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Investigation of quantum chemical parameters of hemp (Cannabis sativa) components (CBD, CBN, THC) using density functional theory (DFT)

Yoğunluk fonksiyonel teorisi (DFT) kullanılarak kenevir (Cannabis sativa) bileşenlerinin (CBD, CBN, THC) kuantum kimyasal parametrelerinin araştırılması

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Abstract

The hemp plant holds significant importance in various fields such as industry, medicine, and chemistry due to its rich and potent chemical composition. In this study, the electronic properties of three major phytocannabinoids found in hemp (Cannabis sativa)—cannabidiol (CBD), tetrahydrocannabinol (Δ9-THC), and cannabinol (CBN)—were examined in detail using density functional theory (DFT). The electronic structures of CBD, THC, and CBN were theoretically analyzed via the DFT method, and their reactivity potentials and quantum parameters were evaluated based on the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energy levels. It was determined that the energy gap between the HOMO and LUMO orbitals, which governs electron transfer, decreases in the order CBD–THC–CBN (5.59, 5.13, and 4.82 eV). The findings indicate that the CBD, THC, and CBN molecules possess high stability. These theoretical descriptors provide valuable insights into the potential biological interactions and applications of hemp-derived compounds.

Keywords: Cannabinoids, DFT, Electronic structure, Chemical reactivity

Öz

Kenevir bitkisi, zengin ve güçlü kimyasal içeriğiyle endüstri, tıp ve kimya gibi pek çok alanda önem arz etmektedir. Bu çalışmada, kenevirde (Cannabis sativa) bulunan üç ana fitokannabinoidin -kanabidiol (CBD), tetrahidrokanabinol (Δ9-THC) ve kanabinol (CBN)- elektronik özellikleri yoğunluk fonksiyonel teorisi (DFT) kullanılarak ayrıntılı olarak incelenmiştir. CBD, THC ve CBN'nin elektronik yapıları DFT yöntemi kullanılarak teorik olarak analiz edildi ve reaktivite potansiyelleri ile kuantum parametreleri, en yüksek dolu moleküler orbital (HOMO) ve en düşük boş moleküler orbital (LUMO) enerji seviyeleri temel alınarak değerlendirilmiştir. Elektron alış-verişinde görevli HOMO ve LUMO bantlarının enerji farkının CBD-THC-CBN (5.59, 5.13 ve 4.82 eV) şeklinde azalarak sıralandığı belirlenmiştir. Bulgular, CBD, THC ve CBN moleküllerinin kararlılıklarının yüksek olduğunu göstermektedir. Bu teorik göstergeler, kenevir bileşiklerinin potansiyel biyolojik etkileşimleri ve uygulamaları hakkında önemli bilgiler sunmaktadır.

Anahtar kelimeler: Kannabinoidler, DFT, Elektronik yapı, Kimyasal reaktivite

1 Introduction

Industrial cannabis (*Cannabis sativa*) is a multi-purpose plant that belongs to the Cannabaceae family, and has significant historical and economic value. Despite the prohibition on production in the 1930s, the industrial use of hemp species containing Δ^9-THC at levels lower than 0.2% was legalized under Regulation 809/2014 of the European Union [1], [2], [3], [4], [5]. In this context, the high fiber content of cannabis, its environmental adaptability, and its rich phytochemical components increase the importance of the plant in medical, cosmetic, and industrial applications [6], [7].

Among more than 100 cannabinoid compounds detected in industrial cannabis are the most common and well-defined CBD, THC, and CBN (Figure 1). THC has a psychoactive feature; CBD is pharmacologically non-psychoactive and has analgesic, anti-inflammatory, anticonvulsant, and anticancerogenic effects. CBN is the oxidative degradation product of THC and is a structurally aromatic compound [8], [9], [10], [11].

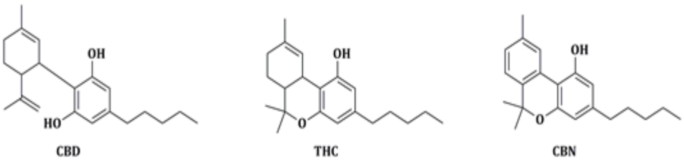

Figure 1. Chemical structures of CBD, THC, and CBN compounds.

The reactivity and stability of molecules such as CBD, THC, and CBN at the molecular level are directly related to the energy levels of the HOMO (the highest occupied molecular orbital) and LUMO (lowest unoccupied molecular orbital) energy levels. The HOMO-LUMO Energy Difference (ΔE) provides important information about electronic stability, chemical reactivity, and photophysical properties of a molecule [12], [13], [14]. The density functional theory (DFT) is a reliable quantum chemical modeling method that is widely used in calculating such molecular parameters [15], [16], [17].

In this study, CBD, THC, and CBN's quantum parameters were theoretically modeled, and the reaction profiles of the molecular reactivity profiles and potential effects were made.

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Thus, theoretical calculations were performed on the compounds known to be abundant in hemp, a plant frequently studied in the literature.

2 Experimental method

2.1 Theoretical modelling

Molecular modeling work was carried out using the Gaussian 09 software package. The initial geometries of molecules were created with ChemDraw and GaussView molecular visualization software. Full geometry optimizations were then made by the DFT method using the Becke-Lee-Yang-Parr (B3LYP) correlation function and the 6-31G base set in gase phase [18]. B3LYP and 6-31G set provide accurate results for organic molecules containing C, H and O [19]. The geometry optimization was considered converged when the energy and force changes fell below the predefined convergence criteria.

2.2 Calculations

The quantum parameters of CBD, THC, and CBN compounds were calculated using the following equations based on the Koopmans theorem [20]. Koopmans' theorem is an approximate theorem when applied to DFT.

$$I = -E_{HOMO} \tag{1}$$

$$A = -E_{LUMO} \tag{2}$$

$$\Delta E = E_{LUMO} - E_{HOMO} \tag{3}$$

$$\chi = \frac{(I + A)}{2} = -\mu \tag{4}$$

$$\eta = \frac{(I - A)}{2} \tag{5}$$

$$\sigma = \frac{1}{\eta} \tag{6}$$

$$\omega = \frac{\chi^2}{2\eta} \tag{7}$$

$$\varepsilon = \frac{1}{\omega} \tag{8}$$

(E_{HOMO}: Orbital energy of the highest full molecules; E_{LUMO}: The energy of the lowest empty molecular orbital; I: Ionization energy; A: Electron affinity; ΔE: Energy range; **χ**: Electronegativity; μ: Chemical potential; η: Chemical hardness; σ: Chemical softness; ω: Electrophilicity; ε: Nucleophilicity)

3 Results

The optimized molecular structures of the CBD, THC, and CBN phytocannabinoid compounds in the industrial cannabis (Cannabis sativa) plant were performed using the B3LYP hybrid function and clearly presented in Figure 2. The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) energies of these compounds, energy gap, ionization potential, electron affinity, electronegativity, chemical potential, chemical hardness-softness, electrophilicity, and nucleophilicity are given in detail in Table 1. All these quantum calculations are reported in the eV (electron volt) unit.

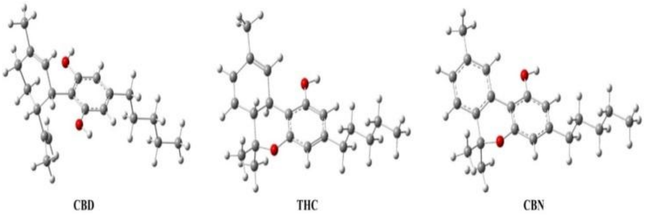

Figure 2. Optimized structures of CBD, THC, and CBN compounds.

Table 1. Various theoretical quantum parameters (eV) of CBD, THC, and CBN Compounds

Compounds	CBD	THC	CBN
E_{HOMO} (eV)	-5.7103	-5.5293	-5.4619
E_{LUMO} (eV)	-0.1173	-0.3946	-0.6422
ΔE (eV)	5.5930	5.1347	4.8197
I (eV)	5.7103	5.5293	5.4619
A (eV)	0.1173	0.3946	0.6422
η (eV)	2.7965	2.5673	2.4098
σ (eV^{-1})	0.3576	0.3895	0.4150
χ (eV)	2.9138	2.9619	3.0520
μ (eV)	-2.9138	-2.9619	-3.0520
ω (eV)	1.1580	1.7086	1.9327
ε (eV)	0.8635	0.5853	0.5174

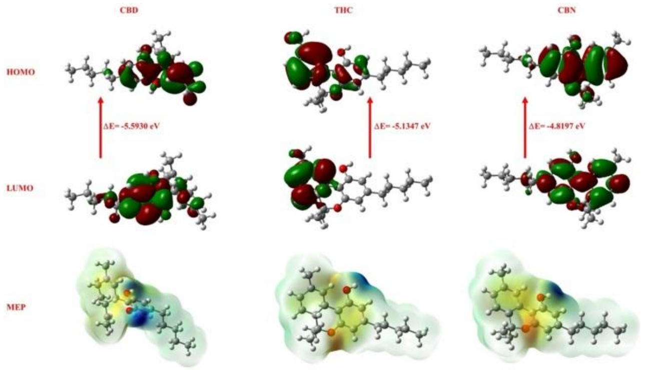

Figure 3. HOMO-LUMO energy levels and molecular electrostatic potential energy surface (MEP) of CBD, THC, and CBN compounds.

3.1 Optimizing geometric structures

The optimized molecular structures of CBD, THC, and CBN compounds are given in Figure 2. The frontier orbital energies, an important indicator in evaluating the electronic properties of a molecule, reflect the molecule's tendency to give electrons (HOMO energy) and the capacity to accept an electron. In this context, the frontier orbitals of CBD, THC, and CBN compounds, optimized with B3LYP function, and the lowest empty molecular orbital levels of the lowest empty molecular orbital (LUMO) levels are presented in Figure 3 via three-dimensional visuals. In the related visuals, the phase areas of the molecules are expressed by color coding, and positive phases are shown in red and negative phases are shown in green tones. HOMO's spatial distribution is in determining the potential of nucleophilic reactivity of compounds; the spatial settlement of LUMO is based on the analysis of electrophilic interaction trends [21], [22].

3.2 The Frontier Orbital Energy Values (HOMO-LUMO)

The energy range of the molecules (ΔE) was calculated by using the frontier orbital energy values (Table 1). This parameter is a critical indicator in evaluating molecular stability. According to the closed shell principle, the size of the ΔE refers to the determination of the molecule (system). Therefore, the HOMO-LUMO energy difference is an important quantum chemical feature that determines both kinetic reactivity and thermodynamic stability. In Table 1, when the ΔE values are examined, it can be said that the kinetic stability of CBD, THC, and CBN molecules is low and chemical reactivity is high. If we compare the molecules in themselves, we can sort chemical reactivity as CBD > THC > CBN. CBD is the easiest electron donor (i.e., the best nucleophile) compound, and CBN is the easiest electron acceptor (i.e., the best electrophile) compound. The compounds exhibit a lower HOMO–LUMO gap, which may indicate higher chemical reactivity and potentially affect the interaction profile [14], [21], [22], [23].

3.3 Ionization Energy (I), Electron Affinity (A)

Ionization energy (I) and electron affinity (A) are the main parameters used to evaluate the electronic stability of a molecule. Ionization energy is the energy required to remove an electron from a neutral molecule in the gas phase, forming a cation. Electron affinity is the energy change that occurs when a neutral molecule in the gas phase gains an electron to form an anion. In this context, the value of I is the value of the molecule to electrophilic attacks; the value of A indicates its predisposition to nucleophilic interactions. Considering the I and A values presented in Table 1, the CBN compound has the highest electron acceptance capacity (i.e., the best electron acceptor); on the other hand, it was determined that the CBD compound shows a high nucleophilic tendency. In general, the ionization energy and electron affinity values of CBD, THC, and CBN molecules support the thermodynamic stability levels of these compounds [24], [25].

3.4 Chemical hardness (η) and softness (σ)

Chemical stiffness and softness were defined by Pearson for the first time according to the hard and soft acid-base principle put forward in the middle of the 20th century. While soft molecules can easily polarize, this is the opposite of the hard. According to the maximum hardness principle, the molecules try to be arranged as hard as possible, i.e., stable. According to this principle, it can be said that hard molecules show higher determination. In Table 1, the chemical hardness (η) and softness (σ) values of the molecules are calculated. When chemical hardness values were evaluated, resistance to changes in the number of electrons was observed in the highest level of CBD molecule (2.7965 eV) and the lowest level in the CBN molecule (2.4098 eV). In line with the maximum stiffness principle, these results show that CBD is a harder molecule compared to the other two compounds and thus exhibits a lower reactivity. Accordingly, the CBD molecule has the most stable structure among these three molecules. In addition, it was determined that chemical softness values (σ) are compatible with chemical hardness and support the behavior of molecules at HOMO-LUMO energy levels [24], [26].

3.5 Electronegativity (χ)

Electronegativity refers to the ability of an atom or molecule to attract electrons within a chemical bond. The electronegativity (χ) values presented in Table 1, which are close to 3.0 eV, suggest that CBD, THC, and CBN exhibit a certain tendency to attract electrons. Among the studied molecules, CBN shows a relatively higher electronegativity value, implying a comparatively greater tendency to accept electrons under the same theoretical framework [21].

3.6 Chemical Potential (μ)

The reactivity of molecules is supported by chemical potential values (Table 1), which are important indicators of the direction of chemical reactions. Chemical potential reflects the change in the Gibbs free energy of molecules and provides important information about the dipole moments, polarities, and interaction potentials of CBD, THC, and CBN. The results generally indicate that CBD, THC, and CBN molecules are prone to electron transfer [27].

3.7 Electrophilicity (ω) and Nucleophilicity (ε)

The electrophilicity parameter (ω) describes a molecule's ability to accept electrons, while nucleophilicity (ε) indicates the tendency of a chemical species to donate or share electrons. Examining the electrophilicity and nucleophilicity values presented in Table 1, it is once again confirmed that CBD is dominated by nucleophilic character, while CBN is dominated by electrophilic character. In general, it can be stated that CBD, THC, and CBN molecules have structures with low electron density and a tendency to accept electrons. Furthermore, it was concluded that the electrophilic and nucleophilic behaviors of these molecules are consistent with their HOMO-LUMO energy levels, kinetic stability, and reactivity properties [28].

3.8 Molecular Electrostatic Potential Energy Surface (MEP)

Molecular electrostatic potential (MEP) maps visualize the spatial distribution of electrostatic potential across the surface of a molecule, allowing the identification of electrophilic and nucleophilic regions. Therefore, MEP analyses are considered an important tool in understanding the reactivity profiles of molecular systems. Electrophilic regions on MEP surfaces are generally defined as areas with high attractive forces and are characterized by negative electrostatic potential values. In contrast, nucleophilic regions are electron-rich and represented by positive electrostatic potential values.

Figure 3 visualizes the electron density distribution and potentially reactive regions in CBD, THC, and CBN molecules. The analyses reveal significant differences in the electrostatic potential distribution among these molecules. MEP surfaces are depicted as color gradients, with blue hues indicating positive electrostatic potential in regions near hydrogen atoms or hydroxyl groups; red hues indicating negative electrostatic potential were observed in regions corresponding to carbonyl or hydroxyl groups. Green hues represent neutral potential regions, and green-yellow hues represent intermediate potential values (transition regions).

Despite the highest HOMO–LUMO energy difference for the CBD molecule (ΔE = 5.5930 eV), significant polarization was observed on the MEP surface. This suggests high local reactivity in the structural regions of the molecule, particularly the presence of positive potential regions around the hydroxyl groups that can form hydrogen bonds and are susceptible to nucleophilic attack. THC presents a more stable MEP surface with a moderate ΔE value (5.1347 eV), indicating the presence of limited but focused reactive sites. CBN, on the other hand, exhibits a less polarized distribution on the MEP surface, despite having the lowest HOMO–LUMO difference (4.8197 eV). This indicates a more neutral electrostatic potential distribution in terms of electron density, despite lower stability.

Consequently, MEP analyses indicate that CBD, THC, and CBN molecules exhibit strong electrophilic characteristics in certain regions and strong nucleophilic characteristics in others. These differences may offer preliminary insights into the intermolecular interaction patterns of these molecules and their potential relevance to biological systems [19], [21], [22], [23], [30].

3.9 The Infrared Spectra of the Cannabinoids

Infrared spectroscopy is an important tool for detecting the presence of specific peaks in an organic compound. Additionally, it serves as a confirmatory method in molecular structure optimization for organic molecules. Infrared spectra of organic compounds can be obtained using DFT calculations. No scaling factor was applied to the calculated vibrational frequencies. In this study, the infrared spectra of cannabidiol (CBD), tetrahydrocannabinol (Δ9-THC), and cannabinol (CBN) compounds, modeled in the range of 4000–400 cm^{-1}, were theoretically determined. In the CBD molecule, two peaks were observed at 3430 and 3377 cm^{-1}, corresponding to the two ν(O–H) vibrations present in the structure. These peaks were experimentally found in the region of 3522 and 3410 cm^{-1}, respectively. Since CBN and THC molecules each contain a single O–H bond, a single peak was observed at 3369 and 3364 cm-1, respectively [32].

4 Conclusions

In this study, the quantum chemical parameters of CBD, THC, and CBN compounds from the cannabis plant were investigated in detail. These parameters provided valuable information about the electronic structure and reactivity of the molecules. DFT calculations and visualizations were performed using the Gaussian 09 software package, using the Lee-Yang-Parr correlation function (B3LYP function) and the 6-31G basis set. Key indicators of chemical reactivity, such as energy differences (ΔE) calculated from the HOMO and LUMO energy levels, ionization potentials (I), electron affinities (A), chemical hardness (η), softness (σ), electrophilicity (ω), and nucleophilicity (ε), were compared.

According to the results, CBD has the highest energy difference (ΔE = 5.5930 eV) and chemical hardness (η = 2.7965 eV) and stands out as the most reactive molecule. In contrast, CBN was identified as the least reactive compound with the lowest energy difference (ΔE = 4.8197 eV) and chemical hardness value (η = 2.4098 eV). THC, on the other hand, was positioned between the properties of both compounds, with intermediate values.

Data obtained from boundary orbital energies revealed the electrophilic nature of CBD, while showing that CBN has a stronger nucleophilic character among these three molecules.

This study aimed to reveal the electronic structures and reactivity properties of three cannabinoid derivative compounds, thereby shedding light on future research.

5 Author contribution statements

In the study conducted, Author 1 contributed to the formation of the idea, design, procurement of resources and materials, data collection, analysis, literature review, evaluation of the results, and writing; Author 2 contributed to the formation of the idea, design, procurement of resources and materials, data collection, analysis, literature review, evaluation of the results, and writing.

6 Ethics committee approval and conflict of interest statement

This article does not require ethics committee approval.

This article has no conflict of interest with any person or institution.

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