structure in the 10 solvents media to look for the dielectric media effect on both the quantum chemical and physicochemical parameters. The same calculation routes were repeated at both the 6-311++G(d,p) and 6-31+G(d,p) basis sets to investigate the basis set effect on the chemical reactivity behavior of these compounds. The Gaussian 09W [23] software package was used for all DFT calculations at B3LYP level of theory which is a combination of Becke's three-parameter hybrid exchange functional [24] and the Lee-Yang-Parr correlation functional. [25] The solvent phase calculations have been employed with IPCM (Polarized Continuum Model (PCM) with Isodensity version) [26- 27] in the 10 solvent environments with ε= 2.37, 4.71, 5.70, 8.93, 9.16, 24.85, 32.61, 36.69, 46.83, 78.36 to simulate Toluene (T), $CHCl_3$ (Chloroform, C), C_6H_5Cl (Chlorobenzene, CB), CH_2Cl_2 (Dichloromethane, DCM), Quinoline (Q), C_2H_5OH (ethanol, E), CH_3OH (Methanol, M), Acetonitrile (A), DMSO (dimethylsulfoxide, DMSO), H_2O (water), respectively.

In according to Koopmans Theorem [28], the Ionization energy (I) and electron affinity (A) can be expressed through HOMO and LUMO orbital energies [29] as follow:

$$I = -E_{HOMO} \quad (1) \qquad A = -E_{LUMO} \quad (2)$$

DFT based global descriptors such as electronic chemical potential (μ), global hardness (η), electrophilicity (ω) and the maximum charge transfer index (ΔNmax) have been represented by Parr R.G. and co-workers [30] as follow:

$$\mu = -\frac{I+A}{2} \quad (3) \qquad \eta = \frac{I-A}{2} \quad (4)$$

$\omega = \frac{\mu^2}{2\eta}$ (5) $\Delta N_{max} = \frac{I+A}{2(I-A)}$ (6)

3. RESULTS AND DISCUSSION

3. 1. Molecular Geometry

Table 1 has shown the selected structural parameters of each studied compounds at B3LYP/6-311++G** level of theory in the water phase. Full optimized parameters of these molecules are given as supporting information of this article (Table S1). There are no important differences between the results obtained from the different solvent media even though they are not the same value. From Table 1, the bond lengths of C11- C15 for the **Basic** molecule and it substituted derivatives have changed in the range of 1.4 Å - 1.5 Å. The biggest changing in the bond lengths with adding the substituent group to the **Basic** structure is calculated for the bond length of C12-H30 (R1), that is, this bond length is calculated as 1.1 Å for **Basic** compound and as 1.5 Å for **A**. It is clear from Table 1 that the bond lengths for each substituted derivative were calculated as bigger than that of the **Basic** compound. If it is looked at the results of the valence angles, there is no significant difference between the **Basic** compounds' valence angles and those of its derivatives except the N17-C4-C3 bond angle. The N17-C4-C3 bond angle is determined as 109.4 ^{0} for the **Basic** structure but this valence angle is about the 129.2 ^{0} for the structure **E**. The N17-C4-C3 bond angle for **E** has distorted with the phenanthrene-9-yl substituent group attached to the **Basic** structure. One of the important things what we should express here is that there is no experimental data about structural parameters of the substituted **Basic** compound in literature. As upon our best acknowledge, there are the bond angles of the 3-carboxylic acid-1,2,3,4-terahydroharmane which is closely related to the derivatives studied in this work and we have compared the structural parameters of the 1-substituted **Basic** compound with those of this compound. Accordingly, the valence angles of C6-C5-C15, C6-C5-C4, C15-C5-C4, N17-C4-C5, C11-N17-C4 for the 3-carboxylic acid-1,2,3,4-terahydroharmane were determined as 134.7^0, 119.5^0, 105.7^0, 108.7^0, 107.6^0 by Codding P.W, in the past. [31] In this work, the same valence angles for the structure **A** is found to be 133.9^0, 120.0^0, 106.0^0, 109.6^0, 108.5^0 by B3LYP/6-311++G(d, p) level of the theory in the aqueous phase, respectively. Here the biggest distortion corresponding to the **Basic** molecule is found to be the N18-C13-C19-O20 dihedral angle for the compound **D** with 2^0 even though there is no big change of this angle. Notwithstanding, the N18-C12-C36-C39 dihedral angle of each substituted structure is quite different from each other. For example, this dihedral angle for the structure **A** is 82.9^0, so it can be said that the substituent part (anthracen-9-yl) of the **A** is nearly perpendicular to the planar indole ring with ~7^0 deviation angle. But for the structure **D** including the 6-methoxynaphthalene-2-yl group substitution at C1-position of the **Basic** structure, the N18-C12-C36-C39 dihedral angle is -47.8^0. Moreover, the same dihedral angle for the structure **C** containing the naphthalene-2-yl group substitution at C1-position of the **Basic** structure is at -48.6^0. so, it seems that the methoxy group at 6- position of the substituent part of the structure **D** doesn't affect the N18-C12-C36-C39 dihedral angle because this angle is calculated very similar to each other for structures **C** and **D**. The N18-C13-C19-O20 torsion angle for **Basic** compound is determined as 0^0 by Dorey G. et al. [32] and it has been computed as -180^0 in this work. For the other substituted structures, **A**, **B**, **C**, **D** and **E**, the N18-C13-C19-O20 torsion angle is close to the 00 which means that the C=O group at C3-position are on the same plane as indole ring.

Table 1. The selected geometric parameters for the structures **A-E** calculated at B3LYP/6-311++G(d,p) basis set in the water phase.

Bond Length (Å)	**Basic**	**A**	**B**	**C**	**D**	**E**
N17-C26	1.5	1.5	1.5	1.5	1.5	1.5
N17-C11	1.4	1.4	1.4	1.4	1.4	1.4
N17-C4	1.4	1.4	1.4	1.4	1.4	1.4
C11-C15	1.4	1.4	1.4	1.4	1.4	1.4
C11-C12	1.4	1.4	1.4	1.4	1.4	1.4
N18-C12	1.3	1.3	1.3	1.3	1.3	1.3
N18-C13	1.4	1.3	1.3	1.3	1.3	1.3
C13-C19	1.5	1.5	1.5	1.5	1.5	1.5
C19-O20	1.3	1.3	1.3	1.3	1.3	1.3
C19-O21	1.2	1.2	1.2	1.2	1.2	1.2
C22-O20	1.4	1.4	1.4	1.4	1.4	1.4
C12-H30 (R1)	1.1	1.5	1.5	1.5	1.5	1.5
Valence angle (^{0})						
N17-C26-H29	109.6	109.2	109.0	111.7	111.7	110.1
N17-C11-C12	130.8	132.3	132.2	132.2	132.2	132.0
N17-C4-C3	109.4	128.9	129.0	129.1	129.1	129.2
C11-C15-C5	106.5	107.1	107.1	107.1	107.1	107.0
C11-C12-N18	121.3	120.1	120.0	119.8	119.7	120.1
N18-C12-H30 (R1)	117.0	115.4	115.6	115.4	115.5	115.9
N18-C13-C14	123.6	123.2	123.3	123.2	123.3	123.3
N18-C13-C19	118.5	118.6	118.6	118.6	118.7	118.6
C13-C19-O20	113.6	113.6	113.6	113.6	113.6	113.6
C13-C19-O21	123.4	123.3	123.3	123.3	123.3	123.3
C19-O20-C22	116.3	116.3	116.3	116.4	116.4	116.3
O20-C19-O21	123.0	123.1	123.1	123.1	123.1	123.1
H25-C22-O20	110.4	110.4	110.4	110.4	110.4	110.4
C3-C4-C5	121.5	121.5	121.4	121.3	121.3	121.2
C12-C36-C39		119.8	119.2	119.4	119.5	120.9
C12-C36-C32		119.6	121.0	121.4	121.5	119.2
Dihedral angle (^{0})						
C4-N17-C26-H29	-42.2	-45.5	-40.5	-92.7	-92.3	-146.8
C11-N17-C26-H29	141.8	137.0	139.1	94.3	95.2	33.9
N17-C11-C12-N18	-179.4	-179.4	-177.9	174.0	173.8	-177.8
C26-N17-C4-C3	2.5	1.1	-1.2	6.6	7.1	-179.0
N17-C11-C15-C5	-0.7	-0.6	-1.1	2.1	2.2	-1.3
C13-N18-C12-H30 (R1)	179.6	179.3	179.0	-175.4	-175.3	177.0
C12-N18-C13-C14	-0.2	-0.3	-0.7	1.0	1.2	-0.5
C12-N18-C13-C19	179.9	179.9	179.8	-179.9	-179.7	-179.9
N18-C13-C19-O20	-180.0	-0.1	-1.0	1.7	2.0	-0.3
N18-C13-C19-O21	0.0	179.9	179.1	-178.5	-178.3	179.7
C13-C19-O20-C22	-179.9	-179.9	-179.9	-179.2	179.9	-179.9
O20-C19-C13-C14	-179.9	-179.9	179.5	-179.2	-178.9	-179.8
H25-C22-O20-C19	60.7	60.7	60.6	60.8	60.9	60.6
N18-C13-C14-H16	-179.7	-179.6	-179.0	178.1	178.0	-179.1
C3-C4-C5-C6	0.5	0.4	0.3	-0.2	-0.2	0.5
N18-C12-C36-C39		82.9	69.9	-48.6	-47.8	78.7
N18-C12-C36-C32		-95.7	-108.0	127.5	128.0	-100.0

Table 2. The Solvation Free Energy (in kcalmol^{-1}) of both the **Basic** compound and its C1- substituted derivatives, in 10 solvent environments with 6-31g(d,p), 6-31+g(d,p) and 6-311++g(d,p) basis sets.

	T (ε=2.37)	**C (ε=4.71)**	**CB (ε=5.70)**	**DCM (ε=8.93)**	**Q (ε=9.16)**	**E (ε=24.85)**	**M (ε=32.61)**	**A (ε=36.69)**	**DMSO (ε=46.83)**	**Water (ε=78.36)**
6-31g(d.p)										
Basic	3.780	5.745	6.138	6.859	6.892	7.733	7.855	7.888	7.973	8.082
A	3.603	5.957	6.465	7.437	7.483	8.705	8.891	8.943	9.075	9.249
B	4.003	6.175	6.649	7.560	7.603	8.667	8.823	8.864	8.970	9.109
C	4.119	6.156	6.580	7.386	7.425	8.459	8.618	8.663	8.778	8.929
D	4.533	6.829	7.314	8.236	8.279	9.435	9.612	9.662	9.789	9.957
E	3.894	6.224	6.716	7.645	7.689	8.849	9.025	9.075	9.201	9.367
6-31g+(d.p)										
Basic	4.208	6.582	7.056	7.826	7.866	8.913	9.066	9.108	9.216	9.357
A	4.930	7.401	7.971	9.040	9.094	10.422	10.611	10.869	10.803	10.977
B	4.502	6.841	7.347	8.320	8.366	9.613	9.804	9.858	9.995	10.176
C	4.801	7.484	8.268	9.142	9.185	10.329	10.479	10.518	10.625	10.756
D	5.120	8.013	8.650	9.935	9.996	11.340	11.515	11.566	11.691	11.854
E	4.217	6.920	7.501	8.624	8.678	10.122	10.343	10.406	10.567	10.777
6-311g++(d.p)										
Basic	4.162	6.416	6.881	7.747	7.788	8.820	8.970	9.012	9.120	9.261
A	4.721	7.819	8.459	9.726	9.797	**9.420**	**9.659**	**9.726**	**9.893**	11.126
B	4.497	6.858	7.363	8.343	8.389	9.659	9.852	9.883	10.048	10.232
C	4.959	7.474	8.023	9.070	9.125	10.319	10.479	10.486	10.639	10.790
D	5.186	8.040	8.680	9.807	9.860	11.188	11.383	11.435	11.570	11.742
E	4.265	6.970	7.553	8.688	8.742	10.208	10.422	10.496	10.663	10.882

3. 2. Physico-Chemical Properties

The solvation free energy changing ongoing from the gas phase to the water phase for **Basic** compound and its aromatic substituted derivatives are shown in Figure 2, the numerical data is given in Table 2. Here, it is clear from Figure 2a that the Solvation free energy for the **Basic** structure increases as the solvent dielectric constant increases, in systematically because of the more dielectric constant causes the more polarization resulting the more stabilization in the molecule. But, this systematic changing in the ordering of the solvation free energy for the **Basic** structure is not calculated for the basis sets used in this work: the solvation free energy for the 6-31+g** basis set (it is indicated by red line) is bigger than that of the 6-311++g** basis set (it is shown by blue line) which is the largest basis set than those of the other basis sets used in this work. Contrary to expectations, as the basis set is increased, the molecule has not become more stable in thermodynamically in according to these results. Here, the important concern is how relative solvation free energy will change by increasing the solvent dielectric constant when one aromatic group is attached to the C1 position of the **Basic** compound. It can be seen from Table 2 that there is no systematic changing in the ordering of the solvation free energy of the C1-substituted **Basic** compound: the free energy changing for these derivatives strongly depends on both the basis set and especially the solvent media. For example, the free energy of these compounds for the toluene has changed in the following order of the **A**(3.603)< **Basic**(3.780)< **E**(3.894)< **B**(4.003)< **C**(4.119)< **D**(4.533) at the 6-31G** basis set while this ordering is found out as follows: **Basic**(4.208)< **E** (4.217)< **B**(4.502)< **C** (4.801)< **A**(4.930)< **D**(5.120) at the 6-31+G** basis set(solvation free energies are in kcalmol^{-1} unit). From Table 2, the solvation free energy is calculated in the same order for both the 6-31+g** and 6-31++g** basis sets in water phase: **Basic**(9.357)<**B** (10.232)< **C**(10.790)< **E** (10.882)< **A**(11.126)< **D**(11.742) for 6-311++g** basis set and **Basic** (9.357)<**B** (10.176)< **C**(10.756)< **E** (10.777)< **A**(10.977)< **D**(11.854) for 6-31+g** basis set. Even the free energy depends on both the solvent media or on the basis set, it is not wrong to say that of each substituent group makes the **Basic** structure stabilized, more or less. Also, among the C1 substituted **Basic** compound, the structure **D** containing the polarizable group as the 6-methoxynaphthalene-2-

yl substitution at C1- position of itself is the more stabilized derivative by increasing the solvent dielectric constant for all basis sets used in this work. It is noticed also from Figure 2d that there is a deviation from the structure **A** for the ethanol, methanol, acetonitrile, and DMSO solvents with the negative imaginary frequency of -8.30 cm^{-1}, 10.36 cm^{-1}, 10.92 cm^{-1}, and 12.30 cm^{-1} respectively. Although these negative frequencies are not great value, they have affected the free energy. For this reason, the results obtained from these solvents at the 6-311++G(d,p) basis set will not be used to predict the chemical reactivity behavior by using the quantum chemical parameters.

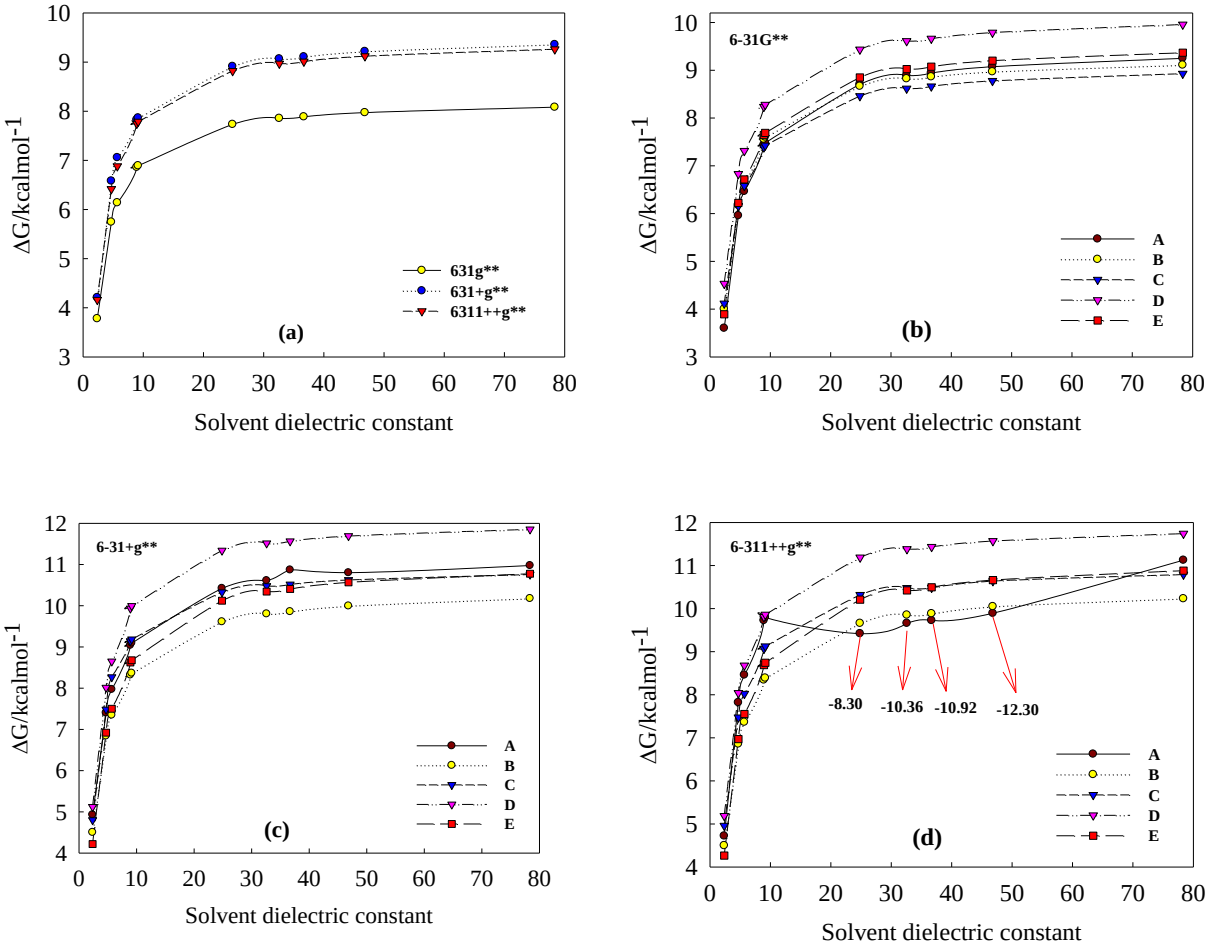

Figure 2. Solvation Free Energies as a function of solvent dielectric constant for **Basic** compound is given in **(a)**. Solvation Free Energies as a function of solvent dielectric constant for 1-substituted **Basic** compound derivatives are given at **(b)** 6-31g(d,p), **(c)** 6-31+g(d,p), **(d)** 6-311++g(d,p) basis sets.

In the many research fields such as biochemical, medicinal, pharmaceutical, biophysical, the solvation free energy has an important role to estimate/evaluate the chemical activity/stability behavior of the molecular systems. The dipole moment based on the electronic structure of any interested molecule is the other physicochemical parameter to predict the chemical stability behavior of the molecular systems. Table 3 has presented the dipole moment of each studied compound obtained from the B3LYP level of theory at three basis sets and in 10 solvent environments. It can be seen from Table 3 that the dipole moment of each compound strongly depends on the solvent media and on the basis set used in this work just like the solvation free energy of them. It can be seen from Table 3 that the dipole moment of each compound strongly depends on the solvent media and on the basis set

used in this work just like the solvation free energy of them. There is no correlation between the solvation free energy and the dipole moment because the dipole moment values for these compounds are very close to each other. For example, the calculated dipole moment with the 6-311++g(d,p) basis set changed in the order of **Basic** (6.4555)< **A**(6.5136)< **C**(6.5323)< **E**(6.5683)< **B**(6.5696)< **D**(8.1315) for the water phase, but it is calculated as **C**(4.2103)< **A**(4.2285)< **E**(4.2883)< **B**(4.3596)< **Basic** (4.4844)< **D**(5.4614) for the gas phase at the same level of the theory. The dipole moment, calculated with 6-31G(d,p) basis set, has increased with the following order: **A**(6.5136)< **C**(6.0537)< **Basic** (6.0604)< **E** (6.0777)< **B** (6.1067)< **D**(7.6947) for water phase and the **C**(4.0708)< **E**(4.1015)< **A** (4.1246)< **B** (4.2255)< **Basic** (4.3178)< **D**(5.3181) for the gas phase. In according to the Table 3, the compound **D**, which we previously identified as the most stable molecule in thermodynamically because of its solvation free energy, has the highest dipole moment whatever the solvent is used to calculate the dipole moment of investigated molecules in this work. In the past, Wiberg K. B [33] had determined the electron delocalization energy of some aromatic systems in the following order: Naphthalene **(60)** < Anthracene **(80)** < Phenanthrene **(85).** Although the naphthalene was determined as the less aromatic system because it has the less delocalization energy by Wiberg K. B [33], we can suggest that the methoxy group on substituent part of the compound **D** is responsible for the highest dipole moment value resulting in the highest free energy of it.

Table 3. The calculated Dipole Moments (in Debye, D) of both the **Basic** compound and its C1- substituted derivatives, in 10 solvent environments with 6-31g(d.p), 6-31+g(d.p) and 6-311++g(d.p) basis sets.

	Gas	**T (ε=2.37)**	**C (ε=4.71)**	**CB (ε=5.70)**	**DCM (ε=8.93)**	**Q (ε=9.16)**	**E (ε=24.85)**	**M (ε=32.61)**	**A (ε=36.69)**	**DMSO (ε=46.83)**	**Water (ε=78.36)**
6-31g(d.p)											
Basic	4.3178	5.1067	5.5330	5.6196	5.7800	5.7873	5.9788	6.0069	6.0147	6.0345	6.0604
A	4.1246	4.8936	5.3632	5.4658	5.6637	5.6732	5.9260	5.9649	5.9759	6.0037	6.0405
B	4.2255	5.0089	5.4664	5.5651	5.7537	5.7627	6.0006	6.0367	6.0468	6.0727	6.1067
C	4.0708	4.8831	5.3728	5.4781	5.6789	5.6884	5.9409	5.9794	5.9901	6.0176	6.0537
D	5.3181	6.3033	6.8852	7.0106	7.2498	7.2612	7.5614	7.6069	7.6197	7.6521	7.6947
E	4.1015	4.9150	5.3978	5.5020	5.7015	5.7110	5.9638	6.0026	6.0134	6.0411	6.0777
6-31g+(d.p)											
Basic	4.5252	5.4160	5.9074	6.0078	6.1929	6.2015	6.4269	6.4602	6.4695	6.4930	6.5238
A	4.2635	5.1451	5.7057	5.8320	6.0797	6.0909	6.4223	6.4747	6.4957	6.5279	6.5788
B	4.4031	5.2871	5.8333	5.9542	6.1887	6.2000	6.5042	6.5515	6.5648	6.5988	6.6438
C	4.2520	5.1800	5.7538	5.8819	6.1312	6.1430	6.4630	6.5120	6.5257	6.5607	6.6067
D	5.5239	6.6155	7.2768	7.4208	7.6939	7.7068	8.0521	8.1057	8.1207	8.1594	8.2105
E	4.3218	5.2241	5.7859	5.9111	6.1551	6.1669	6.4871	6.5369	6.5508	6.5867	6.6341
6-311g++(d.p)											
Basic	4.4844	5.3632	5.8453	5.9445	6.1292	6.1377	6.3599	6.3927	6.4018	6.4251	6.4555
A	4.2285	5.1000	5.6504	5.7752	6.0222	6.0341	6.3631	6.4155	6.4302	6.4681	6.5136
B	4.3596	5.2275	5.7664	5.8858	6.1180	6.1292	6.4309	6.4779	6.4911	6.5249	6.5696
C	4.2103	5.1230	5.6913	5.8181	6.0640	6.0757	6.3911	6.4392	6.4527	6.4870	6.5323
D	5.4614	6.5446	7.2013	7.3431	7.6132	7.6260	7.9722	8.0261	8.0413	8.0801	8.1315
E	4.2883	5.1723	5.7254	5.8490	6.0918	6.1035	6.4209	6.4706	6.4845	6.5210	6.5683

3. 3. NBO Analysis

The Natural Bond Orbital (NBO) analysis is used to evaluate the inter- or intra molecular interactions which are important to understand the chemical phenomena such as the hydrogen bonding and electron delocalization from the occupied (donor) molecular orbital to unoccupied molecular (acceptor) orbital, conjugative interactions. [19, 34] Also, the donor and acceptor interactions in the molecular system obtained from the second order Fock matrix in the NBO basis is used to elucidate /explain the chemical stability behavior of the molecular system. The NBO and the idea of the Natural atomic orbital (NAO) analysis is developed by Weinhold and co-workers [35- 36] to derive

molecular bonds from electron density between atoms by using the one electron density matrix for defining the shape of the atomic orbitals in the molecular orbital environments. The stabilization energy (*E2*) associated with the delocalization i→ j for each donor (i) and acceptor (j) is determined as

$$E(2) = \Delta E_{ij} = qi\frac{(Fij)^2}{(\varepsilon j - \varepsilon i)}$$

qi→donor orbital occupancy, εi, εj →diagonal elements and Fij →the off diagonal NBO Fock matrix element.

In this context, we have performed the NBO analysis to elucidate the intramolecular interaction, hybridization, conjugation associated with the donor-acceptor interaction of the substituted compounds. The calculated second order Fock matrix in NBO basis of the **Basic** molecule and of its substituted derivatives have been summarized in Table 4a and Table 4b. As is known well, the largest E (2) means the stronger interaction between the electron donor and electron acceptor, and the electron delocalization between Lewis (bond or lone pair) and unoccupied non- Lewis (anti-bond or Rydberg) NBO makes the system more stabilized. In according to the Table 4a, one of the most important interaction is calculated for the interaction between the LP (1) N18 → (C5-C6) with the stabilization energy of the 94.18 kcalmol^{-1} because the intramolecular charge transfer from the LP(1) N(18) to (C5-C6) makes the molecule stabilized due to the σ conjugation (σ→ p_v). Another interesting result given in Table 4a is that there has been calculated the electron donation from donor LP(1) N(18) to anti-bonding acceptor (C5- C15), related to the hyperconjugation (σ→ π*), which leads to the strong charge delocalization with the stabilization energy of 46.16 kcalmol^{-1}. The calculated E(2) of the **Basic** structure is mainly due to the interactions π→ π*(related to the resonance) occurring from the π occupied orbital to the π* unoccupied orbital. From Table 4a, the other interaction energies are calculated for the charge transfer to the anti-bond orbital p_v C5-C6 from the bond orbitals of the π C4-N17, π C5-C15, π C11-C12, π C11-N17, π C12-N18, π C13-N18, π C13-C19, and π C14-C15 with the stabilization energies of the 3.25, 8.31, 44.40, 10.53, 41.40, 9.89, 12.02 and 44.12 kcalmol^{-1}, in respectively. From Table 4a, the interaction energies of the charge transfer for π C19-O21→ p_v C5-C6 (E(2): 1.77 kcalmol^{-1} with the occupancy of the 0.20886e) is relatively lower than the other interaction, but each of them is still quite strong interaction. In addition, the very strong interaction has been computed between the p_v C3-C4 and the p_v C5-C6 with the stabilization energy of 63.33 kcalmol^{-1}. Also, the other p-p interactions are found out as the p C3-C4→ p C1-C2, p C5-C6→ p C1-C2, p C13-C14→ p C19-O21 with the stabilization energies of the 11.10, of 9.61, of 10.78 kcalmol^{-1}, respectively. If it is looked at the Table 4a, it can be easily said that another very strong interaction occurs by the electron donating from the p-type orbital containing the lone pair of the N17 to the antibonding orbital p_v C5-C6 (with the stabilization energy of the 35.05 kcalmol^{-1}). Also, the interactions of LP(2)O20→ p C19-O21 and LP(2)O21→ π* C19-O20 have the stabilization energies of 24.81 and of 15.23 kcalmol^{-1} (due to the resonance between the occupied and unoccupied molecular orbitals for both interactions). In according to these results, it can be suggested that the resonance and hyperconjugation effects make the **Basic** structure the more stabilized than the other interactions. Especially, the interaction between the p-type orbital containing the lone pair and the antibonding orbital π* is an important feature and is known well [37-38] that this is necessary to predict the activity behavior of pharmaceutical compounds.

Table 4a. The selected Second Order Perturbation Theory Analysis Results of the Fock Matrix in NBO Basis for the **Basic** structure, at B3LYP/6-311++G** in water phase.

Donor(i)	Hybridization	ED_i/e	Acceptor (j)	Hybridization	ED_j/e	E(2) [a]	E(j)-E(i) [b]	F(i,j) [c]
p_v C1-C2	$0.7197p_{(C1)}+$ $0.6943p_{(C2)}$	0.81564	p_v C3-C4	$p_{(C3)}$-$p_{(C4)}$	0.21090	9.21	0.27	0.064
			p_v C5-C6	$p_{(C5)}$-$p_{(C6)}$	0.20886	46.28	0.07	0.071
p_v C3-C4	$p_{(C3)}$-$p_{(C4)}$	0.81005	p_v C1-C2	$p_{(C1)}$-$p_{(C2)}$	0.19377	11.10	0.29	0.072
			p_v C5-C6	$p_{(C5)}$-$p_{(C6)}$	0.20886	63.33	0.08	0.091
π C4-N17	$0.6115sp^{2.68}_{(C4)}+$ $0.7912sp^{1.98}_{(N17)}$	0.99097	p_v C5-C6	$p_{(C5)}$-$p_{(C6)}$	0.20886	3.25	0.62	0.064
p_v C5-C6	$0.7316p_{(C5)}+$ $0.6817p_{(C6)}$	0.81250	p_v C1-C2	$p_{(C1)}$-$p_{(C2)}$	0.19377	9.61	0.28	0.065
			p_v C3-C4	$p_{(C3)}$-$p_{(C4)}$	0.21090	10.72	0.27	0.069
π C5-C15	$0.7035sp^{2.07}_{(C5)}+$ $0.7107sp^{1.98}_{(C15)}$	0.98332	π* C5-C6	$sp^{1.69}_{(C5)}$-$sp^{1.88}_{(C6)}$	0.01177	8.31	0.89	0.109
π C11-C12	$0.7211sp^{1.65}_{(C11)}+$ $0.6929sp^{1.69}_{(C12)}$	0.98965	p_v C5-C6	$p_{(C5)}$-$p_{(C6)}$	0.20886	44.40	0.52	0.214
			p_v C13-C14	$p_{(C13)}$- $p_{(C14)}$	0.17266	0.50	0.72	0.026
π C11-N17	$0.6149sp^{2.51}_{(C11)}+$ $0.7886sp^{1.95}_{(N17)}$	0.99128	p_v C5-C6	$p_{(C5)}$-$p_{(C6)}$	0.20886	10.53	0.63	0.115
π C12-N18	$0.6394sp^{2.06}_{(C12)}+$ $0.7689sp^{1.74}_{(N18)}$	0.99191	π* C1-C6	$sp^{1.79}_{(C1)}$-$sp^{1.75}_{(C6)}$	0.00687	13.42	1.30	0.167
			p_v C5-C6	$p_{(C5)}$-$p_{(C6)}$	0.20886	41.40	0.66	0.233
			π* C5-C15	$sp^{2.07}_{(C5)}$- $sp^{1.98}_{(C15)}$	0.01537	21.25	1.20	0.202
p_v C13-C14	$0.7332p_{(C13)}+$ $0.6800p_{(C14)}$	0.82810	p_v C19-O21	$p_{(C19)}$-$p_{(O21)}$	0.14118	10.78	0.26	0.069
π C13-N18	$0.6442sp^{2.18}_{(C13)}+$ $0.7649sp^{1.80}_{(N18)}$	0.99170	p_v C5-C6	$p_{(C5)}$-$p_{(C6)}$	0.20886	9.89	0.65	0.113
π C13-C19	$0.7143sp^{2.30}_{(C13)}+$ $0.6999sp^{1.60}_{(C19)}$	0.98658	p_v C5-C6	$p_{(C5)}$-$p_{(C6)}$	0.20886	12.02	0.54	0.114
π C14-C15	$0.6953sp^{1.81}_{(C14)}+$ $0.7187sp^{1.70}_{(C15)}$	0.98692	p_v C5-C6	$p_{(C5)}$-$p_{(C6)}$	0.20886	44.12	0.88	0.277
π C19-O21	$0.5920sp^{1.96}_{(C19)}+$ $0.8059sp^{1.46}_{(O21)}$	0.99777	p_v C5-C6	$p_{(C5)}$-$p_{(C6)}$	0.20886	1.77	0.91	0.057
LP(1) N17	p	0.80218	p_v C3-C4	$p_{(C3)}$-$p_{(C4)}$	0.21090	18.24	0.31	0.095
			p_v C5-C6	$p_{(C5)}$-$p_{(C6)}$	0.20886	35.05	0.10	0.077
LP(1) N18	$sp^{2.59}$	0.95768	p_v C5-C6	$p_{(C5)}$-$p_{(C6)}$	0.20886	94.18	0.95	0.413
			π* C5-C15	$sp^{2.07}_{(C5)}$- $sp^{1.98}_{(C15)}$	0.01537	46.16	1.49	0.336
LP(2) O20	p	0.89064	p_v C19-O21	$p_{(C19)}$-$p_{(O21)}$	0.14118	24.81	0.33	0.116
LP(2) O21	p	0.93004	π* C19-O20	$sp^{2.59}_{(C19)}$- $sp^{2}_{(O20)}$	0.04570	15.23	0.65	0.127
			π* C13-C19	$sp^{2.30}_{(C13)}$- $sp^{1.60}_{(C19)}$	0.03504	8.37	0.69	0.097

*__a__ E(2) means the energy of hyper conjugative interaction (stabilization energy), **b** Energy difference between donor and acceptor i and j NBO orbitals, **c** F(i, j) is the fork matrix element between i and j NBO orbitals.

Table 4b. The selected Second Order Perturbation Theory Analysis Results of the Fock Matrix in NBO Basis for the C1-substituted **Basic c**ompound derivatives from **A- E.**

	Donor(i)	Hybridization	ED_i/e	Acceptor (j)	Hybridization	ED_j/e	E(2) [a]	E(j)-E(i) [b]	F(i,j) [c]
A	π C5-C15	$sp^{2.09}_{(C5)}+ sp^{2.02}_{(C15)}$	0.98132	p_v C42-C43	$p_{(C42)}- p_{(C43)}$	0.10901	27.82	1.48	0.268
	π C11-C12	$sp^{1.63}_{(C11)}+ sp^{1.78}_{(C12)}$	0.98399	p_v C19-O21	$p_{(C19)}- p_{(O21)}$	0.14066	2.22	0.81	0.057
	π C11-N17	$sp^{2.39}_{(C11)}+ sp^{1.94}_{(N17)}$	0.98513	p_v C42-C43	$p_{(C42)}- p_{(C43)}$	0.10901	4.69	1.46	0.110
	p_v C12-N18	$p_{(C12)}$-$p_{(N18)}$	0.88847	p_v C42-C43	$p_{(C42)}- p_{(C43)}$	0.10901	0.52	1.49	0.037
	π C19-O20	$sp^{2.58}_{(C19)}+ sp^{2}_{(O20)}$	0.99689	p_v C42-C43	$p_{(C42)}- p_{(C43)}$	0.10901	50.98	7.08	0.802
	p_v C19-O21	$p_{(C19)}+p_{(O21)}$	0.99262	p_v C13-C14	$p_{(C13)}- p_{(C14)}$	0.17093	1.42	0.41	0.033
	LP(1) N17	p	0.80309	p_v C34-C35	$p_{(C34)}+ p_{(C35)}$	0.10907	20.81	1.76	0.253
	LP(1) N18	$sp^{2.72}$	0.95655	π* C13-C14	$sp^{1.62}_{(C13)}$-$sp^{1.89}_{(C14)}$	0.01393	5.29	0.89	0.088
	LP(2) O20	p	0.89017	p_v C19-O21	$p_{(C19)}$-$p_{(O21)}$	0.14066	22.91	0.27	0.100
	LP(2) O21	p	0.92980	π* C13-C19	$sp^{2.30}_{(C13)}$-$sp^{1.61}_{(C19)}$	0.03547	8.52	0.68	0.098
B	π C5-C15	$sp^{2.09}_{(C5)}$-$sp^{2.02}_{(C15)}$	0.98138	p_v C34-C35	$p_{(C34)}$-$p_{(C35)}$	0.12383	12.56	0.30	0.082
	π C11-C12	$sp^{1.63}_{(C11)}+ sp^{1.79}_{(C12)}$	0.98367	p_v C34-C35	$p_{(C34)}$-$p_{(C35)}$	0.12383	0.49	0.34	0.017
	π C11-N17	$sp^{2.39}_{(C11)}+ sp^{1.94}_{(N17)}$	0.98518	p_v C34-C35	$p_{(C34)}$-$p_{(C35)}$	0.12383	9.07	0.40	0.081
	p_v C12-N18	$p_{(C12)}$-$p_{(N18)}$	0.88765	p_v C13-C14	$p_{(C13)}$-$p_{(C14)}$	0.17041	12.78	0.27	0.077
	π C19-O20	$sp^{2.58}_{(C19)}+ sp^{2}_{(O20)}$	0.99690	p_v C19-O21	$p_{(C19)}$-$p_{(O21)}$	0.14085	9.06	3.49	0.242
	π C19-O21	$sp^{1.96}_{(C19)}+ sp^{1.46}_{(O20)}$	0.99785	p_v C32-C33	$p_{(C32)}$-$p_{(C33)}$	0.12638	8.22	0.38	0.076
	LP(1) N17	p	0.80310	p_v C19-O21	$p_{(C19)}$-$p_{(O21)}$	0.14085	14.01	5.87	0.373
	LP(1) N18	$sp^{2.68}$	0.95672	π* C13-C14	$sp^{1.62}_{(C13)}$-$sp^{1.89}_{(C14)}$	0.01393	12.16	0.27	0.074
	LP(2) O20	p	0.89027	p_v C19-O21	$p_{(C19)}$-$p_{(O21)}$	0.14085	25.85	0.29	0.110
	LP(1) O21	$sp^{0.68}$	0.99012	σ* C39-H46	$sp^{2.51}_{(C39)}$-$s_{(H46)}$	0.00667	27.82	0.04	0.045
C	π C5-C15	$sp^{2.08}_{(C5)}+ sp^{1.97}_{(C15)}$	0.98295	p_v C19-O21	$p_{(C19)}$-$p_{(O21)}$	0.14046	0.31	0.76	0.021
	π C11-C12	$Sp^{1.62}_{(C11)}+ sp^{1.79}_{C12)}$	0.98661	p_v C35-C36	$p_{(C35)}$-$p_{(C36)}$	0.12528	3.30	0.82	0.070
	π C11-N17	$sp^{2.51}_{(C11)}+ sp^{1.94}_{(N17)}$	0.99122	p_v C35-C36	$p_{(C35)}$-$p_{(C36)}$	0.12528	0.75	0.75	0.032
	p_v C12-N18	$p_{(C12)}$-$p_{(N18)}$	0.88259	p_v C13-C14	$p_{(C13)}$-$p_{(C14)}$	0.17293	10.23	0.33	0.076
	π C19-O20	$sp^{2.58}_{(C19)}+ sp^{2}_{(O20)}$	0.99677	p_v C38-C39	$p_{(C38)}$-$p_{(C39)}$	0.11843	1.99	2.42	0.093
	π C19-O21	$sp^{1.96}_{(C19)}+ sp^{1.46}_{(O21)}$	0.99775	p_v C35-C36	$p_{(C35)}$-$p_{(C36)}$	0.12528	22.68	2.20	0.301
	LP(1) N17	p	0.80277	p_v C38-C39	$p_{(C38)}$-$p_{(C39)}$	0.11843	102.66	6.95	1.111
	LP(1) N18	$sp^{2.70}$	0.95583	p_v C38-C39	$p_{(C38)}$-$p_{(C39)}$	0.11843	135.82	55.25	3.594
	LP(1) O20	$sp^{1.59}$	0.98151	p_v C38-C39	$p_{(C38)}$-$p_{(C39)}$	0.11843	46.82	3.06	0.504
	LP(2) O21	p	0.92993	p_v C38-C39	$p_{(C38)}$-$p_{(C39)}$	0.11843	175.59	5.69	1.293
D	π C5-C15	$sp^{2.06}_{(C5)}+ sp^{2.01}_{(C15)}$	0.98289	σ* C39-H50	$sp^{2.50}_{(C39)}$-$s_{(H50)}$	0.00666	37.26	0.14	0.091
	π C11-C12	$sp^{1.61}_{(C11)}+ sp^{1.81}_{(C12)}$	0.98701	p_v C31-C32	$p_{(C31)}$-$p_{(C32)}$	0.14187	0.64	0.50	0.024
	π C11-N17	$sp^{2.52}_{(C11)}+ sp^{1.94}_{(N17)}$	0.99120	π* C30-C39	$sp^{1.89}_{(C30)}$-$sp^{2}_{(C39)}$	0.01366	36.60	0.92	0.232
	p_v C12-N18	$p_{(C12)}$-$p_{(N18)}$	0.88217	p_v C13-C14	$p_{(C13)}$-$p_{(C14)}$	0.17315	10.71	0.33	0.077
	π C19-O20	$sp^{2.58}_{(C19)}+ sp^{2}_{(O20)}$	0.99676	p_v C33-C34	$p_{(C33)}$-$p_{(C34)}$	0.13628	334.55	0.09	0.239
	π C19-O21	$sp^{1.96}_{(C19)}+ sp^{1.46}_{(O21)}$	0.99773	p_v C33-C34	$p_{(C33)}$-$p_{(C34)}$	0.13628	558.36	1.59	1.279
	LP(1) N17	p	0.80298	p_v C3-C4	$p_{(C3)}$-$p_{(C4)}$	0.21198	20.31	0.28	0.096
	LP(1) N18	$sp^{2.68}$	0.95545	π* C11-C12	$sp^{1.61}_{(C11)}$-$sp^{1.81}_{(C12)}$	0.01992	4.76	0.87	0.082
	LP(2) O20	p	0.89030	p_v C19-O21	$p_{(C19)}$-$p_{(O21)}$	0.14054	41.65	0.33	0.149
	LP(1) O21	$sp^{0.68}$	0.99012	π* C13-C19	$sp^{2.31}_{(C13)}$-$sp^{1.60}_{(C19)}$	0.03534	5.77	0.27	0.050
E	π C5-C15	$sp^{2.06}_{(C5)}+ sp^{2}_{(C15)}$	0.98307	p_v C30-C31	$p_{(C30)}$-$p_{(C31)}$	0.10557	0.32	1.79	0.032
	π C11-C12	$sp^{1.64}_{(C11)}+ sp^{1.79}_{(C12)}$	0.98322	p_v C30-C31	$p_{(C30)}$-$p_{(C31)}$	0.10557	20.50	1.77	0.252
	π C11-N17	$sp^{2.39}_{(C11)}+ sp^{1.97}_{(N17)}$	0.98512	p_v C30-C31	$p_{(C30)}$-$p_{(C31)}$	0.10557	11.04	1.93	0.193
	p_v C12-N18	$p_{(C12)}$-$p_{(N18)}$	0.88719	p_v C13-C14	$p_{(C13)}$-$p_{(C14)}$	0.17175	9.15	0.33	0.071
	π C19-O20	$sp^{2.58}_{(C19)}+ sp^{2}_{(O20)}$	0.99677	p_v C40-C41	$p_{(C40)}$-$p_{(C41)}$	0.13758	249.65	0.02	0.090
	π C19-O21	$sp^{1.96}_{(C19)}+ sp^{1.46}_{(O21)}$	0.99762	p_v C40-C41	$p_{(C40)}$-$p_{(C41)}$	0.13758	114.91	1.72	0.604
	LP(1) N17	p	0.80358	p_v C40-C41	$p_{(C40)}$-$p_{(C41)}$	0.13758	343.42	9.46	2.345
	LP(1) N18	$sp^{2.70}$	0.95671	p_v C30-C31	$p_{(C30)}$-$p_{(C31)}$	0.10557	363.60	3.03	1.368
	LP(2) O20	p	0.89015	p_v C19-O21	$p_{(C19)}$-$p_{(O21)}$	0.14060	24.79	0.34	0.117
	LP(2) O21	p	0.92987	p_v C30-C31	$p_{(C30)}$-$p_{(C31)}$	0.10557	8.60	1.41	0.142

*__a__ E(2) means the energy of hyper conjugative interaction (stabilization energy), **b** Energy difference between donor and acceptor i and j NBO orbitals, **c** F(i, j) is the fork matrix element between i and j NBO orbitals.

Up to now, we have tried to show the possible strong interactions providing the stabilization in the **Basic** structure. Now, it is worthwhile to discuss how these interactions change with the substituent group attached to the **Basic** structure. Table 4b has summarized the possible strong interaction for the structures **A** to **E**, at B3LYP/6-311++G** level of theory in the water phase. The highest electron delocalization among the C1-substituted **Basic** compound derivatives is determined for the **D** with π C19-O21→ p_v C33-C34 with the stabilization energy of the 558.36 kcalmol^{-1}. Moreover, the interaction energy for the π C15-C15→ σ* C39-H50 for the compound **D** is found out as 37.26 kcalmol^{-1}

due to this interaction makes the system stabilized by the *negative hyperconjugation* which occurs the charge transfer from the occupied orbital π to the unoccupied orbital σ*. On the other hand, second highest electron delocalization energy is determined for the structure **E:** the interaction of LP(1)N18→ p_v C30-C31 has the stabilization energy of the 363.60 kcalmol^{-1} due to the phenanthrene-9-yl substitution on the C1-position of the **Basic** structure makes the electron delocalization on the substituted compound enhances. The interaction energy of the π C5-C15→ π* C34-C35 for **B** is around of the 12.56 kcalmol^{-1} (with the occupancy of 0.12383e), but this interaction is not observed for the **C**. Instead of the interaction π C5-C15→ π* C34-C35, the interactions of π C5-C15→ π* C42-C43 for the **A** and of π C5-C15→ π* C30-C31 for **E** have been observed with stabilization energies of the 27.82 kcalmol^{-1} and of the 0.32 kcalmol^{-1}, respectively. The charge transfer of p_v C12-N18→ p_v C13-C14 for the compounds **B**, **C**, **D** and **E** has changed from 9.15 to 12.78 kcalmol^{-1}, this interaction is not calculated for the Basic structure. The charge transfer from the LP(2) O20 to the antibonding p_v C19-O21 is calculated for the structures **A**, **B**, **D** and **E** with the stabilization energy of 22.91, 25.85, 41.65 and 24.79 kcalmol^{-1}, respectively. It can be said that the charge transfer between LP(2) O20 and p_v C19-O21 for the structure **D** is two times more than those of the other substituted compounds, also that the maximum electron density for this interaction changed from 0.89015e to 0.89030e in electron donor orbital. Here, we should also express that the maximum electron delocalization from the LP(1) N17 with the occupancy 0.80298e to p_v C3-C4 of with occupancy 0.21198e is calculated for the structure **D** with the stabilization energy of 20.31 kcalmol^{-1}. In this work, it has shown some important interactions resulting in the stabilization.

3. 4. Frontier Molecular Orbital Analysis

Frontier molecular orbitals called both the Highest occupied molecular orbital and the lowest unoccupied molecular orbital are very important parameters used in prediction of the way the molecule interacts with the other species [39]: the HOMO as the electron donor is responsible for donating the electron to the outer species and LUMO as the electron acceptor represents the ability to accept the electron from the outer species. Therefore, the HOMO is directly related to the Ionization potential and the LUMO is related to the electron affinity. In this work, the frontier orbital analysis has been investigated both with three basis sets and in the 10 solvent environments, too. The results obtained from quantum chemical calculations have shown that the frontier molecular orbitals' shape for each compound is very similar to each other for both the basis sets and the solvent environments, but the numerical results of them are different from each other. Here, it is given in Figure 3 the HOMO and of the LUMO amplitudes calculated at the B3LYP/6-311++G** level of theory in the aqueous phase for both the **Basic** compound and its C1 substituted derivatives.

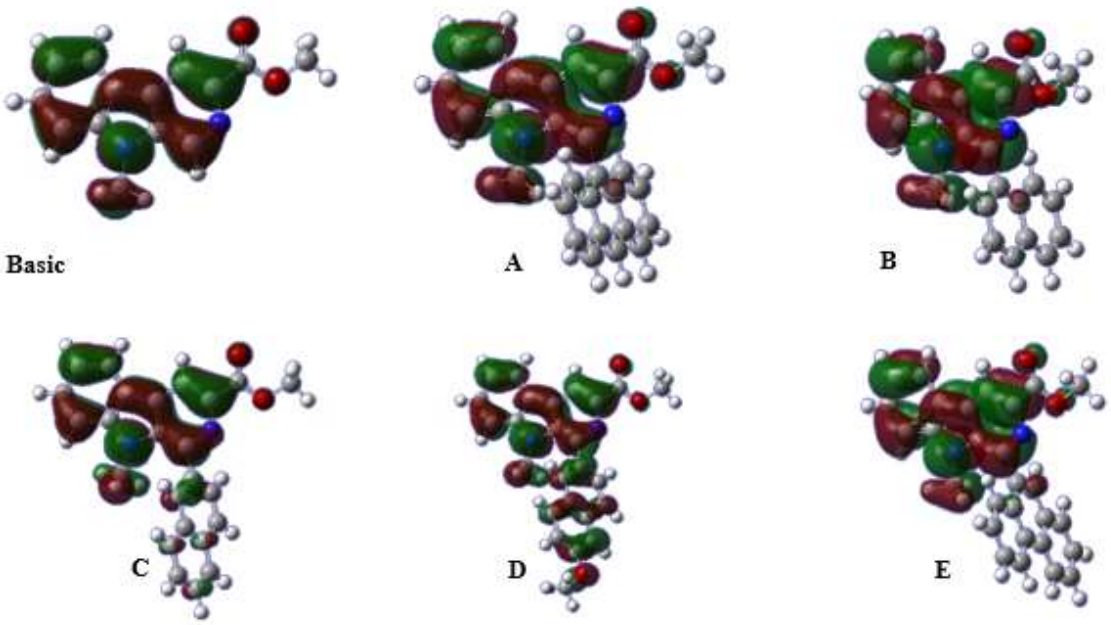

Figure 3a. HOMO amplitudes for both the **Basic** compound and its C1 substituted derivatives calculated at the B3LYP/6-311++G** level of theory in the aqueous phase.

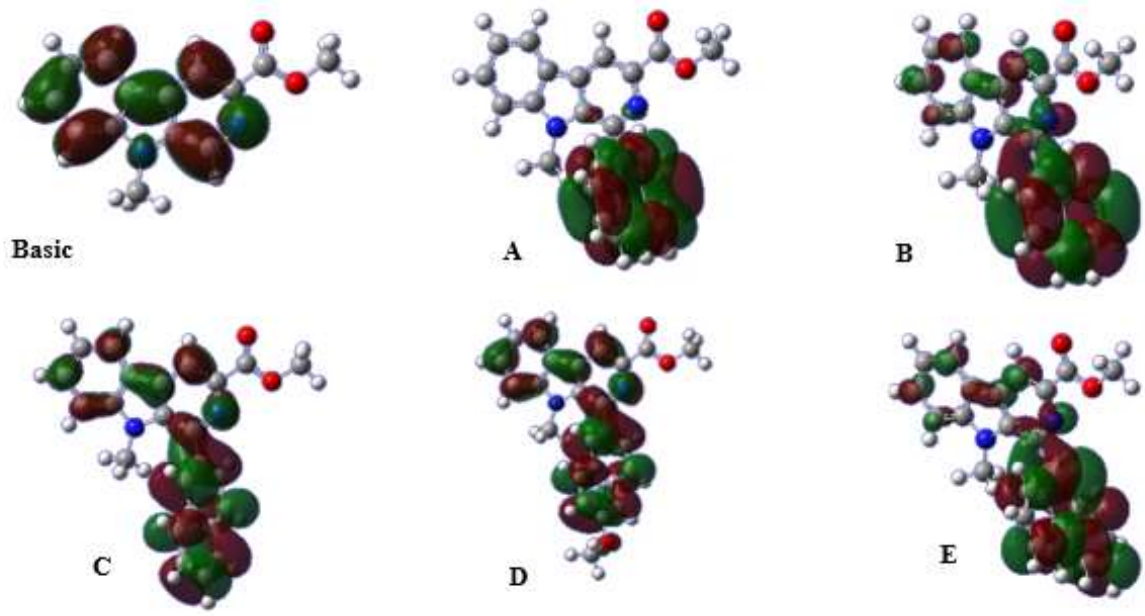

Figure 3b. LUMO amplitudes for both the **Basic** molecule and its C1 substituted derivatives calculated at the B3LYP/6-311++G** level of theory in the aqueous phase.

From Figure 3a, for the **Basic** compound, the HOMO is localized on the full molecular surface of the **Basic** structure except for the methyl group at C3-position of this compound, which means if there is a nucleophilic attack reaction to any molecule/ to the receptor site, then this compound will attack with the electrons located on its HOMO to outer species. On the other hand, from Figure 3b, the LUMO is only localized on the aromatic site of this structure, which means the electrophilic attack

to this structure will occur in this location. At this point, it is worthwhile to ask how the HOMO and LUMO amplitudes on the **Basic** structure change when the substituent group is attached to C1-position of the **Basic** structure. It is clear from Figure 3a that the HOMO amplitude for each C1 substituted compounds is very like the **Basic** structural units' HOMO amplitude, except for the structure **D**, but just a little HOMO is localized on the substituent part of each structure, too. For the structure **D**, the HOMO is localized on the whole molecule including the **Basic** unit, and the substituent group, too. Therefore, it can be suggested that the structure **D** has the highest electron delocalization than that of the other C1-substituted derivatives. On the other hand, the LUMO amplitude for each substituted derivative is different from each other. First, it should be expressed that the carboxymethyl group at C3-position and -CH3 group at N9-position are not very effective for electrophilic attack reactions because there is no any LUMO localization on these groups both **Basic** structure and of its substituted derivatives. Second, the LUMO is localized on the entire molecule for the structure **D**, that is, it should be kept in mind the **D** has the highest dipole moment resulting in the highest thermodynamic stability as it was stated in the free energy section of this work before. Finally, for the structure **A**, the LUMO is only localized on the substituent group which is anthracene 9-yl substitution at C1-position of the **Basic** structure, therefore the electrophilic attack center shifts from the **Basic** part to the substituent part.

3. 5. The Calculated Quantum Chemical Parameters

Until now, we have discussed the sites which the investigated molecules worked to be effective via both the FMO visualization, also we have investigated the structural parameters, solvation free energy, dipole moments and NBO analysis to predict the chemical reactivity behavior of all compounds. Nowadays, the calculated quantum chemical parameters are discussed to explain the chemical reactivity behavior of all compounds because quantum chemical parameters are getting commonly used to predict/explain the chemical behavior of the molecular systems. In this context, the calculated global descriptors which are ΔE, μ, η, ω and ΔNmax are given at Table 5 at only 6-311++G(d,p) basis set in all solvent environments, the other numerical data for the other basis sets combined with all solvents are not given here, they are given supporting information of this text (Table S2). From Table 5, The ΔE (energy gap) has increased in the order of **A** (3.4975)< **D** (3.9821)< **C** (4.1378)< **E** (4.2678)< **B** (4.2948) < **Basic** (4.3854) in the water phase. Moreover, this ordering of the energy is found out to be as the same for more than half of the solvent phases at the other basis sets (supplementary material, S3). In according to this result, it can be suggested that the **A** has the lowest Energy Gap value resulting in the most reactive compound. For the water phase, the μ has increased in the following order of the **A** (-4,0127)< **E** (-3,9791)< **C** (-3,9767)< **B** (-3,9700)< **D** (-3,8662) just like for the DCM, Q, E, M, acetonitrile, and DMSO solvents, but the μ has increased in as follows: **A< C< E< B< D** for the gas and chloroform, chlorobenzene phases, at 6-311++G(d,p) basis set. For the 6-31+G(d,p) basis set, the μ has also increased in the order of **A**< **C**< **E**< **B**< **D** for more than half of the solvent environments. Although there is some changing in the ordering of the μ depending on the solvent media and on the basis set (for example, the **E** and **C** have replaced with each other in the ordering of the μ), the **A** is the most stable compound because it has the lowest electronic chemical potential energy.On the other hand, for all basis sets and for the more than half of the solvents, the η has increased in the following order of **A< D< C< B< E< Basic** which indicates the structure **A** is the soft molecule and therefore it is the most reactive structure among the being studied structures. In according with the electrophilicity index results, it increases as **B< E< D <C < A**, in the toluene, chloroform, chlorobenzene, dichloromethane, quinoline and, ethanol media at 6-311++G(d,p) basis set. The structure **A** has been found to be the best electrophile among the all studied structures. The ΔNmax changes with the ordering of the **B< E < C <D < A** for more than half of the solvents at all

basis sets, and the structure **A** has the capability of the maximum charge transfer.

Table 5. The calculated quantum chemical parameters with the B3LYP/6-311++G** basis set.

Molecule	Solvent	ΔE	μ	η	ω	ΔNmax	Solvent	ΔE	μ	η	ω	ΔNmax
Basic		4.4374	-3.9218	2.2187	3.4662	1.7676		4.3906	-3.9643	2.1953	3.5794	1.8058
A	**Toluen** (ε= 2.37)	3.4893	-3.9259	1.7447	4.4172	2.2503	**Ethanol** (ε= 24.85)	3.4939	-3.9987	1.7470	4.5764	2.2889
B		4.2970	-3.8892	2.1485	3.5201	1.8102		4.2972	-3.9614	2.1486	3.6519	1.8437
C		4.1307	-3.9059	2.0653	3.6934	1.8912		4.1399	-3.9688	2.0700	3.8047	1.9173
D		3.9789	-3.7720	1.9894	3.5760	1.8960		3.9821	-3.8561	1.9911	3.7341	1.9367
E		4.3927	-3.9401	2.1964	3.5341	1.7939		4.2744	-3.9710	2.1372	3.6891	1.8580
Basic		4.4161	-3.9395	2.2081	3.5144	1.7842		4.3887	-3.9661	2.1943	3.5842	1.8074
A	**Chloroform** (ε= 4.71)	3.4918	-3.9544	1.7459	4.4782	2.2650	**Methanol** (ε= 32.61)	3.4942	-4.0021	1.7471	4.5838	2.2907
B		4.3035	-3.9202	2.1517	3.5711	1.8219		4.2964	-3.9643	2.1482	3.6579	1.8454
C		4.1342	-3.9319	2.0671	3.7395	1.9021		4.1394	-3.9715	2.0697	3.8104	1.9189
D		3.9772	-3.8077	1.9886	3.6454	1.9148		3.9821	-3.8597	1.9911	3.7410	1.9385
E		4.2983	-3.9301	2.1492	3.5935	1.8287		4.2722	-3.9737	2.1361	3.6960	1.8603
Basic		4.4115	-3.9437	2.2058	3.5256	1.7879		4.3884	-3.9665	2.1942	3.5851	1.8077
A	**Chlorobenzene** (ε= 5.70)	3.4923	-3.9617	1.7462	4.4942	2.2688	**Acetonitrile** (ε= 36.69)	3.4945	-4.0031	1.7472	4.5857	2.2911
B		4.3035	-3.9276	2.1517	3.5845	1.8253		4.2961	-3.9652	2.1481	3.6598	1.8460
C		4.1359	-3.9382	2.0679	3.7499	1.9044		4.1391	-3.9722	2.0696	3.8120	1.9193
D		3.9775	-3.8160	1.9887	3.6610	1.9188		3.9821	-3.8605	1.9911	3.7426	1.9389
E		4.2945	-3.9375	2.1473	3.6102	1.8337		4.2716	-3.9745	2.1358	3.6980	1.8609
Basic		4.4025	-3.9523	2.2013	3.5481	1.7955		4.3870	-3.9677	2.1935	3.5884	1.8088
A	**Dichloromethane** (ε= 8.93)	3.4931	-3.9768	1.7466	4.5275	2.2769	**DMSO** (ε= 46.83)	3.4945	-4.0055	1.7472	4.5913	2.2925
B		4.3016	-3.9421	2.1508	3.6127	1.8329		4.2953	-3.9673	2.1477	3.6643	1.8473
C		4.1386	-3.9510	2.0693	3.7718	1.9093		4.1386	-3.9741	2.0693	3.8161	1.9205
D		3.9799	-3.8330	1.9900	3.6915	1.9262		3.9821	-3.8629	1.9911	3.7473	1.9401
E		4.2869	-3.9519	2.1434	3.6431	1.8437		4.2703	-3.9765	2.1351	3.7030	1.8624
Basic		4.4020	-3.9529	2.2010	3.5496	1.7959		4.3854	-3.9693	2.1927	3.5927	1.8103
A	**Quinoline** (ε= 9.16)	3.4931	-3.9776	1.7466	4.5293	2.2774	**Water** (ε= 78.36)	3.4975	-4.0127	1.7487	4.6039	2.2946
B		4.3013	-3.9428	2.1507	3.6142	1.8333		4.2948	-3.9700	2.1474	3.6698	1.8488
C		4.1389	-3.9516	2.0694	3.7729	1.9095		4.1378	-3.9767	2.0689	3.8219	1.9221
D		3.9802	-3.8337	1.9901	3.6925	1.9264		3.9821	-3.8662	1.9911	3.7536	1.9418
E		4.2866	-3.9526	2.1433	3.6446	1.8442		4.2678	-3.9791	2.1339	3.7099	1.8647

* ΔE(Energy Gap), μ, η, ω and ΔNmax are in eV

4. CONCLUSION

In this work, we have investigated the **Basic** compound and its C1-substituted derivatives to determine which substituent group makes the chemical reactivity behavior of the **Basic** compound enhanced more. For this reason, we have conducted the comprehensive quantum chemical analysis including the electronic structure analysis, thermodynamic parameters such as dipole moment and free energy, NBO analysis, FMO analysis and quantum chemical parameters. In conclusion, the compound **A** is determined as the most reactive compound because its Energy Gap is the lowest than those of the other compounds. In addition, it is the soft molecule, having the highest electrophilicity index and the capability of maximum charge transfer. It is important to declare that the anthracene-9-yl substitution on the C1 -position of the **Basic** compound has increased the chemical reactivity of the **Basic** compound more than those of the other substituent group. It is supported by the NBO analysis: the highest electron delocalization for the structure **A** was found out π C19-C20$\rightarrow$ p_v C42-C43 with the interaction energy of the 50.98 kcalmol^{-1} due to the anthracene-9-yl substitution on the C1-position of the **Basic** structure makes the electron delocalization on the substituted compound enhances, at 6-311++g**basis set in the water phase. Although it is predicted the **A** including the anthracene-9-yl substituent group on it as the most reactive structure among the investigated compounds, it is necessary to keep in mind that there are a lot of the factors affecting the chemical reactivity behavior. Hopefully, the findings of this study containing the comprehensive quantum

chemical analysis (time-consuming calculations and their analysis) will provide an important information in understanding /be explaining the reactivity behavior of β-Carboline compounds.

Acknowledgments

The authors thank to the Department of the Scientific Research Projects, Cumhuriyet University (Project Nos: EĞT-066 and EĞT-053) for the financial support. All calculations have been conducted at TUBITAK ULAKBIM, High Performance and Grid Computing Center (TR-Grid e- Infrastructure).

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