

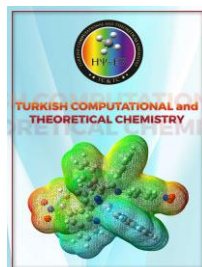
PAPER DETAILS

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

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Research Article

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

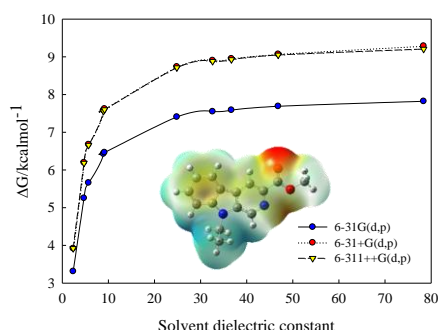
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Abstract: This article deals with the calculation of the quantum chemical parameters of 1-substituted β CCM (methyl 9H-pyrido[3,4-b]indole-3-carboxylate) compounds that can be used as effective drugs in the treatment of many diseases. All DFT (density 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.

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1. Introduction

In many research fields such as biochemistry, medicinal chemistry, pharmacology, neurological chemistry and so on, scientists have studied on β C Carboline (β C) 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, β Cs 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 β Cs have been widely investigated by scientist and the most researchers have suggested that β C'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 β C's and DNA base pairs is still not clear [31-33]. In one another work about the β Cs having a protective role against oxidative stress, Pari, K., and co-workers have confirmed that β Cs 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 al. have synthesized novel 1,3-disubstituted and 1,3,9-trisubstituted β C 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 β C 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 β C derivatives, Gonzales M.M. et al. have confirmed that all studied properties of β C 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 Brahmabhatt K. G. et. al, that is, they have synthesized the novel β C derivatives because of their anti- HIV activity [30]. As we have stated before, there are many research about both the β C 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 β C 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 β C 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 β C derivatives to compare with the observed properties of these group compounds: they found out the β C and cationic- β C 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 (ΔN_{max}) 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.

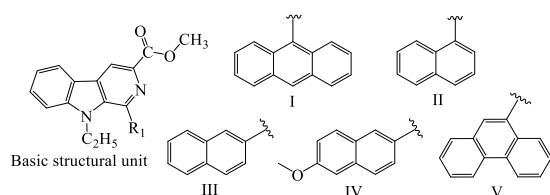


Figure 1. The 9-ethyl- βC -3-carboxylic acid methyl ester as the basic chemical structure (with numbering scheme) and its substituent groups as A (anthracen-9-yl), B (naphthalene-1-yl), C (naphthalene-2-yl), D (6-methoxynaphthalene-2-yl), E (phenanthrene-9-yl)

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 $\epsilon = 2.37, 4.71, 5.70, 8.93, 9.16,$

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.

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 (ΔN_{max}) 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].

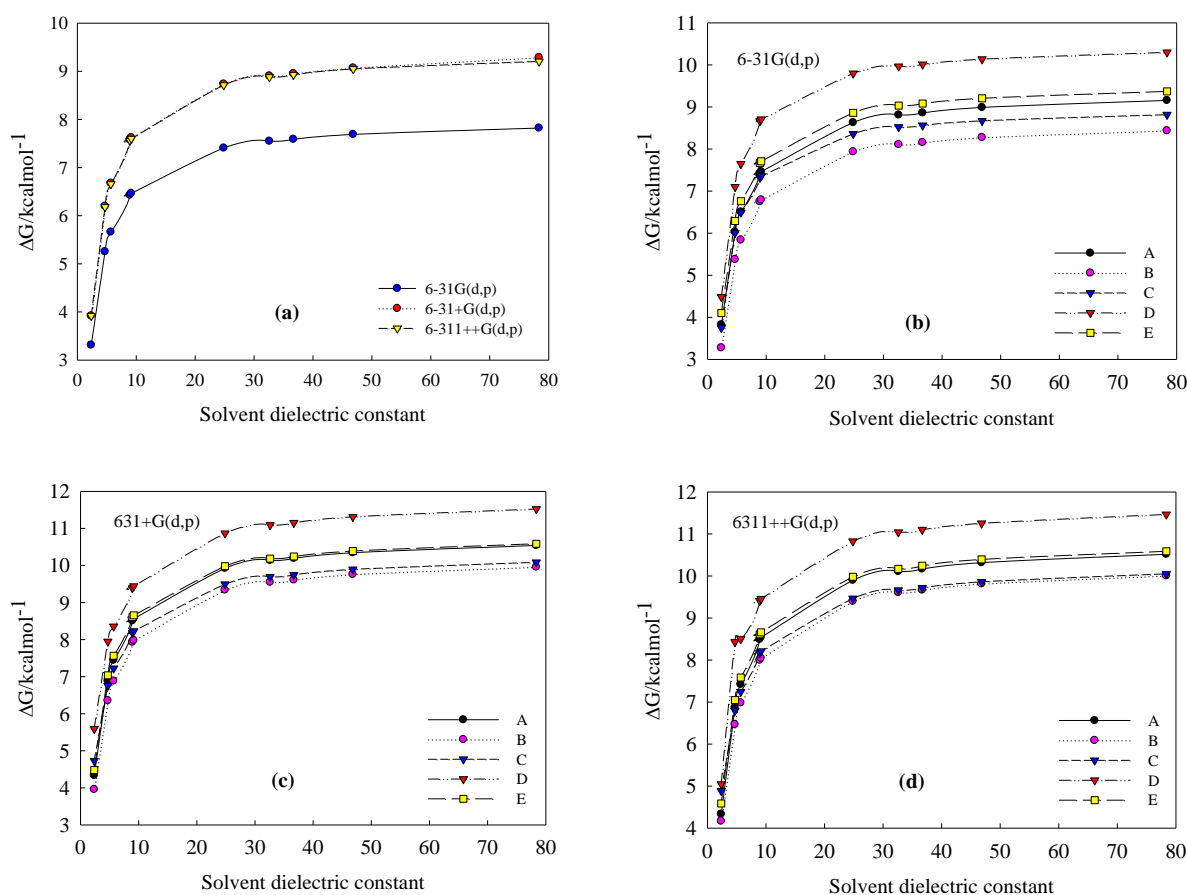


Figure 2. Solvation Gibbs free energies as a function of solvent dielectric constant for: (a) β CCM at three basis sets which are 6-31G(d,p), 6-31+G(d,p) and 6-311++G(d,p); (b) 1-substituted β CCM derivatives for 6-31G(d,p) basis set (c) 1-substituted β CCM derivatives for 6-31+g(d,p) basis set (d) 1-substituted β CCM 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)
β CCM	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 ΔN_{\max} 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 β CCM derivatives has increased in the following order: **A** < **D** < **C** < **E** < **B** < β CCM 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 β CCM (as the basic structure), that is, each of all substituted structures has the lowest energy gap value than the β CCM which means the aromatic group substitution at C1 position on β CCM has decreased the Energy Gap of β CCM 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- β CCM) 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) > -CH₃ (4.3854) > -C₂H₅ (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 β CCM molecules has changed as **A** < **C** < **E** < **B** < β CCM < **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 β CCM.

The global hardness of the studied structures varies as follow: **A** < **D** < **C** < **E** < **B** < β CCM for most of the solvents at all basis sets. The structure **B** after β CCM 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 β CCM < **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 ΔN_{\max} changes with ordering as β CCM < **B** < **E** < **C** < **D** < **A** for more than half of the solvents at all basis sets, and the structure **A** has the highest ΔN_{\max} 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 β CCM (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 β CCM 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	Toluen (ε= 2.37)	4,4248	-3,9055	2,2124	3,4471	1,7653	Ethanol (ε= 24.85)	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		4,3851	-3,8837	2,1926	3,4397	1,7713		4,3541	-3,9632	2,1770	3,6074	1,8204
C		4,1767	-3,9183	2,0883	3,6759	1,8763		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	Chloroform (ε= 4.71)	4,4066	-3,9271	2,2033	3,4999	1,7824	Methanol (ε= 32.61)	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		4,3759	-3,9183	2,1879	3,5086	1,7909		4,3522	-3,9663	2,1761	3,6147	1,8227
C		4,2025	-3,9459	2,1013	3,7050	1,8779		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	Chlorobenze ne (ε= 5.70)	4,4023	-3,9323	2,2011	3,5125	1,7865	Acetonitrile (ε= 36.69)	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		4,3726	-3,9265	2,1863	3,5259	1,7959		4,3516	-3,9672	2,1758	3,6166	1,8233
C		4,2031	-3,9527	2,1015	3,7173	1,8809		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	Dichloromet hane (ε= 8.93)	4,3944	-3,9428	2,1972	3,5376	1,7945	DMSO (ε= 46.83)	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		4,3655	-3,9423	2,1828	3,5600	1,8061		4,3503	-3,9695	2,1751	3,6220	1,8249
C		4,2023	-3,9665	2,1011	3,7439	1,8878		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	Quinoline (ε= 9.16)	4,3938	-3,9433	2,1969	3,5390	1,7949	Water (ε= 78.36)	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		4,3653	-3,9432	2,1826	3,5620	1,8066		4,3484	-3,9723	2,1742	3,6288	1,8270
C		4,2020	-3,9672	2,1010	3,7454	1,8882		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

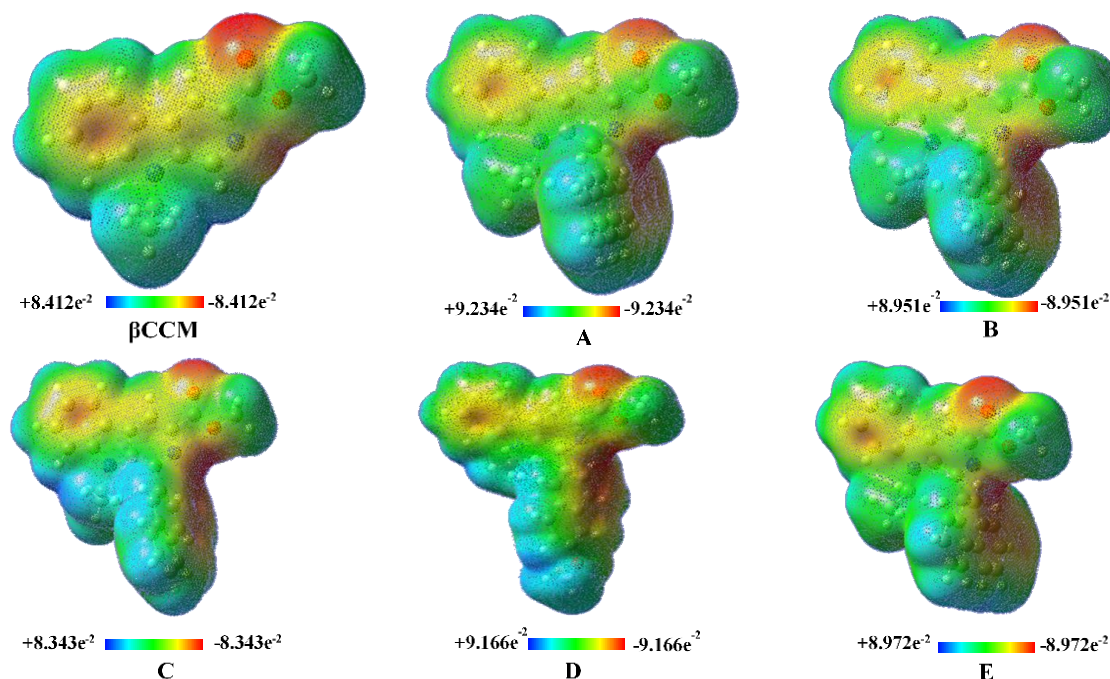


Figure 3. The electron density mapped with ESP for both the β CCM and its C1-substituted derivatives calculated at the B3LYP/6-311++G(d,p) level of theory in the aqueous phase (Iso value:0.0004)

Figure 4 has shown that the HOMO and LUMO amplitudes of both the β CCM 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 β CCM: The HOMO of the β CCM 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 β CCM. First, we should express that both the carboxymethylene group at the C3 position of and -C₂H₅ group at the N9 position of the β CCM 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.

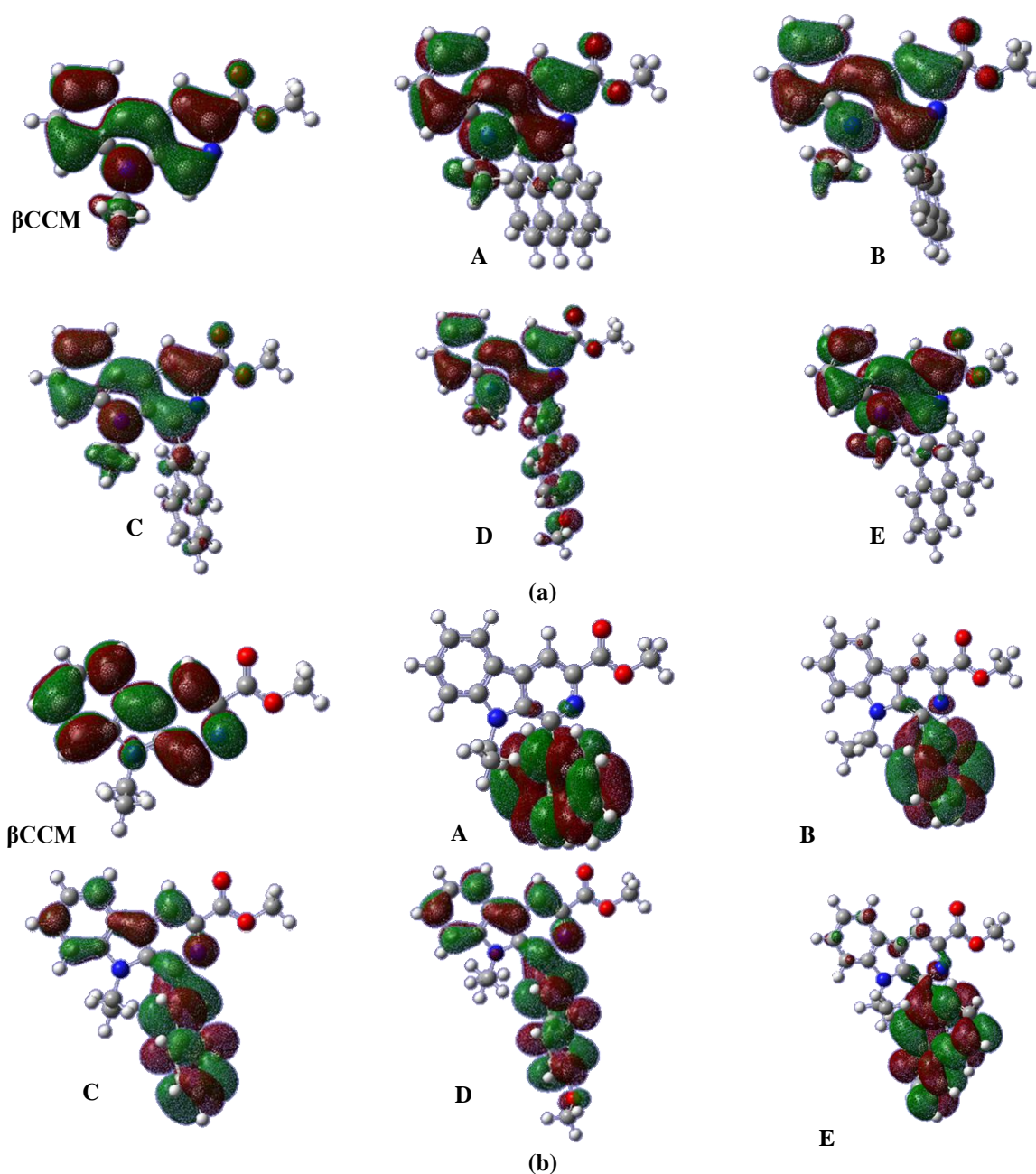


Figure 4. (a) HOMO amplitudes (b) LUMO amplitudes for both the β CCM and its C1 substituted derivatives calculated at the B3LYP/6-311++G(d,p) level of theory in the aqueous phase

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 ΔN_{\max} 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 β CCM agents with lower toxicity and with lower side effect using computational tools to explain the activity of existing drugs.

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