Cumhuriyet Science Journal
CSJ

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

Cumhuriyet Sci. J., Vol.38-4 (2017) 647-660

# DFT Based Quantum Chemical Descriptors of 1-Substituted THβC, DHβC, βC Derivatives

***Goncagul SERDAROGLU*, Mustafa ELIK***

*Department of Math. and Science Education, Cumhuriyet University, Sivas / TURKEY*

Received: 16.02.2017; Accepted: 16.08.2017 *http://dx.doi.org/10.17776/csj.349241*

---

**Abstract:** This research has focused on the chemical reactivity behavior of N-1 substituted βCCM derivatives which are isolated from natural or synthetically sources. These compounds as antitumor agents have an important role in human cancer cell lines as well as antiviral, antimalarial activity and so on. Geometry optimizations have been conducted by using DFT method with several basis sets and in 10 different solvent environments. The Isodensity version of Polarized Continuum Model has been used to evaluate the solvent effect on chemical stability and its related properties. We can suggest that global reactivity descriptors can be used to get the relationship between aromaticity and chemical behavior: the structure unit **2** and its corresponding substituted structures are the most stable structures thermodynamically because these structures are more aromatic than those of the others. The electrostatic potential value on the electron density surface have changed in following order: **2A** ($-9.696e^{-2}$) < **0A** ($-9.689e^{-2}$) < **1A** ($-9.343e^{-2}$) of each molecule including anthracene 9-yl substituted and have changed as **2** (-0.128) < **0** (-0.123) < **1** (-0.114) for corresponding non-substituted structures, at 6311++g(d,p) basis set in water phase. Hopefully, this paper will provide the useful information on evaluation or explanation of chemical properties of the antitumor agents used in cancer treatment.

***Keywords:*** Global hardness, electrophilicity, chemical potential, solvent effect, substituent effect.

---

# 1-Sübstitüeli THβC, DHβC, βC Türevlerinin DFT'ye Dayalı Kuantum Kimyasal Tanımlayıcıları

**Özet:** Bu çalışma ile doğal ya da sentetik olarak elde edilen, N-1 sübstitüeli βCCM türevlerinin kimyasal davranışları incelenmiştir. Antitumor ajanı olan bu bileşikler, antiviral ve anti sıtma aktivitelerinin yanı sıra, insan kanser hücreleri için de önemli bir role sahiptirler. Geometri optimizasyonları farklı temel settler ile 10 farklı çözücü ortamda DFT kullanılarak yapılmıştır. Kimyasal denge ve buna bağlı özelliklerin çözücüye bağlı olarak nasıl değiştiğini değerlendirmek için Polarize Kontinuum Model'in Isodensity versiyonu kullanılmıştır. Kimyasal davranış ve aromatiklik arasında ki ilişkiyi elde etmek için küresel aktiflik tanımlayıcılarının kullanılabileceğini önerebiliriz: **2** no'lu temel yapı ve sübstitüeli türevleri, diğer moleküllerden daha aromatik oldukları için, termodinamiksel olarak daha kararlıdırlar. Antrasen 9-yl sübstitüeli her bir molekülün elektrostatik potansiyel değerleri **2A** ($-9.696e^{-2}$) < **0A** ($-9.689e^{-2}$) < **1A** ($-9.343e^{-2}$) olarak değişirken, sübstitüe grup içermeyen temel moleküllerin elektrostatik potansiyelleri 6311++g(d,p) temel set ve sulu fazda **2** (-0.128) < **0** (-0.123) < **1** (-0.114) olarak hesaplanmıştır. Bu çalışmanın sonuçlarının, kanser tedavisinde kullanılan antitumor ilaçlarının kimyasal özelliklerinin açıklanması ve değerlendirilmesi açısından önemli bilgiler sağlayacağını umuyoruz.

***Anahtar Kelimeler*:** Küresel sertlik, elektrofiliklik, kimyasal potansiyel, çözücü etkisi, substituent etkisi.

---

* Corresponding author. *Email address: Goncagul.serdaroglu@gmail.com*

## 1. INTRODUCTION

In recent years, β-Carboline alkaloids have become increasingly popular by scientist due to their important pharmacological properties such as hallucinogenic, antiviral activity [1, 2], fungicidal activity [1], antimalarial activity [2], antiparasitic activity, especially antitumor activity [2]. The derivatives of this group compound being a range of naturally and synthetic alkaloids have been extracted from natural sources such as plant families, fungi, animal tissues and marine or have been synthesized in the laboratory. Initially, βC-3-carboxylates have been studied because of their antagonist characteristics on BzR (benzodiazepine receptors) [3], after that, it is realized that these compounds have also acted as BzR inverse agonist [4], also it is to be reminded the inverse agonists such as βCCM and βCCE don’t act on identical receptor sites [5]. Cain, M., and co-workers, with their study on βC acting on brain BzR have been proved that the full aromatic βC's have been more potent than their corresponding THβC’s, also have been shown that this group compounds ability to bind Benzodiazepine receptor has increased with the substitution at the C-3 position [6]. In another work focused on BzR, it has been shown that the affinity is augmented with the ester formation at the substituent group at C-3 position of the interested compound, but this strongly depends on molecular size, hydrophobic and electronic properties of the ester type [7]. There are many researches about new synthetic βC’s acting on BzR and their antagonist and inverse agonist characteristics, sometimes combine with structural requirements and electronic properties [8- 10]. Since two decades, the many searches on βC and/or its derivatives have focused on antitumor activity [11, 12], cytotoxic activities against human tumor cell lines in vitro [13- 15] and side effects caused by cytotoxicity [16]. Cao, R., et al. have deduced with their research on the synthesis of substituted βC and on in vitro cytotoxic effect of these novel βC derivatives that the cytotoxic potency has varied considerably with respect to the type of substitute group [13]. Similarly, the substitution effect on antitumor activity and cytotoxicity potency of βC have been studied by Shen, Ya- Ching and co-workers [16], and they have determined that the DHβC derivatives show the much better activity than their corresponding THβC and they have also suggested the double bond between C-1 and C-2 in these derivatives has a critical role in cytotoxicity. One of the recent work about the synthesis of new βC derivatives and their activities against tumor- cell lines, Bai, B. and co-workers have shown that the compounds including H atom substitution at C-3 position have more cytotoxic activity than the methyl group, also the derivatives having ethyl substitution at the position N-9 have less inhibition activity against five human cancer cell lines. In literature, there are many types of researches on the synthesis of βC compounds and on the evaluation of their pharmacological, biological, biochemical, medicinal properties and so on, but the computational analysis or investigations of electronic properties of these group derivatives are limited. Allen, M. S and co-workers have studied on the structural requirements of the 3- substituted βC, γC and di-indoles and they have presented the steric and electrostatic contour maps to provide guidelines for designing more potent ligands acting as BzR inverse agonists and antagonists [17, 18].

In this work, we have computed the quantum chemical parameters such as Energy Gap (ΔE), electronic chemical potential (μ), global hardness (η), electrophilicity (ω), the maximum charge transfer index (ΔNmax), the electronic properties of 1- substituted THβCCM (1, 2, 3, 4- tetrahydro-β- Carboline- Carboxy methylene), DHβCCM (3, 4- dihydro-β- Carboline- Carboxy methylene) and βCCM (β- Carboline- Carboxy methylene) to determine the substituent effect on the chemical stability of these structures and to be able to get the best reactive structure acting as antitumor agent. At this point, we have also conducted all calculations for non- substituted βC because we have wondered how much the chemical stability and the related properties of basic structural units have changed with affiliate group. Finally, we have also compared the obtained parameters of non- substituted βC with the corresponding substituted βC derivatives. Hopefully, this work provided useful information to be able to use in the design of new potent antitumor agents.

## METHOD

In this research, we have studied three βC derivatives as the basic structural unit, and their corresponding N-1 substituted structures depicted in Figure 1 to explain how the chemical reactivity have been affected with the aromaticity of each substituent group. For this way, all DFT jobs have been conducted by using the Gaussian 09W [19] software package at B3LYP level of theory which is a combination of Becke's three-parameter hybrid exchange functional [20] and the Lee-Yang-Parr correlation functional [21]. Firstly, the geometry optimization and frequency calculations have been done in the gas phase, then the optimized structures have been used to get the thermochemical parameters and to get the quantum chemical parameters both in the gas phase and in the other solvent media. We have verified the stable structures by the absence of any imaginary frequency for each solvent media. The isodensity version of Polarized Continuum Model (PCM) [22, 23] have been used to get the thermochemical parameters such as Solvation Free Energy and the quantum chemical parameters such as Energy Gap, electronic chemical potential (μ), global hardness (η), electrophilicity (ω) and the maximum charge transfer index (ΔNmax) to evaluate the effect on the chemical reactivity behavior of selected βC and their 1- substituted derivatives. Geometry optimizations and frequency calculations have been carried out with three basis set just as 6-31G(d,p), 6-31+G(d,p) and 6-311++G(d,p), in the solvent media 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, $CHCl_3$ (Chloroform), $C_6H_5Cl$ (Chlorobenzene), $CH_2Cl_2$ (Dichloromethane), Quinoline, $C_2H_5OH$ (ethanol), $CH_3OH$ (Methanol), Acetonitrile, DMSO (dimethylsulfoxide), $H_2O$ (water), respectively.

### *Theoretical Background*

As the quantum chemical descriptors, global hardness, electronic chemical potential, electrophilicity and maximum charge transfer index are getting used to explain chemical reactivity on any chemical process. The Ionization energy (*I*) and electron affinity (*A*) in according with Koopmans Theorem [24] can be expressed through HOMO and LUMO orbital energies [25] as follow:

$$I = -E_{HOMO} \qquad (1)$$

$$A = -E_{LUMO} \qquad (2)$$

Parr R.G. and co-workers [26] have represented the DFT based global descriptors such as electronic chemical potential (μ), global hardness (η), electrophilicity (ω) and the maximum charge transfer index (ΔNmax) as follow:

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

$$\eta = \frac{I-A}{2} \qquad (4)$$

$$\omega = \frac{\mu^2}{2\eta} \qquad (5)$$

$$\Delta N_{max} = \frac{I+A}{2(I-A)} \qquad (6)$$

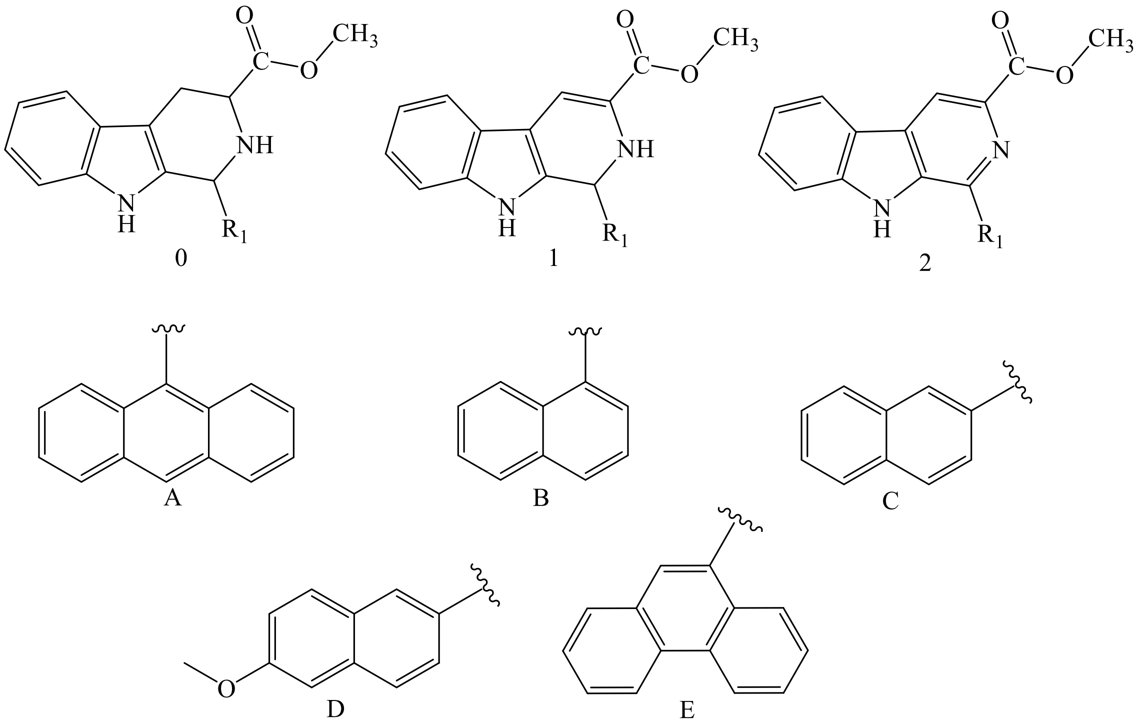

**Figure 1.** The basic chemical structures studied β-Carbolines given as **0** (THβC-3-carboxylic acid methyl ester), **1** (DHβC-3-carboxylic acid methyl ester), **2** (βC-3-carboxylic acid methyl ester) and substituent groups as **A** (anthracen-9-yl)**, B** (naphthalene-1-yl)**, C** (naphthalene-2-yl)**, D** (6-methoxynaphthalene-2-yl)**, E** (phenanthrene-9-yl).

## DISCUSSION

We can start to discuss with the stabilization energy of non-substituted βCs. The stabilization free energy on going from the gas phase to water phase are presented in Figure 2 for non-substituted βCs and Figure 3 for substituted βCs, the full numerical data are given as supporting information of this text (See S1). We can say that all structures are stabilized by solvent dielectric constant. The stabilization free energies for non-substituted molecules have increased in the following order: **0** (8.47 kcal) < **1** (8.55 kcal) < **2** (9.14 kcal) at B3LYP/631G*; **0** (9.43 kcal) < **1** (9.64 kcal) < **2** (10.31 kcal) at B3LYP/631+G* ; **0** (9.32 kcal) < **1** (9.50 kcal) < **2** (10.18 kcal) at B3LYP/6311++G** basis set, except for in the Toluene, in the Chloroform and in the Chlorobenzene, which the free energy ordering of these solvent media's is found out as **1** < **0** < **2**. When the solvent dielectric constant exceeds the value of ε=5.70 for chlorobenzene, the structures 0 and 1 have been replaced each other in the ordering of stabilization energy. It can be said that the structure 2 has the most stabilized structure also there is a systematic increase in solvation free energy with the solvent dielectric constant at all basis sets.

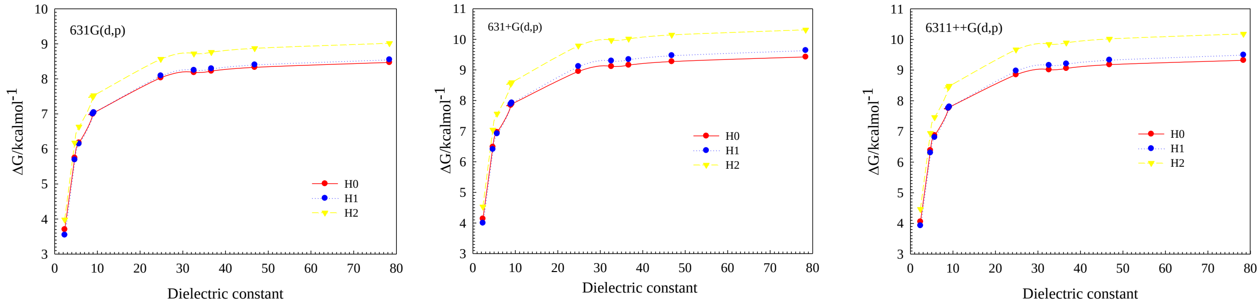

**Figure 2.** Solvation Free Energies as a function of solvent dielectric constant for non-substituted β-Carbolines.

Now, we can continue with discuss the 1-substituted βCs: first, the stabilization free energy ordering of 1-substituted THβC derivatives between the gas phase and the water phase is found out as **0B**( 8.50 kcal) < **0C** (8.87 kcal) < **0A** (9.19 kcal) < **0E** (9.73 kcal) <**0D** (9.91 kcal) at 631G*, the same energy increases in the following order: **0B**( 9.51 kcal) < **0C** (9.73 kcal) < **0A** (10.41 kcal) < **0E** (10.67 kcal) <**0D** (11.34 kcal) at 631+G*and it is found out as **0B**( 9.56 kcal) < **0C** (9.76 kcal) < **0A** (10.52 kcal) < **0E** (10.76 kcal) <**0D** (11.26 kcal) at 6311++G**. Second, the solvation free energy of 1-substituted DHβC derivatives are calculated as **1B** (8.57 kcal) < **1C** (8.83 kcal) < **1A** (9.11 kcal) < **1E** (9.15 kcal) <**1D** (9.77 kcal) at 631G*, **1B** (9.62 kcal) < **1C** (10.01 kcal) < **1E** (10.24 kcal) < **1A** (10.43 kcal) <**1D** (11.12 kcal) at 631+G*, **1B** (9.63 kcal) < **1C** (9.95 kcal) < **1E** (10.45 kcal) < **1A** (10.46 kcal) <**1D** (11.12 kcal) at 6311++G**, respectively. And finally, the stabilization energies of βC derivatives are determined as **2C** (9.37 kcal) < **2B** (9.54 kcal) < **2E** (10.14 kcal) < **2A** (10.32 kcal) <**2D** (10.56 kcal) at 631G*, **2C** (10.64 kcal) < **2B** (10.78 kcal) < **2E** (11.39 kcal) < **2A** (11.84 kcal) <**2D** (12.05 kcal) at 631+G*, **2C** (10.67 kcal) < **2B** (10.71 kcal) < **2E** (11.50 kcal) < **2A** (11.63 kcal) <**2D** (12.07 kcal) at 6311++G**. In according with these results, the most stabilized structures are determined as **D** (6-methoxynaphthalen-2-yl) substituted structures for all βC derivatives. Because **D** substituted β-Carboline derivatives have the 6-methoxynaphthalen-2-yl at C-1 position, and it can be easily concluded that this polar group has more stabilized with solvent dielectric constant than those for the other structures. Here, it is time to talk about the relationship between aromaticity and solvation free energy: the βC derivatives including naphthalene substitutiton at C1 position have the less solvation free energy while the βC derivatives having substituted anthracene or phenanthrene have the bigger solvation free energy. In past, the electron delocalization energy of some aromatic systems is determined by Wiberg KB in the following order: Naphthalene **(60)** <Anthracene **(80)** < Phenanthrene **(85)** [27]. There is a good correlation between the delocalization energy and the solvation free energy: the solvation free energy increases as the delocalization energy increases. On the other hand, if we look for the less stabilized structures, then we can easily see that the **B** (naphthalene-1-yl) substituted structures are the less stable structures in among the THβC and DHβC derivatives, and **C** (naphthalene-2-yl) substituted structure is the less stable for βC though It can also seem that the solvation free energies of the **B** and **C** substituted βC derivatives are very close each other.

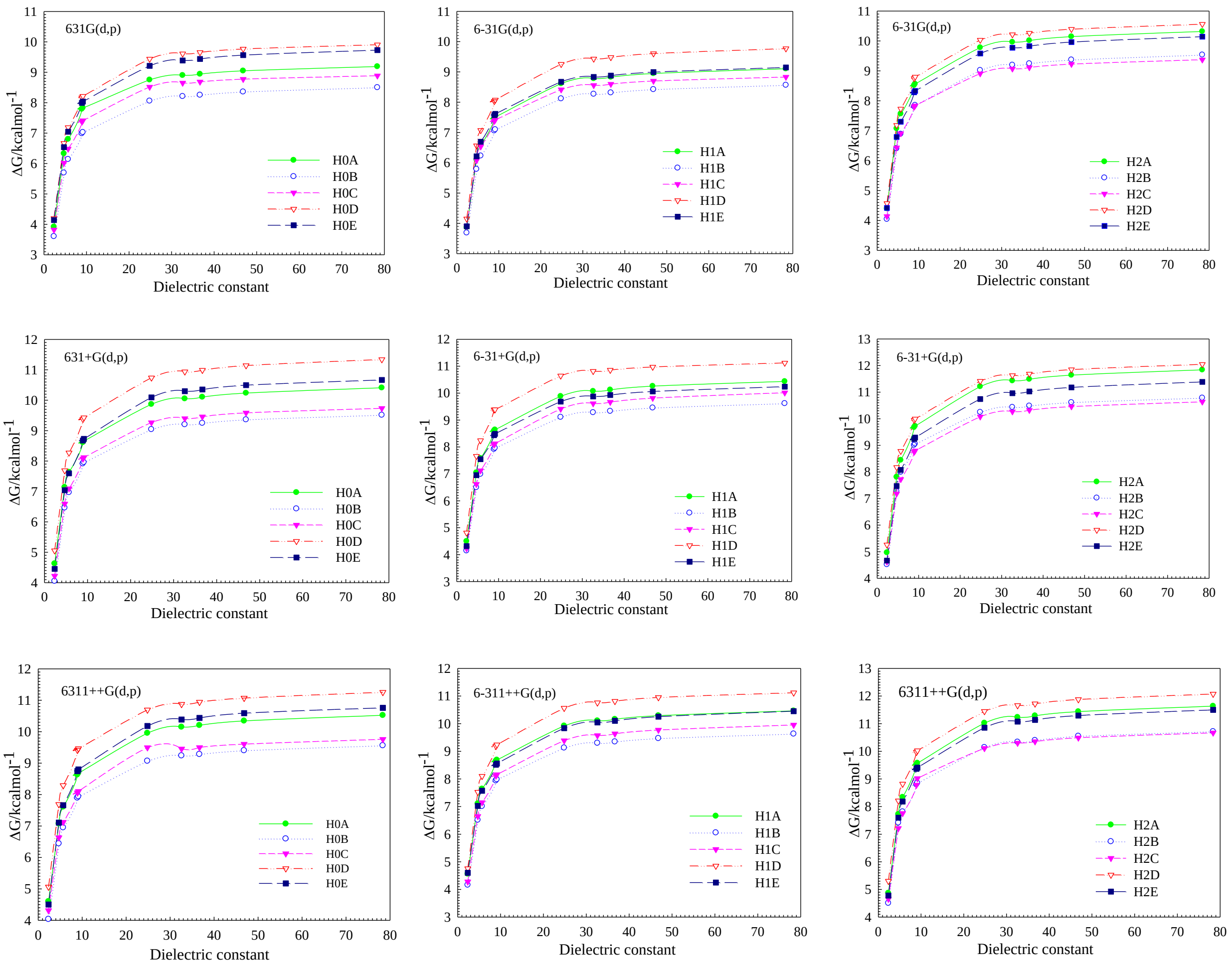

**Figure 3.** Solvation Free Energies as a function of solvent dielectric constant for substituted β-Carbolines.

As well known, the solvation free energy is very important to predict the chemical behavior of any interesting systems which can be biochemical or pharmaceutical, medicinal in living systems. Nowadays, the quantum chemical parameters are also getting used to predict the chemical reactivity behavior of any interesting system. The calculated dipole moments are given in Table 1 for only gas phase and water phases to be able to show the how dipole moment influences strongly with solvent media and with basis set. Also, we can make a conclusion in advance, that is, **2D** is one of the most reactive structures in studied structure because it has the highest dipole moment which means this structure is highly polarizable and therefore it is the soft system.

Here we have wanted to focus on the thermodynamic properties and quantum chemical parameters of each studied structures and have given the calculated quantum chemical parameters at Table 2 for only the B3LYP/6311++G** basis set for the 10 solvents. The calculated parameters for the other basis set are not given here, they are given as supporting information on this research (see S2).

**Table 1.** The calculated Dipole Moments both in the gas phase and the aqueous phase.

| **Molecule** | **Gas** | | | **Water** | | |
|---|---|---|---|---|---|---|
| | **6-31G(d,p)** | **6-31+G(d,p)** | **6-311++G(d,p)** | **6-31G(d,p)** | **6-31+G(d,p)** | **6-311++G(d,p)** |

| | | | | | | |
|---|---|---|---|---|---|---|
| **0A** | 4.0413 | 4.2513 | 4.1733 | 5.8811 | 6.2823 | 6.1910 |
| **0B** | 3.8674 | 4.0328 | 3.9647 | 5.6555 | 6.0318 | 5.9599 |
| **0C** | 4.0737 | 4.2226 | 4.1476 | 5.6620 | 6.0702 | 5.9968 |
| **0D** | 4.3174 | 4.4339 | 4.3414 | 5.5449 | 5.5046 | 5.4007 |
| **0E** | 4.2181 | 4.3196 | 4.2431 | 5.8517 | 6.1783 | 6.1077 |
| **1A** | 4.6910 | 4.9640 | 4.9055 | 6.6457 | 7.1947 | 7.1123 |
| **1B** | 4.4624 | 4.6992 | 4.6355 | 6.3818 | 6.9055 | 6.8293 |
| **1C** | 4.7056 | 4.9230 | 4.8513 | 6.4333 | 6.9237 | 6.8354 |
| **1D** | 4.2799 | 5.5133 | 5.4267 | 6.6965 | 7.1184 | 7.0113 |
| **1E** | 4.9652 | 5.0990 | 5.0341 | 6.7019 | 7.0955 | 7.0214 |
| **2A** | 3.8578 | 3.9471 | 3.9069 | 5.8175 | 6.2217 | 6.1355 |
| **2B** | 3.6894 | 3.8217 | 3.7703 | 5.6453 | 6.0832 | 5.9877 |
| **2C** | 3.7681 | 3.9013 | 3.8537 | 5.7830 | 6.2069 | 6.1082 |
| **2D** | 5.3288 | 5.5013 | 5.4340 | 7.8334 | 8.2982 | 8.2061 |
| **2E** | 3.7532 | 3.8983 | 3.8556 | 5.7954 | 6.1778 | 6.0857 |

Now, we want to evaluate the quantum chemical parameters of each group of derivatives in their own class. The Energy Gap (ΔE) for the THβC derivatives increase in the following order: **0A** < **0D**= **0E** < **0C** <**0B** for gas phase while it changes in following order as **0A**< **0E** < **0C** < **0D** < **0B** for the other solvation phases at B3LYP/6311++G**. Latter ordering is the same for the other two basis sets for most of the solvent environments. Also, the Energy Gap of DHβC has strongly depended on both the solvent media and the basis set. The Energy Gap changing is found out to be as **1A**< **1B** < **1D** < **1C** < **1E** for most of the solvation phases at the B3LYP/6311++G** basis set while it is that as **1A**< **1C** < **1E** < **1D** < **1B** at the 631G* basis set for most of the solvents (it can be also seen from S2). For the βC derivatives, at the B3LYP/6311++G** basis set, the energy gap has changed as ordering: **2A**< **2D** < **2C** < **2B** < **2E** for gas phase; as **2E**< **2A** < **2C** < **2D** < **2B** for the DMSO, and **2A**< **2D** < **2C** < **2E** < **2B** for the other phases except for DMSO and gas phases. Here, one noteworthy feature of these results is that the Energy Gap strongly depend on both the solvent media and the basis set. But still we can generalize something about the stability and energy gap: **0A**, **1A** and **2A** structures for all basis sets and all solvent media seem to be antiaromatic ones and therefore they are less stable structure and therefore these structures are the best reactive ones. On the other hand, **0B** for all solvents and all basis sets; **1E** for most solvent at B3LYP/6311++G (d, p) and **2B** for most basis sets and all solvent media are the most stable structures, respectively. Now, all anthracene substituted βC derivatives are the less stable structures, and the most stable structures are the naphthalene and phenanthrene substituted βC derivatives.

Here, we can continue to discuss with the electronic chemical potential (μ) which has also depended on both the solvent media and basis set. The μ ordering for THβC derivatives is determined as **0A**< **0E** < **0C** < **0B** < **0D** for both the all solvation phases and the all basis sets. But the μ ordering of the DHβC derivatives is determined as **1A**< **1C** < **1E** < **1D** < **1B** at 6311++G(d,p) basis set in water. It is similar the other results found out at the other basis sets and in the other solvent media though there are some exceptional trends in this parameter. For the βC derivatives, μ is changed in the following order: **2C**< **2E** <**2A** <**2B** <**2D** at the B3LYP/6311++G(d,p) for most of the solvents. Still, it can be suggested that the structures **0A**, **1A** and **2C** are the good electrophiles because μ is generally associated with the charge transfer capability of the system in its ground state.

On the other hand, the global hardness index (η) of THβC derivatives increase in the following order: **0A**< **0E** < **0C** < **0D** < **0B** for most of the solvents and the basis sets. Also, when we check out the results of the substituted DHβC, we can see that the η of these group compounds depends on both the solvent media and basis sets. For example is determined as **1A**< **1B** < **1D** < **1C** < **1E** at the 6311++G** basis set for most of the solvent. It is possible to say the same conclusions for the βC derivatives: the η ordering is that as **2A**< **2D** < **2C** < **2E** < **2B** at the B3LYP/6311++G** basis set for most of the solvents. These results have shown that the **0A, 1A** and **2A** structures have the highest chemical reactivity because they have the lowest hardness in their class for all solvent media.

The electrophilicity index as another global descriptor used to get an electronic charge from environment for the studied structures increase in following order: **0D**< **0B** < **0C** < **0E** < **0A** for THβC derivatives at all basis sets and in all solvents; **1B**< **1E** < **1D** < **1C** < **1A** DHβCs at the B3LYP/6311++G** basis set in water phase; **2B**< **2E** < **2D** < **2C** < **2A** for βCs for most of the solvents at the B3LYP/6311++G** basis set. Here, it can be concluded that the **0A, 1A** and **2A** structures having the anthracene substituted on each of them are the best electrophiles, and the most reactive structures in all βC derivatives, for all basis sets and for the all dielectric constants.

The max charge transfer index (ΔNmax) of THβCs increases as follow: **0B** ≅ **0D** < **0C** < **0E** < **0A** for most of the solvent phases and basis sets. The ΔNmax of DHβC derivatives increase in following order: **1E**< **1B** < **1D** < **1C** < **1A** at the B3LYP/6311++G** basis set in water phase. The ΔNmax index of βC derivatives increase as follow: **2B**< **2E** < **2C** < **2D** < **2A** at the B3LYP/6311++G** basis set in water. In according with these results, it can be easily predicted that the **0A, 1A** and **2A** structures have the biggest ΔNmax in their own class of derivatives.

For now, we have tried to give some important results about βC derivatives to get a prediction about their chemical reactivity changing and -related properties, but they are in their own class. Now, we can start with the discussion how non-substituted structures are affected by the aromatic group substitution.

The Energy Gap (ΔE) of the basic structural units increase in the following order: **1**(DHβC) < **2** (βC) < **0** (THβC) for all solvent medias at the 631+G** and 6311++G** basis sets. A similar ordering is obtained for B3LYP/631G(d,p) basis set except for the acetonitrile (**0**< **1**< **2**), water (**0**< **1**< **2**) and the chloroform (**1**< **0**< **2**). Now, maybe we should express that the all obtained quantum chemical parameters at the 631+G(d,p) and 6311++G(d,p) basis sets are fully compatible with each other though there are a slight differences in ordering of the Energy Gap (ΔE) at the B3LYP/631G(d,p) for only several solvent media.

**Table 2.** The calculated quantum chemical parameters with the B3LYP/6311++G** basis set.

| Molecule | Solvent | ΔE | μ | η | ω | ΔNmax | Solvent | ΔE | μ | η | ω | ΔNmax |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **0A** | **Toluen**<br>(ε= 2.37) | 3,404 | -3,905 | 1,702 | 4,479 | 2,294 | **Ethanol**<br>(ε= 24.85) | 3,478 | -3,964 | 1,739 | 4,519 | 2,280 |
| **0B** | | 4,087 | -3,589 | 2,043 | 3,153 | 1,757 | | 4,161 | -3,656 | 2,080 | 3,212 | 1,757 |
| **0C** | | 4,053 | -3,605 | 2,027 | 3,206 | 1,779 | | 4,149 | -3,666 | 2,074 | 3,239 | 1,767 |
| **0D** | | 4,064 | -3,569 | 2,032 | 3,133 | 1,756 | | 4,155 | -3,647 | 2,078 | 3,201 | 1,755 |
| **0E** | | 4,047 | -3,638 | 2,024 | 3,271 | 1,798 | | 4,126 | -3,701 | 2,063 | 3,319 | 1,794 |
| **1A** | | 2,754 | -3,660 | 1,377 | 4,864 | 2,658 | | 2,856 | -3,701 | 1,428 | 4,797 | 2,592 |
| **1B** | | 3,408 | -3,353 | 1,704 | 3,299 | 1,968 | | 3,459 | -3,411 | 1,730 | 3,363 | 1,972 |
| **1C** | | 3,419 | -3,395 | 1,710 | 3,371 | 1,986 | | 3,486 | -3,450 | 1,743 | 3,415 | 1,979 |
| **1D** | | 3,424 | -3,362 | 1,712 | 3,301 | 1,964 | | 3,480 | -3,441 | 1,740 | 3,403 | 1,978 |
| **1E** | | 3,386 | -3,394 | 1,693 | 3,402 | 2,005 | | 3,514 | -3,446 | 1,757 | 3,378 | 1,961 |
| **2A** | | 3,504 | -3,954 | 1,752 | 4,463 | 2,257 | | 3,510 | -4,015 | 1,755 | 4,593 | 2,288 |
| **2B** | | 4,229 | -3,954 | 2,114 | 3,696 | 1,870 | | 4,251 | -4,009 | 2,125 | 3,780 | 1,886 |
| **2C** | | 4,110 | -4,013 | 2,055 | 3,918 | 1,953 | | 4,102 | -4,057 | 2,051 | 4,012 | 1,978 |
| **2D** | | 3,933 | -3,849 | 1,966 | 3,768 | 1,958 | | 3,927 | -3,913 | 1,963 | 3,899 | 1,993 |
| **2E** | | 4,204 | -3,962 | 2,102 | 3,734 | 1,885 | | 4,210 | -4,017 | 2,105 | 3,833 | 1,908 |
| **0A** | **Chl** | 3,444 | -3,933 | 1,722 | 4,491 | 2,284 | **Meth** | 3,479 | -3,966 | 1,739 | 4,522 | 2,280 |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **0B** | | 4,123 | -3,618 | 2,062 | 3,174 | 1,755 | | 4,163 | -3,658 | 2,082 | 3,215 | 1,758 |
| **0C** | | 4,101 | -3,630 | 2,050 | 3,214 | 1,771 | | 4,146 | -3,674 | 2,073 | 3,255 | 1,772 |
| **0D** | | 4,109 | -3,605 | 2,054 | 3,163 | 1,755 | | 4,158 | -3,650 | 2,079 | 3,203 | 1,755 |
| **0E** | | 4,086 | -3,665 | 2,043 | 3,287 | 1,794 | | 4,129 | -3,703 | 2,064 | 3,322 | 1,794 |
| **1A** | | 2,802 | -3,676 | 1,401 | 4,824 | 2,624 | | 2,859 | -3,703 | 1,430 | 4,796 | 2,590 |
| **1B** | | 3,444 | -3,372 | 1,722 | 3,301 | 1,958 | | 3,458 | -3,414 | 1,729 | 3,370 | 1,974 |
| **1C** | | 3,462 | -3,414 | 1,731 | 3,367 | 1,973 | | 3,487 | -3,453 | 1,744 | 3,420 | 1,981 |
| **1D** | | 3,461 | -3,393 | 1,731 | 3,326 | 1,961 | | 3,480 | -3,445 | 1,740 | 3,409 | 1,980 |
| **1E** | | 3,447 | -3,415 | 1,724 | 3,384 | 1,982 | | 3,518 | -3,448 | 1,759 | 3,379 | 1,960 |
| **2A** | | 3,506 | -3,979 | 1,753 | 4,515 | 2,269 | | 3,510 | -4,018 | 1,755 | 4,599 | 2,289 |
| **2B** | | 4,250 | -3,975 | 2,125 | 3,718 | 1,870 | | 4,250 | -4,011 | 2,125 | 3,786 | 1,888 |
| **2C** | | 4,108 | -4,031 | 2,054 | 3,956 | 1,963 | | 4,102 | -4,059 | 2,051 | 4,016 | 1,979 |
| **2D** | | 3,931 | -3,877 | 1,965 | 3,824 | 1,973 | | 3,927 | -3,915 | 1,963 | 3,904 | 1,994 |
| **2E** | | 4,210 | -3,985 | 2,105 | 3,771 | 1,893 | | 4,210 | -4,019 | 2,105 | 3,837 | 1,910 |
| **0A** | **Chlorobenzene** (ε= 5.70) | 3,451 | -3,939 | 1,726 | 4,496 | 2,283 | **Acetonitrile** (ε= 36.69) | 3,479 | -3,967 | 1,740 | 4,523 | 2,280 |
| **0B** | | 4,131 | -3,625 | 2,065 | 3,180 | 1,755 | | 4,164 | -3,659 | 2,082 | 3,216 | 1,758 |
| **0C** | | 4,110 | -3,636 | 2,055 | 3,217 | 1,769 | | 4,147 | -3,674 | 2,074 | 3,256 | 1,772 |
| **0D** | | 4,118 | -3,613 | 2,059 | 3,169 | 1,754 | | 4,159 | -3,651 | 2,079 | 3,204 | 1,756 |
| **0E** | | 4,094 | -3,671 | 2,047 | 3,292 | 1,794 | | 4,129 | -3,704 | 2,065 | 3,322 | 1,794 |
| **1A** | | 2,812 | -3,681 | 1,406 | 4,817 | 2,618 | | 2,860 | -3,704 | 1,430 | 4,796 | 2,590 |
| **1B** | | 3,450 | -3,377 | 1,725 | 3,306 | 1,958 | | 3,459 | -3,415 | 1,729 | 3,372 | 1,975 |
| **1C** | | 3,468 | -3,420 | 1,734 | 3,372 | 1,972 | | 3,487 | -3,454 | 1,744 | 3,421 | 1,981 |
| **1D** | | 3,466 | -3,401 | 1,733 | 3,336 | 1,962 | | 3,480 | -3,446 | 1,740 | 3,412 | 1,980 |
| **1E** | | 3,460 | -3,421 | 1,730 | 3,382 | 1,977 | | 3,518 | -3,449 | 1,759 | 3,380 | 1,960 |
| **2A** | | 3,507 | -3,985 | 1,754 | 4,528 | 2,272 | | 3,510 | -4,018 | 1,755 | 4,601 | 2,290 |
| **2B** | | 4,254 | -3,981 | 2,127 | 3,725 | 1,872 | | 4,249 | -4,012 | 2,125 | 3,788 | 1,888 |
| **2C** | | 4,107 | -4,036 | 2,054 | 3,965 | 1,965 | | 4,101 | -4,059 | 2,051 | 4,017 | 1,979 |
| **2D** | | 3,930 | -3,884 | 1,965 | 3,838 | 1,976 | | 3,927 | -3,916 | 1,963 | 3,906 | 1,995 |
| **2E** | | 4,211 | -3,990 | 2,105 | 3,781 | 1,895 | | 4,209 | -4,020 | 2,105 | 3,839 | 1,910 |
| **0A** | **Dichloromethane** (ε= 8.93) | 3,465 | -3,951 | 1,733 | 4,505 | 2,280 | **DMSO** (ε= 46.83) | 3,480 | -3,968 | 1,740 | 4,525 | 2,281 |
| **0B** | | 4,144 | -3,638 | 2,072 | 3,193 | 1,756 | | 4,165 | -3,661 | 2,083 | 3,218 | 1,758 |
| **0C** | | 4,128 | -3,649 | 2,064 | 3,225 | 1,768 | | 4,149 | -3,676 | 2,075 | 3,257 | 1,772 |
| **0D** | | 4,135 | -3,627 | 2,068 | 3,182 | 1,754 | | 4,161 | -3,653 | 2,080 | 3,207 | 1,756 |
| **0E** | | 4,108 | -3,684 | 2,054 | 3,303 | 1,793 | | 4,131 | -3,706 | 2,066 | 3,324 | 1,794 |
| **1A** | | 2,831 | -3,689 | 1,416 | 4,808 | 2,606 | | 2,863 | -3,705 | 1,432 | 4,795 | 2,588 |
| **1B** | | 3,457 | -3,390 | 1,729 | 3,324 | 1,961 | | 3,458 | -3,417 | 1,729 | 3,377 | 1,977 |
| **1C** | | 3,478 | -3,432 | 1,739 | 3,386 | 1,973 | | 3,488 | -3,456 | 1,744 | 3,425 | 1,982 |
| **1D** | | 3,474 | -3,417 | 1,737 | 3,361 | 1,967 | | 3,481 | -3,448 | 1,740 | 3,416 | 1,981 |
| **1E** | | 3,484 | -3,431 | 1,742 | 3,379 | 1,970 | | 3,520 | -3,451 | 1,760 | 3,383 | 1,961 |
| **2A** | | 3,508 | -3,997 | 1,754 | 4,555 | 2,279 | | 3,511 | -4,020 | 1,755 | 4,604 | 2,290 |
| **2B** | | 4,255 | -3,992 | 2,128 | 3,746 | 1,876 | | 4,249 | -4,014 | 2,124 | 3,792 | 1,889 |
| **2C** | | 4,105 | -4,045 | 2,053 | 3,985 | 1,971 | | 4,101 | -4,060 | 2,051 | 4,020 | 1,980 |
| **2D** | | 3,929 | -3,896 | 1,965 | 3,864 | 1,983 | | 4,209 | -4,021 | 2,105 | 3,842 | 1,911 |
| **2E** | | 4,211 | -4,002 | 2,105 | 3,803 | 1,901 | | 3,494 | -4,006 | 1,747 | 4,591 | 2,292 |
| **0A** | **Quinoline** (ε= 9.16) | 3,466 | -3,951 | 1,733 | 4,505 | 2,280 | **Water** (ε= 78.36) | 3,481 | -3,970 | 1,740 | 4,527 | 2,281 |
| **0B** | | 4,145 | -3,638 | 2,072 | 3,194 | 1,756 | | 4,167 | -3,664 | 2,084 | 3,221 | 1,758 |
| **0C** | | 4,129 | -3,649 | 2,064 | 3,225 | 1,768 | | 4,152 | -3,679 | 2,076 | 3,259 | 1,772 |
| **0D** | | 4,136 | -3,628 | 2,068 | 3,182 | 1,754 | | 4,163 | -3,655 | 2,082 | 3,209 | 1,756 |
| **0E** | | 4,109 | -3,684 | 2,055 | 3,303 | 1,793 | | 4,134 | -3,708 | 2,067 | 3,327 | 1,794 |
| **1A** | | 2,832 | -3,690 | 1,416 | 4,807 | 2,605 | | 2,866 | -3,707 | 1,433 | 4,793 | 2,586 |
| **1B** | | 3,457 | -3,391 | 1,729 | 3,325 | 1,961 | | 3,457 | -3,421 | 1,729 | 3,384 | 1,979 |
| **1C** | | 3,479 | -3,432 | 1,739 | 3,387 | 1,973 | | 3,489 | -3,459 | 1,744 | 3,430 | 1,983 |
| **1D** | | 3,475 | -3,418 | 1,737 | 3,363 | 1,967 | | 3,481 | -3,452 | 1,740 | 3,423 | 1,983 |
| **1E** | | 3,485 | -3,431 | 1,743 | 3,378 | 1,969 | | 3,521 | -3,454 | 1,761 | 3,389 | 1,962 |
| **2A** | | 3,508 | -3,998 | 1,754 | 4,556 | 2,279 | | 3,511 | -4,023 | 1,755 | 4,610 | 2,292 |
| **2B** | | 4,255 | -3,993 | 2,128 | 3,747 | 1,877 | | 4,247 | -4,016 | 2,124 | 3,797 | 1,891 |
| **2C** | | 4,105 | -4,045 | 2,052 | 3,986 | 1,971 | | 4,101 | -4,062 | 2,050 | 4,024 | 1,981 |
| **2D** | | 3,929 | -3,897 | 1,964 | 3,865 | 1,984 | | 3,926 | -3,920 | 1,963 | 3,915 | 1,997 |
| **2E** | | 4,211 | -4,002 | 2,105 | 3,804 | 1,901 | | 4,209 | -4,024 | 2,104 | 3,847 | 1,912 |

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

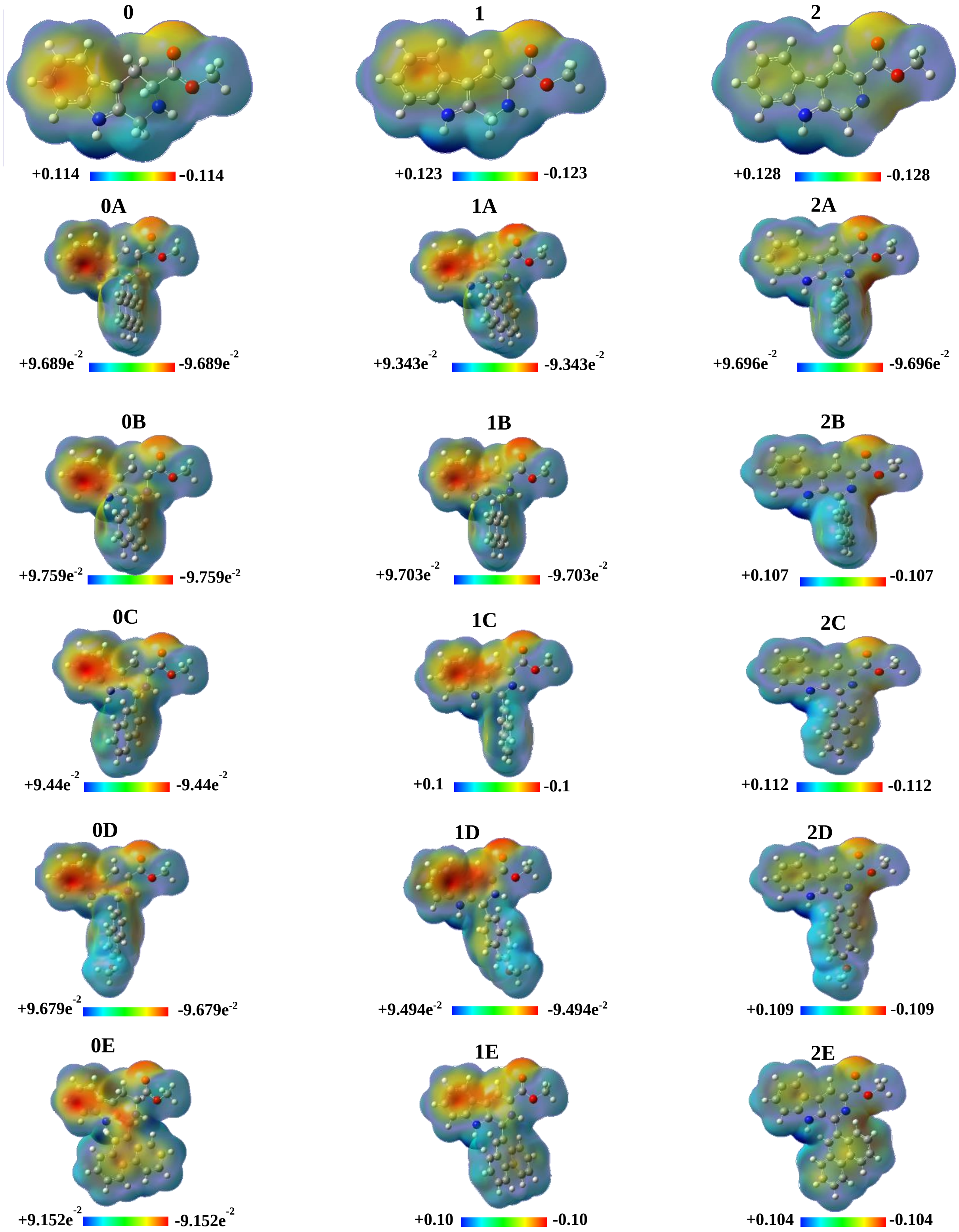

**Figure 4.** The electron density from total SCF density mapped with ESP for non-substituted and substituted β-Carbolines calculated by B3LYP/6-311++G** level of theory, in the aqueous phase.

It is also necessary to question how the electronic chemical potential of the non-substituted compounds are affected by a substituent. The electronic chemical potential of non-substituted βCs mostly changes as **2** (βC) < **1**(DHβC) < **0** (THβC) at the all basis sets for all solvent environments except for the acetonitrile, water, and the chloroform phases. On the other hand, this ordering have changed with substitution **A** to these basic structures as follow: (**2A** < **0A** < **1A**) for all basis sets and for solvent dielectric medias; with substitution **B** as (**2B** < **0B** < **1B**) almost; with substitution **C** as (**2C** < **0C** < **1C**) almost; with substitution **D** as (**2D**< **0D**< **1D**) almost, with substitution **E** as (**2E**< **0E** < **1E**) almost (see S2). Here we can conclude that the **2** is the most stable structure and therefore the less reactive structure and there is no any substituent effect on it, but chemical behaviour for the other molecules has changed with substituent: that is, the structure **0** has the less electronic chemical potential without substituent on it, but it is replaced with the structure **1** when the substituent group attached to on it.

The global hardness index has changed as **1**(DHβC) < **2** (βC) < **0** (THβC) the at all basis sets for all solvent environments except for the acetonitrile just like the electronic chemical potential. How does this index change with substitution? This ordering have changed with substitution **A** to these basic structures as follows: (**1A**< **0A**< **2A**) for all basis sets and for solvent dielectric medias; with substitution **B** as (**1B**< **0B**< **2B**) mostly, with substitution **C** as (**1C**< **0C**< **2C**) mostly; with substitution **D** as (**1D**< **2D**< **0D**) almost, with substitution **E** as (**1E**< **0E**< **2E**) almost (see S2). It seems the structure **1** has the less hardness index and more reactive than the others for non-substituted structures.

The electrophilicity index has represented the following order: **0** (THβC) < **1**(DHβC) < **2** (βC) at the all basis sets for all solvent environments except for the acetonitrile, water, and the chloroform phases. This index have changed with substitution **A** to these basic structures as follows: (**0A**< **2A**< **1A**) mostly, with substitution **B** as (**0B**< **1B**< **2B**) mostly, with substitution **C** as (**0C**< **1C**< **2C**) mostly, with substitution **D** as (**0D**< **1D**< **2D**) almost, with substitution **E** as (**0E**< **1E**< **2E**) mostly (see S2). Here, one can predict here that the structure **2** is the strong electrophile either with a substituent or not while the structure **0** is the less electrophile, mostly.

The max charge transfer index (ΔNmax) have ordered as follows: **0** (THβC) <**2** (βC) < **1**(DHβC) at the all basis sets for all solvent environments except for the acetonitrile, water, and the chloroform phases. ΔNmax of the substituted βC have changed with substitution **A** to these basic structures as follows: (**0A**< **2A**< **1A**) mostly, with substitution **B** as (**0B**< **2B**< **1B**) mostly, with substitution **C** as (**0C**< **2C**< **1C**) mostly, with substitution **D** as (**0D**< **1D**< **2D**) mostly, with substitution **E** as (**0E**< **2E**< **1E**) mostly (see S2). Finally, here we have confirmed that the correlation between electrophilicity and max charge transfer for the structure **0**.

Figure 4 presents the electrostatic potential mapped on the electron density surface calculated by B3LYP/6-311++G** level of theory for non-substituted and substituted βC derivatives, in the aqueous phase. The blue region shows the electrophilic attack center and red region shows the nucleophilic attack center in Figure 4. So, we can strongly suggest that the structure **2** without substituent is the most reactive structure because it has the biggest negative and biggest positive charge centers and it seems to be the most reactive and most aromatic and less stable structure. On the other hand, Figure 4 shows only the ESP mapped for 6311++G (d, p) basis set and it seems something strange, for example, the electron density on all molecular surface of anthracene 9-yl substituted structures have changed in the following order: **2A** ($9.696e^{-2}$) < **0A** ($9.689e^{-2}$) < **1A** ($9.343e^{-2}$) just like the other substituted structures. Although this ordering seems very satisfactory, but we are to talk about why the electron density ordering of the substituted **0** and **1** structures are replaced with each other: as mentioned in the discussion section, the stability orders of structures **0** and **1** have only been calculated differently from each other for 6311++G (d, p). Here we can say that the electron density on the molecular surface has changed with solvent media and with basis set. The visualization of the electron density of each structure is mostly supported with the global chemical descriptors such as global hardness, chemical potential, max charge transfer capability despite there is some inconsistent results for only several solvent media or basis set. Here we shouldn't make suggestion precisely about it because there are many factors that affect the chemical reactivity. So, we have just presented the electron density distribution for water phase to give a realistic prediction about the chemical behavior of these molecules because all chemical events in the living body occur in the aqueous phase.

In this research, we have tried to explain the relationship between chemical behavior and quantum chemical parameters at several basis sets and in the 10 solvent environments including gas phase to compare with each other and to show the computed parameters strongly depend on the basis set and on the solvent media. We have calculated as the structure **2** either with substituted or not is the most stable (thermodynamically) and most aromatic structure, also we have supported it with the other calculated parameters. We hope this work provided important data on evaluation or explanation of chemical properties of the antitumor agents used in cancer treatment.

## Acknowledgments

The authors wish to acknowledge the financial support of the Scientific Research Projects of Cumhuriyet University (Project No: EĞT-053). The all calculations have been conducted at TUBITAK ULAKBIM, High Performance and Grid Computing Center (Tr-Grid)

## REFERENCES

[1] Songh H., Liu Y., Liu Y, Wang L., Wang Q. Synthesis and Antiviral and Fungicidal Activity Evaluation of β-Carboline, Dihydro-β-carboline, Tetrahydro-β-carboline Alkaloids. Journal of Agricultural and Food Chemistry 2014; 62: 1010-1018.

[2] Laine A.E, Lood C, Koskinen A.M.P., Pharmacological Importance of Optically Active Tetrahydro-β-carbolines and Synthetic Approaches to Create the C1 Stereocenter. Molecules 2014; 19: 1544-1567.

[3] Braestrup C, Nielsen M, Olsen C.E., Urinary and brain β-carboline-3-carboxylates as potent inhibitors of brain benzodiazepine receptors. Neurobiology 1980; 77(4):2288-2292.

[4] Hagen T.J., Skolnick P, Cook J.M., Synthesis of 6-Substituted β -Carbolines That Behave as Benzodiazepine Receptor Antagonists or Inverse Agonists. J. Med. Chem.1987; 30: 750-753.

[5] Dodd R.H., Ouannes C, Potier M.C., Carvalho L.P., Rossier J., Potiert P., Synthesis of β -Carboline-Benzodiazepine Hybrid Molecules: Use of the Known Structural Requirements for Benzodiazepine and β -Carboline Binding in Designing a Novel, High-Affinity Ligand for the Benzodiazepine Receptor. J. Med. Chem.1987; 30: 1248-1254.

[6] Cain M, Weber R.W., Guzman F.., Cook J.M., Barker S.A., Rice KC., Crawley J.N., Pau1 S.M., Skolnick P. β-Carbolines: Synthesis and Neurochemical and Pharmacological Actions on Brain Benzodiazepine Receptors. J. Med. Chem. 1982; 25:1081-1091.

[7] Lippke K.P., Schunack W.G., Wenning W., Muller W.E., β -Carbolines as Benzodiazepine Receptor Ligands. 1. Synthesis and Benzodiazepine Receptor Interaction of Esters of β -Carboline-3-carboxylic Acid. J. Med. Chem.1983; 26: 499-503.

[8] Sharma S.D., Bhaduri S., Kaur G., Diastereoselective synthesis of 1,3 disubstituted 1,2,3,4 tetrahydro-β- Carbolines

using Pictet- Spengler reaction in non- acidic aprotic media. Indian Journal of Chemistry 2006;45B: 2710-2715

[9] Dong J., Meng T.Z., Shi X.X., Zou W.H., Lu X. Highly stereoselective transformation of (1S,3S)-cis-1,3-disubstituted tetrahydro-β-carbolines into (1S,3R)-trans-1,3-disubstituted tetrahydro-β-carbolines: an improved asymmetric synthesis of tadalafil from L-tryptophan. Tetrahedron: Asymmetry 2013; 24: 883-893.

[10] Martin L., Leon A., Martin M.A., Castillo B.., Menendez J.C., Detection and characterization of cyclodextrin complexes with β-carboline derivatives by spectroscopic techniques. Journal of Pharmaceutical and Biomedical Analysis 2003; 32: 991-1001.

[11] Cao R., Fan W., Guo L., Ma Q., Zhang G., Li J., Chen X., Ren Z., Qiu L. Synthesis and structureeactivity relationships of harmine derivatives as potential antitumor agents European Journal of Medicinal Chemistry 2013; 60: 135-143.

[12] Savariz F.C., Foglio M.A., Carvalho J.E., Ruiz A.L.T.G., Duarte M.C.T., Rosa M.F., Meyer E., Sarragiotto M.H., Synthesis and Evaluation of New β-Carboline-3-(4-benzylidene)-4H-oxazol-5-one Derivatives as Antitumor Agents. Molecules 2012; 17: 6100-6113.

[13] Cao R., Peng W., Chen H., Hou X., Guan H., Chen Q., Ma Y., Xu A., Synthesis and in vitro cytotoxic evaluation of 1,3-bisubstituted and 1,3,9-trisubstituted β-carboline derivatives. European Journal of Medicinal Chemistry 2005;40: 249-257

[14] Bai B., Li X.Y., Liu L., Li Y., Zhu H.J., Syntheses of novel β-carboline derivatives and the activities against five tumor-cell lines. Bioorganic & Medicinal Chemistry Letters 2014;24: 96-98.

[15] Bai B., Li X.Y., Liu L.., Li Y, Zhu H.J., Design, synthesis and cytotoxic activities of novel β -amino alcohol derivatives. Bioorganic & Medicinal Chemistry Letters 2011; 21: 2302–2304.

[16] Shen Y.C., Chen C.Y., Hsieh P.W., Duh C.Y., Lin Y.M., Ko C.L., The Preparation and Evaluation of 1-Substituted 1,2,3,4-Tetrahydro- and 3,4-Dihydro- β -carboline Derivatives as Potential Antitumor Agents. Chem. Pharm. Bull. 2005;53(1): 32- 36.

[17] Allen M.S., Tan Y.C., Trudell M.L., Narayanan K., Schindler L.R., Martin MJ, Schultz C, Hagen TJ, Koehler K.F., Codding PW, Skolnick P., Cook J. M., Synthetic and Computer-Assisted Analyses of the Pharmacophore for the Benzodiazepine Receptor Inverse Agonist Site. J. Med. Chem. 1990;33: 2343-2357.

[18] Allen M.S, LaLoggia A.J., Darn L.J., Martin M.J., Costantino G., Hagen T.J., Koehler K.F., Skolnick J.P., Cook J.M., Predictive Binding of β -Carboline Inverse Agonists and Antagonists via the CoMFA/GOLPE Approach. J. Med. Chem. 1992;35: 4001-4010.

[19] Frisch M.J., Trucks G.W., Schlegel H.B., Scuseria G.E., Robb M.A., Cheeseman J.R.., Scalmani G, Barone V., Mennucci B., Petersson G.A., Nakatsuji H., Caricato M., Li X., Hratchian H.P., Izmaylov A.F., Bloino J., Zheng G., Sonnenberg J.L., Hada M., Ehara M., Toyota K., Fukuda R., Hasegawa J., Ishida M., Nakajima T., Honda Y., Kitao O., Nakai H., Vreven T., Montgomery J.A. Jr., Peralta J.E., Ogliaro F., Bearpark M., Heyd J.J., Brothers E., Kudin K.N., Staroverov V.N., Keith T., Kobayashi R., Normand J., Raghavachari K., Rendell A., Burant J.C., Iyengar S.S., Tomasi J., Cossi M., Rega N., Millam J.M., Klene M., Knox J.E., Cross J.B., Bakken V., Adamo C., Jaramillo J., Gomperts R., Stratmann R.E., Yazyev O., Austin A..J, Cammi R., Pomelli C., Ochterski J.W., Martin R.L., Morokuma K., Zakrzewski V.G.., Voth GA., Salvador P., Dannenberg J..J, Dapprich S., Daniels A.D., Farkas O., Foresman J.B., Ortiz J.V., Cioslowski J., Fox D.J., (2013)

Gaussian 09 D.01. Gaussian, Inc, Wallingford CT.

[20] Becke A.D., A new mixing of Hartree–Fock and local density-functional theories. J Chem Phys 1993;98: 1372-1377.

[21] Lee C., Yang W., Parr R.G., Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. Phys Rev 1988; B37: 785-789.

[22] Foresman J.B., Keith T.A., Wiberg K.B, Snoonian J., Frisch M.J., Solvent Effects. 5. Influence of Cavity Shape, Truncation of Electrostatics, and Electron Correlation on ab Initio Reaction Field Calculations. J Phys Chem 1996; 100: 16098-16104.

[23] Tomasi J., Mennuci B., Cammi R., Quantum Mechanical Continuum Solvation Models. Chem Rev 2005;105: 2999-3093.

[24] Fukui K., Role of frontier orbitals in chemical reactions. Science 1982; 218(4574): 747-754.

[25] Jensen F., Introduction to Computational Chemistry, John Wiley and Sons Ltd., West Sussex, Chapter 6, p. 257, 2007.

[26] Parr R.G., Szentpaly L.V., Liu S., Electrophilicity Index. J. Am. Chem. Soc.1999;121: 1922-1924.

[27] Wiberg K.B., Properties of Some Condensed Aromatic Systems. J. Org. Chem. 1997;62: 5720-5727.