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Theoretical investigation on chemical and biochemical activities of 5,6-dihydro-11H-benzo[α]carbazole and its derivatives

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Abstract

In this study, 5,6-dihydro-11H-benzo[α]carbazole (BDHC) with electron-withdrawing, **1(a–h)–5(a–h)** and donating, **6(a–h)–10(a–h)** substituents were performed at B3LYP/6-31G* level of theory. BDHC and its derivatives with chemical and biochemical activities are described in terms of various quantum chemical descriptors which are the global hardness (η), the chemical potential (μ), electrophilicity index (ω) and dipole moment (DM). For electron-withdrawing groups, **1(a–h)–5(a–h)** on A and D rings of BDHC, it is proven that electrophilicity index, the chemical potential and the global hardness sequences are consistence within each other, but DM values of **1(a–h)–5(a–h)** do not. In contrast, the substitution at **a–h** positions of BDHC with electron-donating groups, **6(a–h)–10(a–h)** do not display an enourmous diversity in all calculated quantum chemical descriptors, according to all electron-withdrawing groups, **1(a–h)–5(a–h)**. As seen at the chemical descriptors, it is found that –**OCH**$_3$ (in **c**-position on A ring) and –**OH** (in **g**-position on D ring) are most effective structures. According to these calculations, we conclude that the most probable predicted biochemicaly active structures are –**NO**$_2$ substituent (in **d**- and **f**-position on A and D rings) among electron-withdrawing groups and –**OCH**$_3$ (in **c**-position on A ring), –**OH** (in **h**-position on D ring) substituents among electron-donating groups.

According to the calculated molecular electron density of BDHC and its derivatives, **c**- and **d**-positions on A ring and **e**- and **f**-positions on D ring are more effective on electron-withdrawing and -donating substituted structures, so different substituents **1(a–h)–10(a–h)** do not also have any distinct effect on charge distributions of BDHC derivatives.

Keywords: Benzodihydro[α]carbazole; Quantum chemical descriptors; Biochemical activity; B3LYP/6-31G*; Biological activity

1. Introduction

Benzodihydro[α]carbazoles (BDHC) have been reported as starting compounds for the synthesis of various drugs and possess important biological, pharmacological and medicinal activities [1–10]. They are associated with anticancer, antimicrobial and antifungal activities [7,8]. In most cases, the biological activity related to BDHC structures containing heteroatom depends on interaction potential with DNA. Many experimental studies indicate that the size, shape and planarity of this structure are important criteria in such an interaction [11]. N. Poliakoff and coworker have also observed that the biological effect produced by chemical modification at the region of the compounds containing an N-substituted indole nucleus, the benzene ring [12].

In structure-activity studies, to determine theoretically a priori, the most promising molecule as well as inactive one is very useful in design and development of new and better drugs. In particular, net atomic charges, HOMO–LUMO energies, have been used to correlate with various biological activities [13]. Density functional theory based descriptors have found immense usefulness in the prediction of reactivity of atoms and molecules as well as site selectivity [14–17]. The resourcefulness of density functional descriptors in the development of QSAR has been recently reviewed by Chattaraj et al. [18] Chemical hardness (η),

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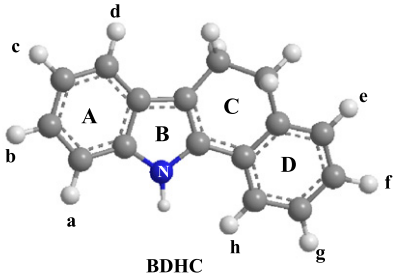
chemical potential (μ) and softness are known as global reactivity descriptors. Recently Parr et al. [19] have defined a new descriptor to quantify the global electrophilic power of the molecule as electrophilicity index (ω), which defines a quantitative classification of the global electrophilic nature of a molecule within a relative scale. The earlier works of Maynard et al. [20] have formed the strong foundation for the electrophilicity index, which provided the direct relationship between the rates of reaction and the ability to identify the function or capacity of an electrophile and the electrophilic power of the inhibitors. Subsequently, quantum-chemical methods and molecular modeling techniques enable the definition of a large number of molecular and local quantities characterizing the reactivity, shape and binding properties of a complete molecule as well as of molecular fragments and substituents.

Nowadays, the biochemical activity of BDHC and its derivatives are not encountered in theoretical applications. Hence, in this study, the chemical and biochemical activities of BDHC and its derivatives are to be investigated with the quantum chemical descriptors [19–21] at B3LYP/6-31G* level of theory Scheme 1.

2. Computations

A series of eighty BDHC molecules **1(a–h)–10(a–h)** were employed in all the calculations on A and D rings of BDHC, (Scheme 1). The initial structures of these compounds were built on the basis of the structure of BDHC. All the geometries were optimized and vibrational frequencies of BDHC's derivatives were calculated and all stationary points were located and characterized as true minima by using Gaussian 03 [22] package program. The total energy (E), the eigenvalues of HOMO and LUMO, the global hardness (η), the chemical potential (μ), electrophilicity index (ω) and dipole moments (DM) on BDHC and its derivatives have been calculated at B3LYP/6-31G* level [23] of theory and given as Table-1 and Table-2 in supplementary data.



BDHC

electron-withdrawing substituents	structures	electron-donating substituents	structures
$-NO_2$	1a,1b,1c,1d 1e,1f,1g,1h	$-N(CH_3)_2$	6a,6b,6c,6d 6e,6f,6g,6h
-CN	2a,2b,2c,2d 2e,2f,2g,2h	$-NH_2$	7a,7b,7c,7d 7e,7f,7g,7h
-F	3a,3b,3c,3d 3e,3f,3g,3h	$-OCH_3$	8a,8b,8c,8d 8e,8f,8g,8h
-Cl	4a,4b,4c,4d 4e,4f,4g,4h	$-CH_3$	9a,9b,9c,9d 9e,9f,9g,9h
-Br	5a,5b,5c,5d 5e,5f,5g,5h	-OH	10a,10b,10c,10d 10e,10f,10g,10h

Scheme 1. General structure of 5,6-dihydro-11H-benzo[α]carbazole (BDHC).

3. Results and discussion

In order to investigate the chemical and biochemical activities of BDHC's derivatives, the effects of both electron-withdrawing –F, –Cl, –Br, –CN, and $-NO_2$ substituents, **1(a–h)–5(a–h)** and electron-donating $-N(CH_3)_2$, $-NH_2$, $-OCH_3$, $-CH_3$, and –OH substituents, **6(a–h)–10(a–h)** have been calculated with different substitution positions **(a–h)** on A and D rings of BDHC structure, (Scheme 1).

3.1. Electron-withdrawing groups *1(a–h)–5(a–h)*

As shown in Figs. 1 and 2, the calculated results of these structures at DFT method are show that $-NO_2$ substituent, **1** has a prominent difference for all quantum chemical descriptors, according to both electron-withdrawing and donating groups **1(a–h)–10(a–h)**. The NO_2 substituted BDHC structures **1(a–h)** have also lowest energy gap value on A and D rings of BDHC. The second lower energy gap value belongs to –CN substituted structures **2(a–h)**. The –F, –Cl and –Br substituents **3(a–h)–5(a–h)** have shown the similar energy gap values. For A ring, the energy gap values of $-NO_2$ substituent have aligned in this sequence: **a-** > **b-** > **d-** > **c-**, but the lowest and highest energy gap values of –CN substituent belong to **d-** and **c**-positions. The halogen groups **(3-5)** have same $\Delta\varepsilon$ sequence in themselves on A ring, whereas they show different ordering each themselves on D ring. The most effective position of **1** belongs to **a**-position on A ring and **h**-position on D ring; on the other hand, the **3**'s $\Delta\varepsilon$ values increase, while the energy gap values of **4**–**5** decrease in all positions on D ring. Because of this behaviour of –F substituent on D ring, the HOMO–LUMO interaction of –F substituent decreases with decreasing its chemical softness, and this effect leads to increase the global hardness of structures. As the global hardness increases, the thermodynamic stabilitiy of structures will increase.

Moreover, the chemical potentials (μ) of the calculated structures, **1(a–h)–5(a–h)** increase with decreasing their global hardness. The μ's order on A and D rings of BDHC decreases in this order; **1(a–h)** > **2(a–h)** > **3(a–h)** > **4(a–h)** > **5(a–h)**, (compounds: **1**–**5**, position: **a**–**h**). The softest structure, **1** having $-NO_2$ groups substituents has the highest chemical potential within studied system.

It is known that various biological activities [24–27] have shown to correlate with global hardness, chemical potential and dipole moment (DM), as electrophilicity index value (ω) do. Parr et al. [19] and Maynard et al. [20] have reported that the ω values increase with increasing chemical and biological activities for the reacting species in a biological system. Also Parr et al. [19] have proposed the electrophilicity index as a measure of energy