Turkish Computational and Theoretical Chemistry

Turkish Comp Theo Chem (TC&TC)

Volume(Issue): 2(1) – Year: 2018 – Pages: 1-11

ISSN: 2587-1722 / e-ISSN: 2602-3237

Received: 31.05.2017 ***Accepted:*** 06.01.2018 *Research Article*

A Computational study predicting the chemical reactivity behavior of 1-substituted 9-ethyl-βCCM derivatives: DFT- Based Quantum Chemical Descriptors

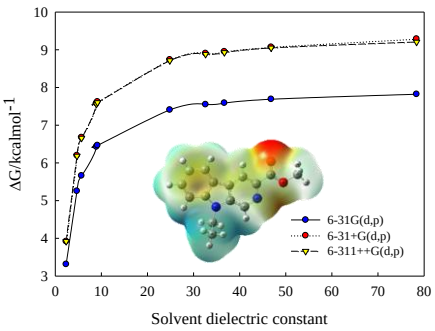
Goncagül Serdaroğlu[1], Mustafa Elik

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

Abstract: This article deals with the calculation of the quantum chemical parameters of 1-substituted βCCM (methyl 9H-pyrido[3,4-b]indole-3-carboxylate) compounds that can be used as effective drugs in the treatment of many diseases. All DFT (density functional) geometry optimizations and frequency calculations have been performed to explain both the solvent and basis set effects on chemical reactivity behavior using 10 different solvent environments (by using the PCM, Polarized Continuum Model) except for the gas phase and with 3 different basis sets which are 6-31G(d,p), 6-31+G(d,p) and 6-311++G(d,p). The study revealed that the anthracen-9-yl substituted structure is the most reactive structure because its energy gap is the lowest one among the other structures, also in according with calculated global hardness values of the each di-substituted structure it is the soft structure which means it can easier interact with any receptor site than the other di-substituted structures while the structure 6-methoxynaphthalene-2-yl substituted compound has the highest energy gap which seems it is the less reactive structures in according with these results. Quantitative chemical identifiers were used to determine which molecules were more active or less active but also mapped electric potential (MEP) diagrams were drawn to illustrate the reactive sites of the molecules which were easier interact with an external molecule group in electrophilic/ nucleophilic reactions and, to show whether they possess electrophilic or nucleophilic properties. We expect that the findings of this study obtained from extensive and time-consuming calculations and analyzes will be an important source of information in the synthesis of less side effect ligands or compounds that can treat many diseases in the future.

Keywords: *Quantum chemical descriptors, Solvent effect, Substituent effect, Chemical reactivity*

Graphical Abstract



- The stable structures of all studied molecules were determined by DFT method.
- Solvation phase calculations were performed in 10 solvent media with three basis sets.
- The physicochemical properties were predicted to found the chemical stability behavior of each compound.
- Quantum chemical descriptors were calculated to predict the reactivity behavior.
- FMO, MEP diagrams were visualized to show the reactive site of each compound.

[1] Corresponding Author

e-mail: goncagul.serdaroglu@gmail.com

1. Introduction

In many research fields such as biochemistry, medicinal chemistry, pharmacology, neurological chemistry and so on, scientists have studied on βeta Carboline (βC) because these compounds have a very broad spectrum of action on different receptors such as Benzodiazepine Receptor (BzR), imidazoline and serotonin receptors [1-8]. As known well, βCs are natural-occurring in many medicinal plants as well as they are produced as secondary metabolism from the marine organism and human tissues [9-10]. Because of their action on different receptor sites in CNS (Central Nervous System), they have very important pharmacological properties, which are cytotoxic effect [11-14], oxidative stress/ metabolism [10,15], photochemical metabolism [16-23], insecticidal activity [11], anticonvulsant [2], antiviral activity and fungicidal activity [24], antimalarial activity [25], antitumor activity recently discussed [26-29], anti-HIV activity [30]. Although there are many kinds of research in the literature about the novel drug/agent synthesis and their activities on several receptors and their basic biochemical properties have been clarified, but there are still controversial matters about it. For example, the cytotoxicity activities of the βCs have been widely investigated by scientist and the most researchers have suggested that βC's actions are related to their interaction with DNA with high affinity because of their polycyclic aromatic structures, but the exact explanation of relationship between βC's and DNA base pairs is still not clear [31-33]. In one another work about the βCs having a protective role against oxidative stress, Pari, K., and co-workers have confirmed that βCs have protection against oxidative stress to the human tissues in which they are accumulated despite their physiological role is not clear in according to earlier researchers [10]. Cao R. et all have synthesized novel 1,3-disubstituted and 1,3,9-trisubstituted βC derivatives to investigate the cytotoxic activity of these compounds and they have suggested that the position 1- and 9- are very important to increase the cytotoxic potency, also the molecular structure of these group derivatives have been very important to be able to be used as a good antitumor drug [19]. As known well, the cytotoxicity in vivo and in vitro can be affected by light because of their photochemical properties and the scientist have also widely studied on photochemical properties of these group compounds [16-23]. Tarzi O.I. and co-worker have investigated the chlorine effect as a substituent on both the photochemical and on acid-base properties of some βC alkaloids and, they have shown that both the substituent group type and its location in the interested compound have a great role to explain the photochemical and acid- base properties [21]. In another research about the spectroscopic, photochemical and photophysical properties of βC derivatives, Gonzales M.M. et all have confirmed that all studied properties of βC derivatives strongly depend on the molecular structure and have shown the aqueous media is the important to explain the photophysical properties of these compounds [22]. Recently, one of the interesting papers have been published by Brahmbhatt K. G. et. al, that is, they have synthesized the novel βC derivatives because of their anti- HIV activity [30]. As we have stated before, there are many research about both the βC and its derivatives due to their pharmaceutical importance, but still the fundamental biochemical phenomena underlying these properties have been speculative. Nowadays, computational tools are used to explain the underlying causes of biological phenomena. At this point, there are computational searches of these group compounds and their derivatives are limited [4-5, 10, 34]. Allen M. S., and et al., have studied about the structural requirements of βC derivatives which are synthesized and designed by them, and they have also analyzed these group compounds with 3D-QSAR to define the inverse agonist activity on BzR of the new synthesized compounds, they have confirmed that the electron-releasing substituents at the 3-position of the βC enhance the hydrogen-bonding strength the pyridine nitrogen atom via the resonance [4, 5]. Ponce M.A. and co-worker have conducted the single point calculations using semi-empirical methods to get the static charge distribution for full aromatic βC derivatives to compare with the observed properties of these group compounds: they found out the βC and cationic-βC derivatives have higher charge density values positioned at 6-C and 8-C and so these positions of each derivative are very attractive against incoming NO2 group in according with the observed results [34]. In this paper, we aim to get the global descriptors such as electronic chemical potential (μ), global hardness (η), electrophilicity

(ω), energy gap (ΔE), the maximum charge transfer index (ΔNmax) to explain the physicochemical reasons underlying key biochemical phenomena that play an important role in developing or investigating of the more potent agents with lower toxicity and side effect. For this reason, we have selected the full aromatic βC and aromatic substituent groups depicted in Figure 1 to evaluate the substituent effect on the physicochemical behavior of these compounds. Hope, the calculated results in this paper will provide useful information for future drug design studies by assessing the relative chemical behavior of the compounds being studied.

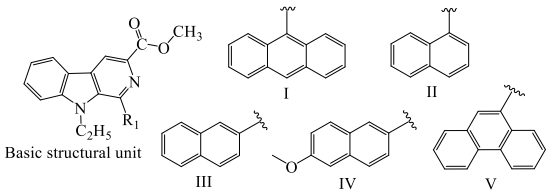


Figure 1. The 9-ethyl- βC-3-carboxylic acid methyl ester as the basic chemical structure (with numbering scheme) and its substituent groups as A (anthracen-9-yl), B (naphthalene-1-yl), C (naphthalene-2-yl), D (6-methoxynaphthalene-2-yl), E (phenanthrene-9-yl)

2. Method

The geometry optimizations and frequency calculations of all studied structures have been carried out with 6-31G(d,p) basis set in the gas phase, and the optimized structures have been used for subsequent calculations in 10 solvent media. The same calculation route has been repeated for the other basis sets which are 6-31+G(d,p) and 6-311++G(d,p) being used in this work. All DFT calculations have been performed at B3LYP level of theory which is a combination of Becke's three-parameter hybrid exchange functional [35] and the Lee-Yang-Parr correlation functional [36] by using the Gaussian 09W [37] software package. The stable structures have been verified by the absence of any imaginary frequency for both the gas phase and the solvent environments. The Polarized Continuum Model (PCM) with Isodensity version [38-39] have been used to obtain the stabilization energy and the quantum chemical identifiers to look for the solvent effect on chemical behavior of di-substituted βCCM derivatives 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, CHCl3 (Chloroform), C6H5Cl (Chlorobenzene), CH2Cl2 (Dichloromethane), Quinoline, C2H5OH (ethanol), CH3OH (Methanol), Acetonitrile, DMSO (dimethylsulfoxide), H2O (water), respectively.

2.1. Theoretical Background

The quantum chemical descriptors mentioned above are becoming increasingly widespread today to elucidate and explain physicochemical processes in many research areas. As known well, in according with Koopmans Theorem [40], the Ionization energy (I) and electron affinity (E) can be expressed through HOMO and LUMO orbital energies [41] as follow:

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

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

Parr R.G. and co-workers [42] 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:

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

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

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

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

3. Results and discussion

Figure 2 shows the solvation free energy for the basic structural unit and its aromatic derivatives, the full numerical data are given as supporting information of this text (See S1). The solvation free energy increases as the solvent dielectric constant increases in systematically. The solvation free energy changes in the following order: B< C< A< E< D for all solvent media and for all basis sets used in this work except for the Toluene media at 6-311++G(d,p) basis set, that is, this ordering has calculated as B< A< E< C< D for Toluene at 6-311++G(d,p) basis set. But still the structure B is

the less stabilized molecule with solvent dielectric constant while the structure D is the most stabilized one, at all basis sets and in all solvent media, because the structure D includes the polarizable group as 6-methoxynaphthalene-2-yl substitution at C1 position while the structure B has the naphthalene-1-yl substitution at C1 position which this substituent group is the less aromatic group than the other substituent groups investigated in this work. This result is quite consistent with the results of the work done by Wiberg in the past, that is, Wiberg KB has determined the electron delocalization energy of some aromatic systems in the following order: Naphthalene (60) < Anthracene (80) < Phenanthrene (85) [43].

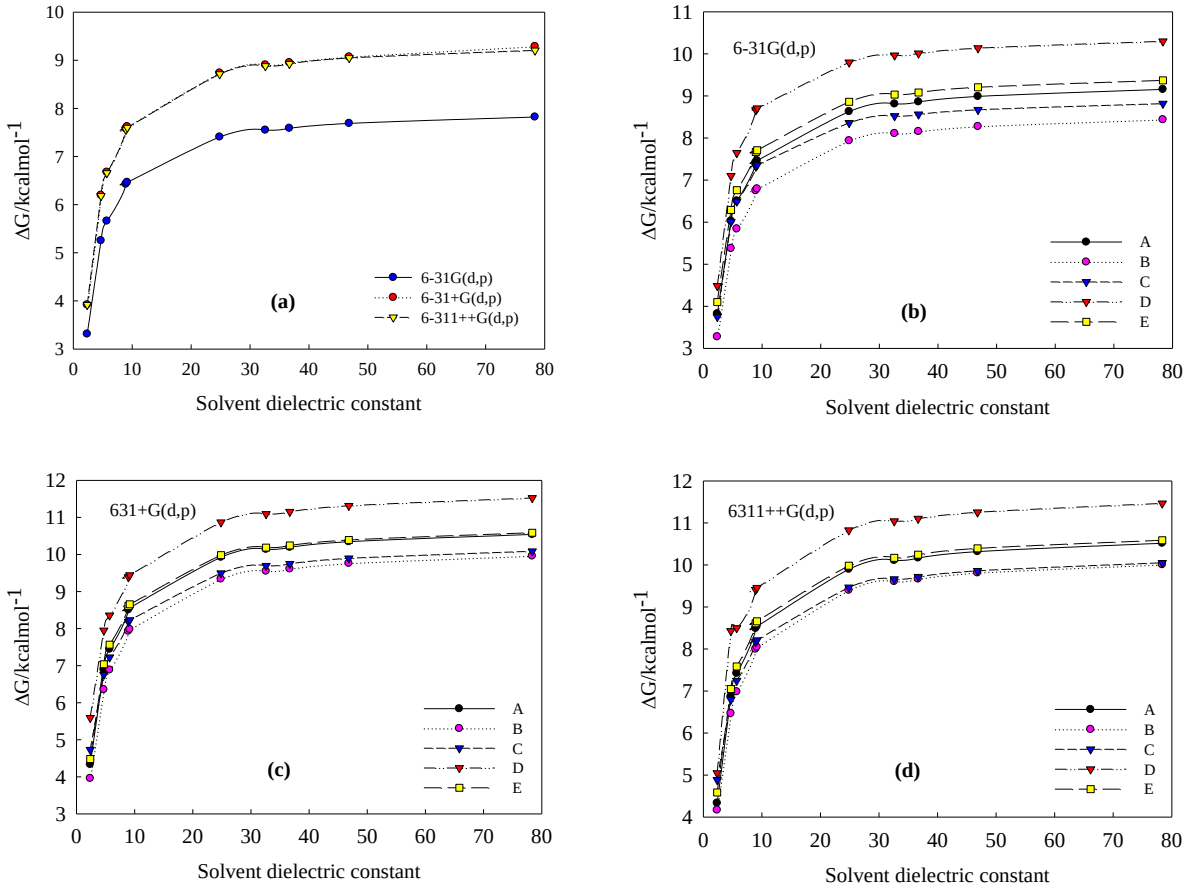


Figure 2. Solvation Gibbs free energies as a function of solvent dielectric constant for: **(a)** βCCM at three basis sets which are 6-31G(d,p), 6-31+G(d,p) and 6-311++G(d,p); **(b)** 1-substituted βCCM derivatives for 6-31G(d,p) basis set **(c)** 1-substituted βCCM derivatives for 6-31+g(d,p) basis set **(d)** 1-substituted βCCM derivatives for 6-311++g(d,p) basis set

Table 1. The calculated Dipole Moments (in *Debye, D*) both in the gas phase and in 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)**
βCCM	4.4111	4.6521	4.6176	6.1416	6.6414	6.5818
A	4.1552	4.3526	4.3222	6.0426	6.6667	6.6099
B	4.2846	4.4800	4.4391	6.1242	6.7105	6.6503
C	4.0469	4.2861	4.2464	6.0197	6.6482	6.5734
D	5.2170	5.4577	5.3927	7.5249	8.0619	7.9825
E	4.2162	4.4399	4.3941	6.1207	6.7349	6.6708

In many research fields, which are biochemical, medicinal, pharmaceutical, biophysical, the molecular stabilization energy plays an important role to estimate/evaluate the chemical activity behavior of any interested system. On the other hand, the dipole moment based on the electrostatic properties of any interested molecule is the other physicochemical parameter to predict the chemical reactivity behavior of an investigated system. Table 1 has shown that the dipole moment of all studied structures at three basis sets for only the gas and the water phases. We can easily say the dipole moment has changed very much with solvent dielectric constant, this work revealed that the most stabilized structure D has the highest dipole moment value.

Nowadays, the DFT based quantum chemical descriptors have provided the very useful information about the biochemical important molecules to explain their chemical activity behavior and to use them in the design of the new agent/drug used in cancer treatment. In this context, the calculated global descriptors such as ΔE, μ, η, ω and ΔNmax are given at Table 2 for only 6-311++G(d,p) basis set in all solvent environments, the other numerical data for the other basis sets are given in supporting information of this text.

The ΔE (energy gap) for the 1-substituted βCCM derivatives has increased in the following order: **A< D< C< E <B < βCCM** for both all solvents and all basis sets. The structure **B** has the highest energy gap which means it is the less reactive structures in according with these results. It is worthwhile to mention the energy gap of the **βCCM** (as the basic structure), that is, each of all substituted structures has the lowest energy gap value than the **βCCM** which means the aromatic group substitution at C1 position on **βCCM** has decreased the Energy Gap of **βCCM** more or less depending on both the their aromaticity and their electron delocalization potency on the molecule. In our previous work, we have calculated the energy gap ordering for the 1-substituted methyl 9-methyl-9H-pyrido[3,4-*b*]indole-3-carboxylate derivatives as follow: **A** (3.4975)< **D** (3.9821)< **C** (4.1378)< **E** (4.2678)< **B** (4.2948) < **Basic** (4.3854) in the water phase [44]. We can say that the order of the energy gap does not change depending on the ethyl or methyl group in the N9-position. Also, we have predicted the energy gap of the methyl-9H-pyrido[3,4-*b*]indole-3-carboxylate as 4.523 eV by B3LYP/6-311++G(d,p) [45]. In this work, we have determined the energy gap of the methyl 9-ethyl-9H-pyrido[3,4-*b*]indole-3-carboxylate (9-ethyl-βCCM) as 4.379 eV. In according to these results, it can be easily seen that the energy gap has increased depending on the substituent group (or atom) in N9 position as follow: -H (4.523) > -CH_3 (4.3854) > -C_2H_5 (4.379) by B3LYP/6-311++G(d,p) level of the theory in the water phase.

The electronic chemical potential for the 1-substituted βCCM molecules has changed as **A< C< E< B< βCCM< D** for all solvent media and also for the basis sets used in this work. Here, we have found out that the structure **A** has the lowest electronic chemical potential while the structure **D** has the highest electronic chemical potential because **D** has the more polarizable group at the C1 position of **βCCM.**

The global hardness of the studied structures varies as follow: **A < D < C < E < B< βCCM** for most of the solvents at all basis sets. The structure **B** after **βCCM** seem to be the hardest one of the all studied derivatives because it has the highest global hardness value. On the other hand, the structure **A** is the soft molecule, therefore it is the most reactive structure among being studied structures.

The electrophilicity index ordering of the studied molecules has calculated as **βCCM< B < E < D < C < A** at all basis sets in all solvents. In accord with these results, the structure **A** seems to be the best electrophile among the all studied structures.

The ΔNmax changes with ordering as **βCCM< B < E < C< D < A** for more than half of the solvents at all basis sets, and the structure **A** has the highest ΔNmax which means the structure A has the best charge transfer capability. Here we can say that the ordering of all quantum chemical parameters of the substituted **βCCM** (ethyl 9-methyl-9H-pyrido[3,4-*b*]indole-3-carboxylate) derivatives are similar to the substituted methyl-9-methyl-9H-pyrido[3,4-*b*]indole-3-carboxylate derivatives.

Figure 3 shows the electron density mapped with ESP (electrostatic potential) for both the N9-substituted and the 1-substituted βCCM calculated at the B3LYP/6-311++G(d,p) level of theory in the aqueous phase. The electrophilic attack site is shown by the blue region and the nucleophilic

attack center is shown with the red region. The electron density on molecule surface have changed in the following order: **A** ($9.234e^{-2}$) < **D** ($9.166e^{-2}$) < **E** ($8.972e^{-2}$) < **B** ($8.951e^{-2}$) < **βCCM** ($8.412e^{-2}$) < **C** ($8.343e^{-2}$) in positive side, vice versa in negative side. It is important point to emphasize that the A has the lowest electron density on molecule surface mapped with ESP while the structure **C** has the highest one, so it can be confirmed by MEP (mapped electrostatic potential) diagrams that the structure **A** is the most reactive structure than the others as like supported with the global chemical descriptors. Here, we have given only the results of the aqueous phase to give a relatively good prediction about the biochemical/physical behavior of these studied structures. But it is necessary to keep in mind that there are many factors that affect the chemistry of living things, so we avoided making striking conclusions.

Table 2. The calculated quantum chemical parameters with the B3LYP/6-311++G(d,p) basis set

Molecule	Solvent	ΔE	μ	η	ω	ΔNmax	Solvent	ΔE	μ	η	ω	ΔNmax
βCCM		4,4248	-3,9055	2,2124	3,4471	1,7653		4,3835	-3,9569	2,1917	3,5719	1,8054
A		3,4972	-3,9261	1,7486	4,4075	2,2453		3,4986	-4,0008	1,7493	4,5750	2,2871
B	**Toluen**	4,3851	-3,8837	2,1926	3,4397	1,7713	**Ethanol**	4,3541	-3,9632	2,1770	3,6074	1,8204
C	(ε= 2.37)	4,1767	-3,9183	2,0883	3,6759	1,8763	(ε= 24.85)	4,1984	-3,9850	2,0992	3,7824	1,8983
D		4,0213	-3,7867	2,0107	3,5659	1,8833		4,0436	-3,8782	2,0218	3,7195	1,9182
E		4,3633	-3,8952	2,1817	3,4772	1,7854		4,3239	-3,9748	2,1619	3,6538	1,8385
βCCM		4,4066	-3,9271	2,2033	3,4999	1,7824		4,3819	-3,9589	2,1909	3,5767	1,8069
A		3,4978	-3,9544	1,7489	4,4706	2,2611		3,4986	-4,0043	1,7493	4,5831	2,2891
B	**Chloroform**	4,3759	-3,9183	2,1879	3,5086	1,7909	**Methanol**	4,3522	-3,9663	2,1761	3,6147	1,8227
C	(ε= 4.71)	4,2025	-3,9459	2,1013	3,7050	1,8779	(ε= 32.61)	4,1976	-3,9878	2,0988	3,7885	1,9000
D		4,0414	-3,8265	2,0207	3,6229	1,8936		4,0431	-3,8817	2,0215	3,7268	1,9202
E		4,3470	-3,9303	2,1735	3,5535	1,8083		4,3223	-3,9780	2,1611	3,6612	1,8407
βCCM		4,4023	-3,9323	2,2011	3,5125	1,7865		4,3816	-3,9595	2,1908	3,5781	1,8074
A		3,4980	-3,9621	1,7490	4,4878	2,2653		3,4986	-4,0054	1,7493	4,5856	2,2897
B	**Chlorobenze**	4,3726	-3,9265	2,1863	3,5259	1,7959	**Acetonitrile**	4,3516	-3,9672	2,1758	3,6166	1,8233
C	**ne** (ε= 5.70)	4,2031	-3,9527	2,1015	3,7173	1,8809	(ε= 36.69)	4,1976	-3,9886	2,0988	3,7901	1,9004
D		4,0461	-3,8364	2,0230	3,6376	1,8964		4,0428	-3,8827	2,0214	3,7289	1,9208
E		4,3429	-3,9383	2,1715	3,5714	1,8137		4,3217	-3,9789	2,1609	3,6632	1,8413
βCCM		4,3944	-3,9428	2,1972	3,5376	1,7945		4,3802	-3,9610	2,1901	3,5820	1,8086
A		3,4983	-3,9778	1,7491	4,5229	2,2741		3,4988	-4,0080	1,7494	4,5912	2,2910
B	**Dichloromet**	4,3655	-3,9423	2,1828	3,5600	1,8061	**DMSO**	4,3503	-3,9695	2,1751	3,6220	1,8249
C	**hane** (ε= 8.93)	4,2023	-3,9665	2,1011	3,7439	1,8878	(ε= 46.83)	4,1971	-3,9906	2,0985	3,7942	1,9016
D		4,0466	-3,8544	2,0233	3,6712	1,9050		4,0423	-3,8851	2,0211	3,7341	1,9222
E		4,3350	-3,9540	2,1675	3,6064	1,8242		4,3204	-3,9812	2,1602	3,6686	1,8430
βCCM		4,3938	-3,9433	2,1969	3,5390	1,7949		4,3789	-3,9631	2,1894	3,5868	1,8101
A		3,4983	-3,9786	1,7491	4,5248	2,2746		3,4988	-4,0115	1,7494	4,5993	2,2930
B	**Quinoline**	4,3653	-3,9432	2,1826	3,5620	1,8066	**Water**	4,3484	-3,9723	2,1742	3,6288	1,8270
C	(ε= 9.16)	4,2020	-3,9672	2,1010	3,7454	1,8882	(ε= 78.36)	4,1963	-3,9931	2,0981	3,7998	1,9032
D		4,0466	-3,8552	2,0233	3,6728	1,9054		4,0417	-3,8884	2,0209	3,7409	1,9241
E		4,3348	-3,9546	2,1674	3,6078	1,8246		4,3187	-3,9839	2,1594	3,6750	1,8449

* ΔE(energy gap), μ, η, ω and ΔNmax are in eV

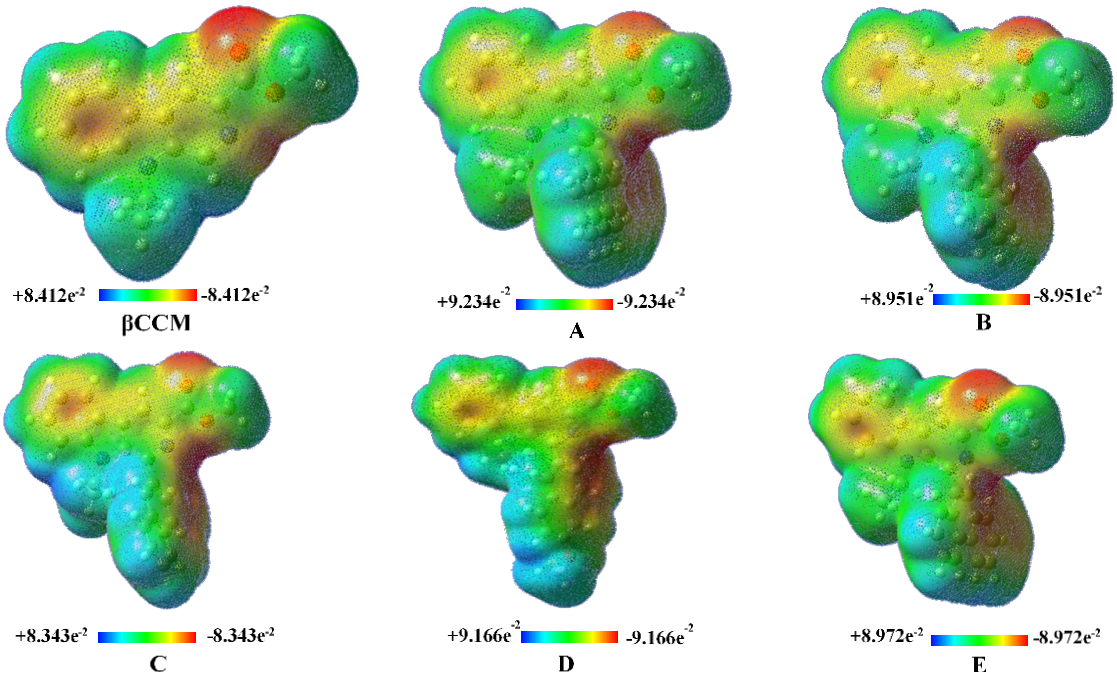


Figure 3. The electron density mapped with ESP for both the βCCM and it's C1-substituted derivatives calculated at the B3LYP/6-311++G(d,p) level of theory in the aqueous phase (Iso value:0.0004)

Figure 4 has shown that the HOMO and LUMO amplitudes of both the βCCM and its C1 substituted derivatives at B3LYP/6-311++G(d,p) basis set in the water phase. Here, it can be a good starting point to discuss the HOMO and LUMO for the βCCM: The HOMO of the βCCM is localized on the whole molecule surface of the basic structure, just a little on the alkyl chain part, except for the methyl group, at the C3 position of this structure. Which means, if there is a nucleophilic attack reaction to any molecule or to any receptor site, then this structure will attack to the molecule with the electrons located on the HOMO of this structure. On the other hand, LUMO is only localized on the aromatic site of this structure which means the electrophilic attack to this structure will have occurred in this location.

How has the HOMO and LUMO amplitudes on the basic structure been effected when one substituent group is attached to the C1 position of the basic structure? The HOMO amplitudes of each derivative is very similar to the basic structural units' HOMO, that is, HOMO distributes on the substituent part of each structure more or less, except for the structure **D**. For the structure **D**, it can be seen from Figure 4 that the HOMO expanded on the whole molecule surface including both the basic unit and the substituent part. So, it looks like that the electron delocalization for the structure **D** is calculated more than the other derivatives.

On the other side, it has also been seen that the LUMO amplitudes of each structure is different from that of the βCCM. First, we should express that both the carboxymethylene group at the C3 position of and $-C_2H_5$ group at the N9 position of the βCCM are not very effective for electrophilic attack reactions because there is no any LUMO localization on these groups for both the basic structure and its substituted structures. Second, the most LUMO distribution area/ volume is calculated for the structure **D**. And last, LUMO for the structure **A** is only localized on the substituent part which is the anthracen 9-yl substitution at the C1 position of the basic structure.

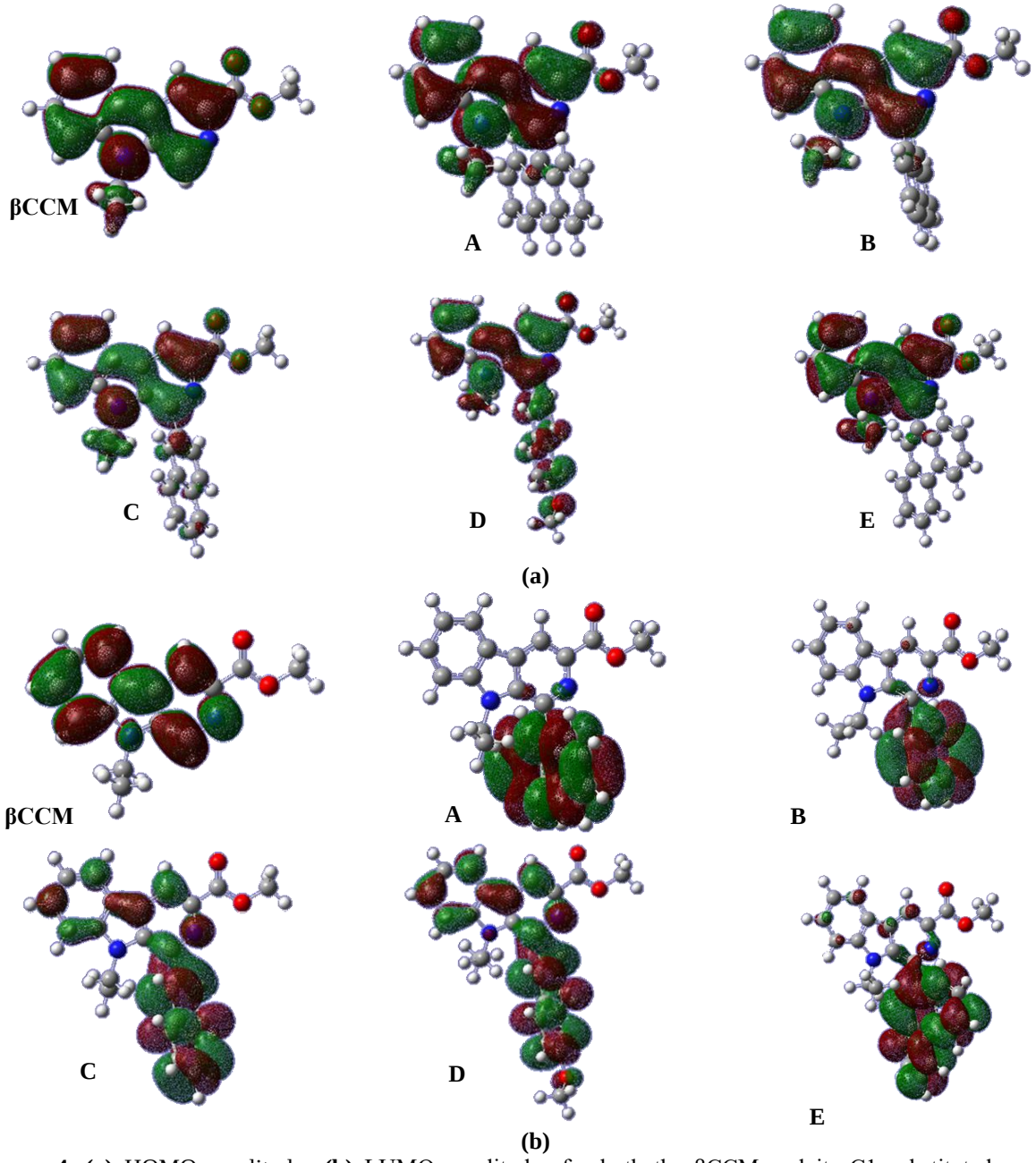


Figure 4. (a) HOMO amplitudes **(b)** LUMO amplitudes for both the βCCM and its C1 substituted derivatives calculated at the B3LYP/6-311++G(d,p) level of theory in the aqueous phase

4. Conclusion

In summary, it can be concluded that the structure A is the most reactive structure because A has the lowest energy gap more than those of the other structures. In according to calculated global hardness values of the each substituted structure, A is the soft molecule, which means it can easily interact with any receptor site or any molecule than the other substituted structures. Moreover, this structure is the more active than the other structures for the electrophilic attack reactions because of its highest electrophilicity value. Finally, the calculated ΔNmax value also shows that the structure A is the highest electron transfer capability for electron transfer reactions. This paper has revealed that the calculated parameters can be used to predict the best reactive structure or the less

reactive structure although there are some incompatibilities in the chemical potential results.

We hope that the results of this study will provide very useful information that plays an important role in the development or in improving the more potent βCCM agents with lower toxicity and with lower side effect using computational tools to explain the activity of existing drugs.

Acknowledgments

The author thanks for acknowledging the financial support of the scientific research projects of Cumhuriyet University (Project No: EĞT-066). All calculations have been conducted at TUBITAK ULAKBIM, High Performance and Grid Computing Center (TR-Grid Infrastructure).

References

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

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

[3] G. Dorey, G. Poissonnet, M. C. Potier, L. P. Carvalho, P. Venault, G. Chapouthier, J. Rossier, P. Potier, R. H. Dodd, Synthesis and Benzodiazepine Receptor Affinities of Rigid Analogues of 3-Carboxy- β-carbolines: Demonstration That the Benzodiazepine Receptor Recognizes Preferentially the s-Cis Conformation of the 3-Carboxy Group. J Med Chem 32 (1989) 1799-1804.

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

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

[6] R. H. Dodd, C. Ouannes, M. C. Potier, L. P. Carvalho, J. Rossier, P. Potiert, 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 30 (1987) 1248-1254.

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

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

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

[10] K. Pari, C. S. Sundari, S. Chandani, D. Balasubramanian, β -Carbolines That Accumulate in Human Tissues May Serve a Protective Role against Oxidative Stress. THE JOURNAL OF BIOLOGICAL CHEMISTRY 275(4) (2000) 2455–2462.

[11] Y. Zeng, Y. Zhang, Q. Weng, M. Hu, G. Zhong, Cytotoxic and Insecticidal Activities of Derivatives of Harmine, a Natural Insecticidal Component Isolated from Peganum harmala. Molecules 15 (2010) 7775-7791.

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

[13] Z. Chen, R. Cao, B. Shi, L. Guo, J. Sun, Q. Ma, W. Fan, H. Song, Synthesis and biological evaluation of 1,9-disubstituted β -carbolines as potent DNA intercalating and cytotoxic agents. European Journal of Medicinal Chemistry 46 (2011) 5127-5137.

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

[15] T. Herraiz, H. Guillen, V. J. Aran, Oxidative Metabolism of the Bioactive and Naturally Occurring β -Carboline Alkaloids, Norharman and Harman, by Human Cytochrome P450 Enzymes. Chem Res Toxicol 21 (2008) 2172–2180.

[16] D. Reymana, M. J. Tapiab, C. Carcedob, M. H. Vinasc, Photophysical properties of methyl β-carboline-3-carboxylate mediated by hydrogen-bonded complexes-a comparative study in different solvents. Biophysical Chemistry 104 (2003) 683–696.

[17] C. Carmona, M. Balon, A. S. Coronilla, M. A. Munoz, New Insights on the Excited-State Proton-Transfer Reactions of Betacarbolines: Cationic Exciplex Formation. J Phys Chem A 108 (2004) 1910-1918.

[18] A. Mallick, N. Chattopadhyay, Photophysics of norharmane in micellar environments: a fluorometric study. Biophysical Chemistry 109 (2004) 261–270.

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

[20] O. I. Tarzi, R. Erra-Balsells, Photochemistry of the alkaloids eudistomin N (6-bromo-nor-harmane) and eudistomin O (8-bromo-nor-harmane) and other bromo- β -carbolines. Journal of Photochemistry and Photobiology B: Biology 80 (2005) 29–45.

[21] O. I. Tarzi, R. Erra-Balsells, Effect of chlorine as substituent on the photochemistry and acid–base properties of β-carboline alkaloids. Journal of Photochemistry and Photobiology B: Biology 82 (2006) 79–93.

[22] M. M. Gonzalez, J. Arnbjerg, M. P. Denofrio, S. R. Erra-Balsell, P. R. Ogilby, F. M. Cabrerizo, One- and Two-Photon Excitation of β-Carbolines in Aqueous Solution: pH-Dependent Spectroscopy, Photochemistry, and Photophysics. J Phys Chem A 113 (2009) 6648–6656.

[23] M. J. Tapia, D. Reyman, M. H. Viñas, A. Arroyo, J. M. L. Poyato, An experimental and theoretical approach to the acid–base and photophysical properties of 3-substituted β-carbolines in aqueous solutions. Journal of Photochemistry and Photobiology A: Chemistry 156 (2003) 1–7.

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

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

[26] Y. C. Shen, C. Y. Chen, P. W. Hsieh, C. Y. Duh, Y. M. Lin, C. L. Ko, 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 53(1) (2005) 32- 36.

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

[28] A. Daoud, J. Song, F. Y. Xiao, J. Shang, B-9-3, a novel β-carboline derivative exhibits anti-cancer activity via induction of apoptosis and inhibition of cell migration in vitro. European Journal of Pharmacology 724 (2014) 219- 230.

[29] F. C. Savariz, M. A. Foglio, J. E. Carvalho, A. L. T. G. Ruiz, M. C. T. Duarte, M. F. Rosa, E. Meyer, M. H. Sarragiotto, Synthesis and Evaluation of New β-

Carboline-3-(4-benzylidene)-4H-oxazol-5-one Derivatives as Antitumor Agents. Molecules 17 (2012) 6100- 6113.

[30] K. G. Brahmbhatt, N. Ahmed, S. Sabde, D. Mitra, I. P. Singh, K. K. Bhutani, Synthesis and evaluation of β -carboline derivatives as inhibitors of human immunodeficiency virus. Bioorganic & Medicinal Chemistry Letters 20 (2010) 4416- 4419.

[31] M. Balon, M. A. Munoz, C. Carmona, P. Guardado, M. Galan, A fluorescence study of the molecular interactions of harmane with the nucleobases, their nucleosides and mononucleotides. Biophysical Chemistry 80 (1999) 41-52.

[32] R. Cao, W. Peng, H. Chen, Y. Ma, X. Liu, X. Hou, H. Guan, A. Xu, DNA binding properties of 9-substituted harmine derivatives. Biochemical and Biophysical Research Communications 338 (2005) 1557–1563.

[33] H. Guan, X. Liu, W. Peng, R. Cao, Y. Ma, H. Chen, A. Xu, β -Carboline derivatives: Novel photosensitizers that intercalate into DNA to cause direct DNA damage in photodynamic therapy. Biochemical and Biophysical Research Communications 342 (2006) 894–901.

[34] H. J. Zhu, J. X. Jiang, S. Saebo, Jr. C.U Pittman, Chiral Ligands Derived from Abrine 8. An Experimental and Theoretical Study of Free Ligand Conformational Preferences and the Addition of Diethylzinc to Benzaldehyde. J Org Chem 70 (2005) 261-267.

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

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

[37] Gaussian 09, Revision A.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian, Inc., Wallingford CT, 2009.

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

[39] J. Tomasi, B. Mennuci, R. Cammi, Quantum Mechanical Continuum Solvation Models. Chem Rev 105 (2005) 2999- 3093.

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

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

[42] R. G. Parr, L. V. Szentpaly, S. Liu, Electrophilicity Index. J Am Chem Soc 121 (1999) 1922-1924.

[43] K. B. Wiberg, Properties of Some Condensed Aromatic Systems. J Org Chem 62 (1997) 5720-5727.

[44] M. Elik, G. Serdaroğlu, A Computational Study of 1-Substituted Methyl 9-Methyl-9H-Pyrido[3,4- *b*]indole-3-Carboxylate: Quantum Chemical Descriptors, FMO and NBO Analysis. *Cumhuriyet Sci. J., 38-4* (2017) *Supplement: 138-155.*

[45] G. Serdaroğlu, M. Elik, DFT Based Quantum Chemical Descriptors of 1-Substituted THβC, DHβC, βC Derivatives. Cumhuriyet Sci. J., 38-4 (2017) 647-660.