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Articles

Conceptual DFT as a Chemoinformatics Tool for the Study of Ibuprofen and Paracetamol

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Abstract

In the field of chemical reactivity, quantum chemistry is an essential complement to experimentation, and has become an important tool for studying the stereo selectivity of concerted reactions. Quantum methods are used to solve problems relating to structure and chemical reactivity. Ibuprofen containing derivatives represent one of the most important heterocycles in drug molecules. Variously substituted ibuprofen derivatives bear a variety of functional groups and display versatile biological activities. Therefore, they have gained considerable attention in the field of medicinal chemistry. In this paper, Ibuprofen and paracetamol are optimized by computational DFT that include B3LYB, CAM-B3LYP, HSEH1PBE, HCTH and WB97XD of theory and ionization potential (IP), electron affinity (EA), and other MDs are determined. Further, non-linear optical (NLO) descriptors such as dipole moment (DM) and polarizability (α) are also determined.

Keywords: ibuprofen, paracetamol, computational DFT, B3LYP, NLO, electron affinity, ionization potential, dipole moment, polarizability.

1. Introduction

Ibuprofen is an aromatic compound that is manufactured to be used as a drug in the pharmaceutical industry (Nethra et al., 2007). It is a nonsteroidal analgesic and anti-inflammatory drug (NSAID) that thins the blood and treats headaches, muscle and menstrual pain, fever and arthritis (BIAM et al., 2011; Pepin et al., 2006). It belongs to the group of 2-arylpropanoic acids, which exists in two enantiomeric forms R and S (Kim et al., 1999). Ibuprofen is one of the most widely consumed pharmaceuticals in the world. Although ibuprofen can be biodegraded, the environmental risk of its presence in water remains high because of the formation of intermediates generated during biological degradation (Ambuludi et al., 2012). Ibuprofen possesses, like acetylsalicylic acid, an anti-inflammatory activity linked to an inhibition of prostaglandin synthesis (Tim et al., 2004). It is very effective on the fever of the child. In the form of oral suspension, the maximum serum concentration is reached approximately 90 minutes after oral administration.

Ibuprofen is used in the treatment of fever the body temperature exceeds 38 ° C (Monassier et al., 2005). Ibuprofen is available without a prescription in the form of oral suspension suitable

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for children and infants older than 3 months (Kathryn et al., 2012; Vidal et al., 2013). Ibuprofen treats migraine of the child known by: shorter crises, an often bilateral character, and digestive symptoms often in the foreground, frequent facial pallor (Joriot et al., 2005; Donnet et al., 2004). Ibuprofen is also used in the treatment of the dysmenorrhea is mainly found in young women during the first days of the menstrual cycle. The symptoms encountered are cramping pains in the lower abdomen, which can lead to nausea, vomiting, diarrhea and great fatigue (Ramya et al., 2012; Lumsden et al., 2005).

Paracetamol(I, N-acetyl-p-aminophenol, acetaminophen) is a long-established and one of the most extensively employed "over the counter" drugs in the world. Firstly used in medicine by Von Mering in 1893. However, it was first discovered to have both analgesic and antipyretic properties in the late 19th century. It is noncarcinogenic and an effective substitute to aspirin for patients with sensitivity to aspirin (Goyal et al., 2005). Unlike aspirin, however, paracetamol anti-inflammatory activity is considered weak and is, thus, not routinely used in inflammatory conditions such as rheumatoid arthritis. Nevertheless, it is used to reduce fever cough and cold, and reduce mild to moderate pain, including instances of tension headache, migraine headache, muscular aches, chronic pain, neuralgia, backache, joint pain, general pain and toothache (Tjølsen et al., 1991; Bianchi et al., 1996; Atta et al., 2011). It is also useful in osteoarthritis therapy (Björkman et al., 1994) and it is sometimes used for management of cancer pain. Recent research suggests that paracetamol may help to protect from changes leading to hardening of arteries that cause cardiovascular disease (Hunskaar et al., 1985) (Figure 1).

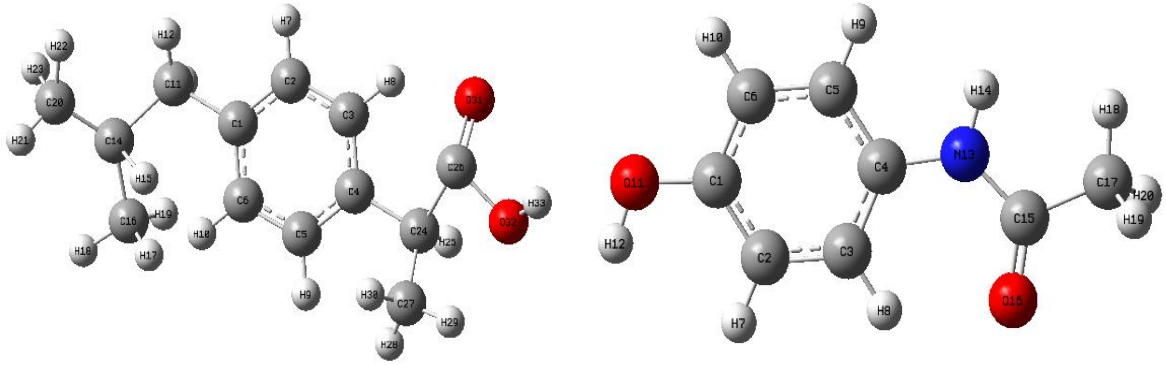


Fig. 1. Chemical structure of ibuprofen (P1) and paracetamol (P2)

Computational methods

All geometry optimizations computation was executed using the Gaussian 09 programs (Frisch et al., 2009). The geometries of the products were fully optimized through DFT calculations using the B3LYP functional (Becke et al., 2009; Lee et al., 1988) jointly in addition to the 6-311G(d,p)basis set (Francl et al., 1982). Initial structures were cleaned repeatedly to obtain normalized geometry. Each of the P1 and P2 was then subjected for successive optimization using semi-empirical (PM3), Hartree-Fock, and DFT methods in conjunction with appropriate basis sets. Final optimization of these molecules is achieved using DFT/B3LYP/6-311G (d, p) method. For computation of linear and NLO properties, the additional key of "optical" was included in the study. Following equations are used for the extraction of parameters and properties of these products. HOMO and LUMO energies are directly extracted from the LOG file of the corresponding optimized structure. The following formula is then used to obtain other dependent QM parameters. IP is the amount of energy required to take away one electron from a neutral molecule (M) and EA, oppositely, is the amount of energy released when an electron is added to a Molecule.

Thus, $I = E(M^+) - E(M)$ $\quad M + I \longrightarrow M^+ + e$

Thus, $A = E(M) - E(M^-)$ $\quad M + e \longrightarrow M^- + A$

μ is the ability of a molecule to participate in the chemical reaction. It can either be positive or negative. It is one of the very important parameters for the determination of the reactivity nature of a molecule. It is referred to as negative of electronegativity (χ) which is estimated as:

$$\mu = -\left(\frac{\delta E}{\delta N}\right)_V = -\left(\frac{\delta E}{\delta \rho}\right)_V = -\left(\frac{I+A}{2}\right); \quad \chi = \left(\frac{I+A}{2}\right)$$

η is a very important parameter that allows understanding of the chemical reactivity of a molecule. It is the slope of the curve of μ, in electronic energy (E) versus electron number plot. In other words, η is the curvature of the μ curve. The value is always positive. However, lower the value, the higher the reactivity of the molecule. η and its reciprocal (i.e., σ) are computed as:

$$\eta = \frac{1}{2}\left(\frac{\delta c}{\delta N}\right)_V = \frac{1}{2}\left(\frac{\delta^2 E}{\delta N^2}\right) = \left(\frac{I-A}{2}\right); \quad \sigma = \frac{1}{\eta}$$

Global electrophilicity index (ω) has been worked out using the μ and η parameters $\omega = \frac{\mu^2}{2\eta}$.

2. Discussion and results

2.1. Optimized structure, electronic parameters and properties

The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) for Ibuprofen (P1) and Paracetamol (P2) are presented in Figure 1, along with their optimized structures. While HOMO delocalizes over bonds of P1, and P2, it is less prominent for P1 and P2. Notably, the delocalization is uniform in P1. By the use of DFT/B3LYP/6- 311G (d, p) level of theory, the extracted energies for HOMO, LUMO, and ΔE for P1 and P2 are presented in (Table 1).

The HOMO and LUMO analyses are carried to explain the molecular characteristics of molecules. The chemical hardness (η), the chemical potential (μ), the softness, and the electrophilicity index of all the three compounds are evaluated with the magnitudes of frontier molecular orbitals to elucidate their molecular characteristics as follows:

Table 1. HOMO, LUMO, and band gap energies for P1 and P2 (HOMO and LUMO are directly extracted from the LOG file of the Gaussian optimized structure. The band gap is computed by ELUMO – EHOMO)

Molecule	HOMO (eV)	LUMO (eV)	Band gap (eV)
Ibuprofen (P1)	-6.6474	-0.7134	5.9339
Paracetamol (P2)	-5.8494	-0.4952	5.3541

We have computed adiabatic IP and adiabatic EA for P1 and P2 and presented in (Table 2). Value deviates from the mean value are highlighted by underline. IP: Ionization potential, EA: Electron affinity, μ: Chemical potential, χ: Electronegativity, η: Chemical hardness, σ: Chemical softness (1/η), ω: Electrophilicity index.

Table 4. Computation of electron affinity, ionization energy, chemical potential, electronegativity, chemical hardness, chemical softness, and electrophilicity index for P1 and P2 products

All Molecule units are in (eV)							
Molecule	IP	EA	M	X	η	Σ	Ω
P1	-6.6474	-0.7134	3.6804	-3.6804	-2.9567	0.2717	2.2906
P2	-5.8494	-0.4952	3.1723	-3.1723	-2.6771	0.3152	1.8795

*Mean of IP and EA is 7.5 eV and 0.4 eV, respectively (Schipper et al., 2000).

We note from Table 4, the following points are inferred:

*The ionization potential of the mesogenic compound (P1) has lower potential energy when compared with the complex formed with that of (P2), indicating the equilibrium nature of the mesogen formed.

*Electron affinity and electronegativity of the complex formed have a remarkable increase when compared with the individual compounds revealing the ability of donating and accepting the electron of complex and the mesogenic nature respectively.

*Electrophilicity index revealing the capacity of the electrophile to accept the maximal number of electrons in a neighboring reservoir of electrons is proved in the complex so formed between P1 and P2.

The highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) for P1 and P2 are presented in (Figure 2), along with their optimized structures, While HOMO delocalizes over bonds of P1 and P2, it is less prominent of P1 and P2. Notably, the delocalization is uniform in P1. In turn, the LUMO is mostly located for P1 and P2. By the use of DFT/B3LYP/6- 311G (d,p) level of theory.

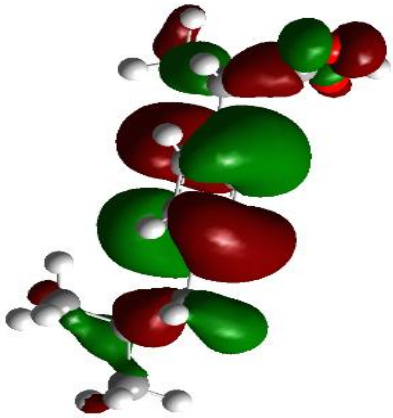
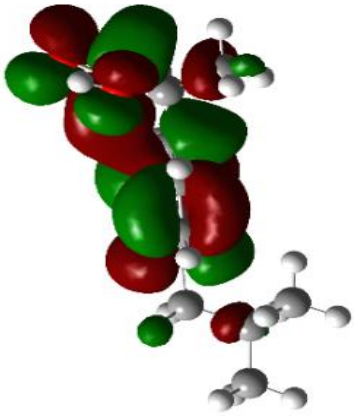
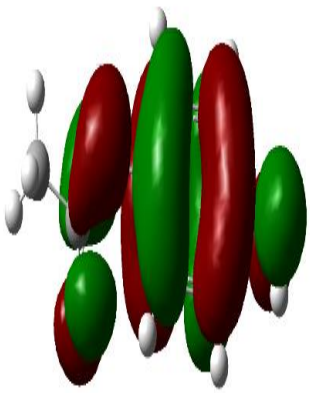
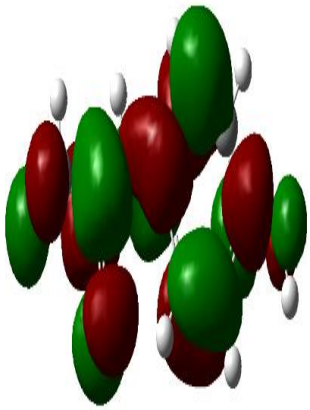
Molecules	HOMO Energy	LUMO Energy
P1		
P2		

Fig. 2. Energy optimized structures (left column) along with highest occupied molecular orbitals (middle panel) and lowest unoccupied molecular orbitals (right panel) or frontier molecular orbitals of P1 and P2

The Table 2 shows that IP of P2 is higher than IP of P1. Here, P2 is seen to be anomalously high and P1 almost similaras the mean value. High IP implies low tendency for the formation of the

cation. On the other hand, higher the EA, greater is the tendency for the formation of an anion. Although, the mean value of EA for normal 0.4 eV, the posses shigh P2 and low (for P1) values of EA, μ, χ, η, σ, and electrophilicity index (ω) properties are also presented in (Table 4). All these properties are dependable on IP and EA. It is seen that ω value follows the similar order as EA, P2 > P1.

2.2. Nonlinear optical (NLO) of P1 and P2

Intermolecular interactions the P1 and P2 are largely understood by DM, α, and first-order and second-order hyperpolarizability energy terms (GJ. Hurst et al., 2000), which are reliably computed by B3LYP/6-311G (d,p) level of the theory (Ansary et al., 2017). How are these parameters affected for P1 and P2. To check this above basis set is used and dipole moments (DM), α, and first- and second-rank hyperpolarizability are determined (u.a). Isotropic DM is presented in (Table 3).

Table 3. Cartesian components and net electric dipole moments (DM in Debye) for P1 and P2

Names	DMx	DMy	DMz	DM_{Total}
P1	0.9820	-0.8826	1.1431	1.7074
P2	-0.6249	2.2759	0.0005	2.3601

It is seen that the X and Y components are zero in all the cases with the Z component constituting the total DM. Higher and lower DM_{TOTAL} than the reported mean value are highlighted by the (Table 4). Here, P1 and P2 show higher and lower DMTOTAL, respectively.

Molecular complexity is the criterion that can be related with Δα (Chen et al., 2017; Aihara et al., 1999; Obot et al., 2009; Ghanadzadeh et al., 2000; Zhan et al., 2003; Xue et al., 2004; Harris et al., 1999; Lim et al., 1999; Hansch et al., 2003; Desharnais et al., 2003). More the complexity of structure more is the anisotropy of polarizability (Δα).

While dipole moment (DM) is the measure of α of a molecule in its ground state, α is the intrinsic capacity of a molecule of having a dipole when it is assaulted with an external electric field. If a molecule is present in a weak, static electric field (of strength, F), then the total energy (E) of the molecule can be express as a Taylors series.

$$E_F = E_0 - \mu_\alpha F_\alpha - \frac{1}{2!}\alpha_{\alpha\beta}F_\alpha F_\beta - \frac{1}{3!}\alpha_{\alpha\beta\gamma}F_\alpha F_\beta F_\gamma - \frac{1}{4!}\alpha_{\alpha\beta\gamma\delta}F_\alpha F_\beta F_\gamma F_\delta - \ldots$$

E_o denotes the energy of the molecule in the absence of an external electrical field. Energy (E_o), dipole moment (μα), polarizability (ααβ), and first- and second-order hyperpolarizability (βαβγ and $\gamma_{\alpha\beta\gamma\delta}$, respectively) denote the molecular properties. First polarizability and second hyperpolarizabilities are expressed as tensor quantities, whereas subscripts single, double, etc., denote the first-rank and second-rank tensor, etc., in Cartesian coordinate (Zhang et al., 2007).

If the external field lies on any one of the three orthogonal Cartesian axes, then the components of the induced moments will be parallel to the field. In that case, off-diagonal terms of the tensor, ααβ vanish. Under these conditions, the expected value of αand DM obtained as:

$$\mathrm{DM} = \sqrt{\left(\mu_X^2 + \mu_Y^2 + \mu_Z^2\right)} \quad \text{Or} \quad \langle \alpha_{STATIC} \rangle = \frac{\left(\alpha_{XX} + \alpha_{YY} + \alpha_{ZZ}\right)}{3}$$

In case of the anisotropic orientation of the external field, the anisotropy of the polarizability (<Δα>) can be computed as:

$$\langle \Delta\alpha \rangle = \left[\frac{(\alpha_{XX} - \alpha_{YY})^2 + (\alpha_{YY} - \alpha_{ZZ})^2 + (\alpha_{YY} - \alpha_{ZZ})^2 + 6\left(\alpha_{XY}^2 + \alpha_{XY}^2 + \alpha_{YZ}^2\right)}{2}\right]^{\frac{1}{2}}$$

Similarly, the first-order (βαβγ) and second-order (γαβγδ) hyperpolarizability is calculated from components of respective tensors that are obtained from the Gaussian 09 output file.

$$\langle \beta_{STATIC} \rangle = \left[\beta_X^2 + \beta_Y^2 + \beta_Z^2 \right]^{\frac{1}{2}}$$

$$\beta_i = \beta_{iii} + \frac{1}{3} \sum_{i \neq k} \left(\beta_{ikk} + \beta_{kik} + \beta_{kki} \right)$$

$$\langle \beta_{STATIC} \rangle = \left[\left(\beta_{XXX} + \beta_{XYY} + \beta_{XZZ} \right)^2 + \left(\beta_{YYY} + \beta_{YZZ} + \beta_{YXX} \right)^2 + \left(\beta_{ZZZ} + \beta_{ZXX} + \beta_{ZYY} \right)^2 \right]^{\frac{1}{2}}$$

$$\langle \gamma_{STATIC} \rangle = \frac{\gamma_{XXXX} + \gamma_{YYYY} + \gamma_{ZZZZ} + 2\gamma_{YYXX} + 2\gamma_{YYZZ} + 2\gamma_{ZZXX}}{5}$$

All these optical terms have been calculated using appropriate basis set that contains polarized and diffused functions for high accuracy, in that DFT/B3LYP/6-311G(d,p) was preferred.

The electric dipole moment (D), polarizability (α), and hyperpolarizability (β total) values of P1 and P2 products are given in Table 4.

Table 4. Electric dipole moment (D), polarizability (α), and hyperpolarizability (β_{total}) values of compound P1

	Parameter	Product P1	Product P2
Dipole moment (D)	μx	0.9820	-0.6249
	μy	-0.8026	2.2759
	μz	1.1431	0.0005
Polarizability α	Axx	-89.6440	-60.8544
	Axy	3.8062	-16.8812
	Ayy	-92.9482	-59.8594
	Axz	-3.8210	-0.0015
	Ayz	2.0932	-0.0006
	Azz	-91.2702	-68.1532
	α × 10-24(esu)	45.2973	-34.2917
Hyperpolarizability	Bxxx	-42.2585	-30.3707
	Bxxy	-33.3970	-10.3155
	βxyy	-16.3048	26.7684
	βyyy	-6.1547	8.0302
	βxxz	9.5343	0.0039
	βxyz	-21.6974	-0.0006

α, its components, and anisotropic terms are shown in (Table 4). The α of P1 is seen to be much lower than α in compound P2 case. In these aspects, P2 is seen to be less affected (Table 6).

Similar is the case for the anisotropy of polarizability (Δα) and diagonal components of polarizability (α_{XX}, α_{YY}, and α_{ZZ}), where compound P1 have much lower value than compound P2. Is there any relation of α with chemical reactivity. Wher compound P2 is most polarizable and which one is most active chemically.

2.3. Molecular electrostatic potential

For the understanding of the molecular interactions in a given molecule, the molecular electrostatic potential (MEP) is a crucial tool. Furthermore, the relative reactivity sites for electrophilic and nucleophilic attack, hydrogen bonding interactions, studies of zeolite, molecular cluster and crystal behaviour, investigation of biological recognition and the correlation and prediction of a wide range of macroscopic properties can be interpreted bconsidering the molecular electrostatic potential (Stamboliyska et al., 2008; Scrocco et al., 1979; Lopez et al., 2000).

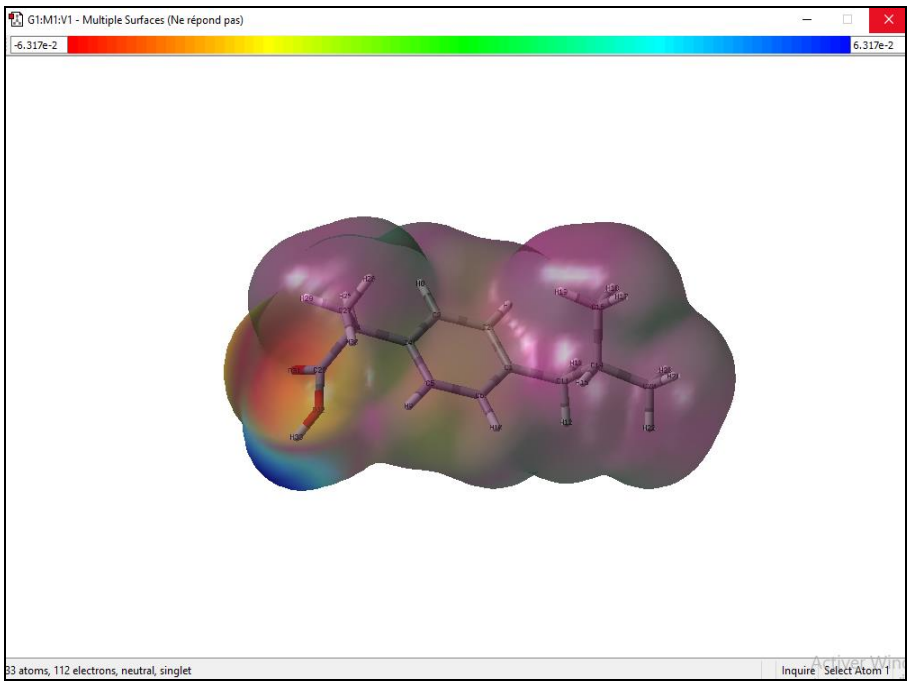


Fig. 3. MEP surface of the compound P1 obtained at the B3LYP/6-311G(d,p) level

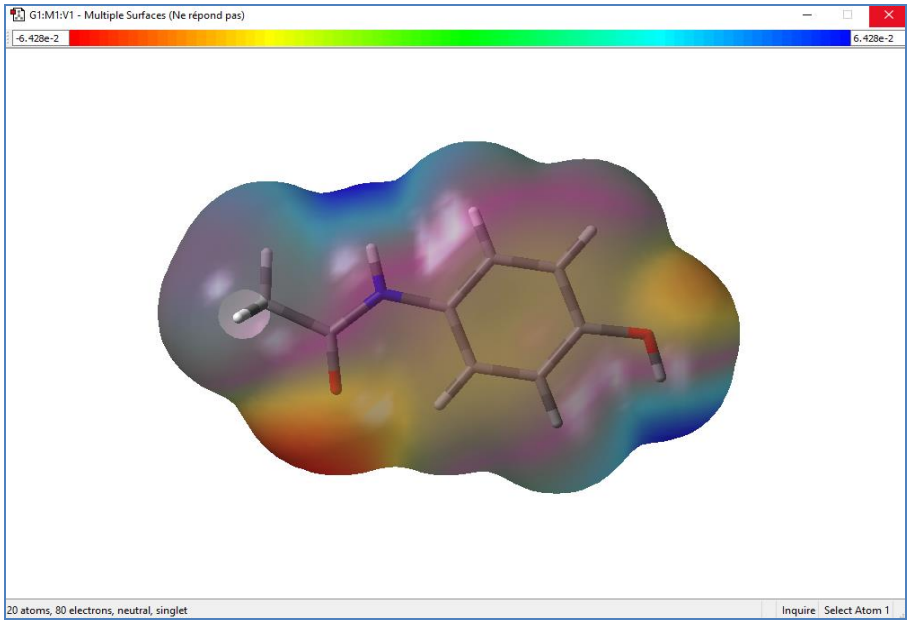


Fig. 4. MEP surface of the compound P2 obtained at the B3LYP/6-311G(d,p) level

The 3D plot of the MEP for the P1 and P2 are exhibited in (Figure 4) obtained at the B3LYP/6-311G(d,p) level. As seen in Fig. 5, the electrostatic potentials at the surface of the mentioned molecule are shown by different colours. The red colour parts indicate the regions of negative electrostatic potential, the blue sites represent the regions of positive electrostatic potential and the parts with green colour represent the regions of zero potential. Furthermore, the negative regions (red colour) of MEP are related to electrophilic reactivity and the positive ones (blue colour) are related to nucleophilic reactivity. The order for the potential increment can be considered as red < orange < yellow < green < blue. The MEP map shows the negative potential sites are on R-COOH function as well as the positive potential sites around the hydrogen atoms.

2.4. NBO analysis

The analysis of the results obtained in the study aimed at verifying that the DFT procedure was fulfilled. On doing it previously, several descriptors associated with the results that HOMO and LUMO calculations obtained are related with results obtained using the vertical I and A following the ΔSCF procedure. A link exists between the three main descriptors and the simplest conformity to the Koopmans' theorem by linking ϵH with -I, ε_L with -A, and their behavior in describing the HOMO-LUMO gap as JI = $|\varepsilon_H + Egs(N-1) - Egs(N)|$, JA = $|\varepsilon_L + Egs(N) - Egs(N+1)|$ and JHL= $\sqrt{J_L{}^2 + J_A{}^2}$. Notably, the JA descriptor consists of an approximation that remains valid only when the HOMO that a radical anion has (the SOMO) shares similarity with the LUMO that the neutral system has. Consequently, we decided to design another descriptor ΔSL (the difference between the SOMO and LUMO energies), to guide in verifying how the approximation is accurate (Weigend et al., 2005; Pereira et al., 2017). The results of this analysis are presented in (Tables 5 and 6).

Table 5. Electronic energies of the neutral, positive and negative molecular systems (in au), the HOMO, LUMO, and SOMO orbital energies (in eV), JI, JA, JHL, and ΔSL descriptors (also in eV) calculated with DFT/B3LYB, CAM-B3LYP, HSEH1PBE, HCTH407 and WB97XD for compound P1

	E_o	E^+	E^-	HOMO	LUMO	SOMO	J_i	J_A	J_{HL}	ΔS_L
B3LYP	-656.6809	-655.4589	-656.9874	-6.6613	-0.6993	-4.8572	8.4627	2.0408	8.6804	4.1361
CAM-B3LYP	-656.3212	-655.4567	-656.8756	-8.0627	0.7020	-5.3796	9.7144	0.3809	9.7144	6.2314
HSEH1PBE	-655.9498	-654.0658	-655.9887	-6.4735	-0.8435	-4.6041	7.5647	1.1156	7.6464	3.7551
HCTH407	-656.6133	-655.4521	-656.7663	-5.9402	-1.5537	-3.9619	11.3199	1.9047	11.4559	2.3946
WB97XD	-656.4673	-655.2546	-656.6825	8.6042	1.3197	-5.4830	9.3879	0.2711	9.3879	6.8028

Table 6. Electronic energies of the neutral, positive and negative molecular systems (in au), the HOMO, LUMO, and SOMO orbital energies (in eV), JI , JA, JHL, and ΔSL descriptors (also in eV) calculated with the eight DFT density functionals and the 6-311G(d,p) basis set using water for compound P2

	E_o	E+	E^-	HOMO	LUMO	SOMO	J_i	J_A	J_{HL}	ΔSL
B3LYP	-515.4682	-514.7852	-515.6894	-5.8493	-0.4952	-4.9294	11.5757	4.5143	12.4248	4.4342
CAM-B3LYP	-515.2107	-514.5684	-515.6231	-7.2172	0.8710	-5.4752	12.5553	1.6735	12.6663	6.3462
HSEH1PBE	-514.9127	-513.7852	-514.9888	-5.6550	-0.6293	-4.3964	10.7158	1.4721	10.8164	5.0257
HCTH	-515.3869	-514.2775	-515.6523	-5.1252	-1.2773	-2.5706	7.3334	2.4898	7.7445	1.2773
WB97XD	-515.2880	-514.3354	-515.7412	-7.7555	1.4805	-4.7945	12.2179	1.0285	12.2611	6.2750

The overall conclusion that can be extracted from the inspection of the results presented in Tables 5 and 6 is that in agreement with our previous studies on ibuprofen and paracetamol, the model chemistries involving the CAM-B3LYP and WB97XD density functionals are the best for verifying our proposed criteria of good behavior, that is, the values of JI, JA, JHL, and ΔSL are close to zero.

3. Conclusion

In this paper, we have presented a new study performed on the chemical reactivity of ibuprofen and paracetamol on conceptual DFT as a tool to explain molecular interactions.

HOMO and LUMO energy gaps justify the eventual charge transfer interactions taking place within the molecule.

The LUMO and HOMO energy provides information regarding ionization potential, chemical potential and other chemical descriptors and the results obtained shows that compound 1 is the most reactive.

The Conceptual DFT descriptors are useful in characterizing and describing the preferred reactive sites and in comprehensively explaining the reactivity of the molecules.

4. Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper. Also, they declare that this paper or part of it has not been published elsewhere.

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