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Spectroscopic and Density Functional Theory Approach to Study the Interaction of Ibuprofen with Water Molecule

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Abstract

The fundamental understanding of drug-water interaction is pivotal to ensure the bioavailability of a drug as it depends on the solubility profile of the drug candidate. The present work is undertaken to investigate the molecular interaction between a non-steroidal anti-inflammatory drug, Ibuprofen, and water molecule at the atomic level using Density Functional Theory. Gaussian 09W software is used to optimize the molecules using the Becke–Lee–Yang–Parr/6-31 G (d, p) level. The newly formed intermolecular hydrogen bonds O34-H36---O1 (2.58 Å) and O34-H35---O2 (2.08 Å) dominate the Raman spectra of the compound in the higher wavenumber region, and a remarkable spectral shift is observed in the interacting state. NBO analysis validates the transfer of charges in the interacting state via O-H---O with a stabilization energy of 35.32 kcal/mol. AIM analysis reveals the existence of a moderate (O34−H35···O2) and a weak hydrogen bond (O34−H36···O1) between the two monomers. The compound's experimentally recorded UV absorption spectrum exhibits an absorption peak at 216.59 nm. The corresponding energy gap of 5.72 eV agrees with the calculated energy gap of the interacting state (5.90 eV). MEP surface of the ibuprofen + Water is evaluated, which will further help in biological recognition.

Keywords: Ibuprofen; Water; DFT; Raman; FTIR.

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1. Introduction

Understanding drug interactions with biomolecules is essential in order to comprehend their actions at the atomic level. The medications have very specific target receptors because they are intended to treat certain specific diseases. Protein receptors are typically the target receptors. Though the drug molecules interact with the target receptors through electrostatic as well as hydrogen bond interactions, they are also influenced by biological water molecules [1]. Since about 70-80 % of the human body consists of water molecules, the interaction of drugs with water molecules is crucial. Drug molecules form hydrogen bonds with water molecules, through which they can improve their solubility as well as bioavailability for pharmaceutical uses. The poor aqueous solubility of a drug limits its

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bioavailability due to its low dissolution rate. Therefore, it is essential to understand the drug-water interactions at a fundamental level to elucidate their possible interactions when dissolved in water. The inter- and intra-molecular interactions of molecules can be understood theoretically using Density Functional Theory (DFT), and their interactions can be studied experimentally using vibrational spectroscopic techniques (Raman and FTIR) [2]. The current work addresses the interaction of Ibuprofen with water molecules using DFT and spectroscopic techniques.

Non-steroidal anti-inflammatory drugs, or NSAIDs, like Ibuprofen, are primarily used to treat fever, edema, and pain. There are also reports of Ibuprofen being used to treat different types of cancer [3]. Researchers are studying the interaction of Ibuprofen with other molecules of biological importance [1,4-9]. Escobar *et al*. [1] carried out experimental and theoretical (DFT) investigations on the interaction of anionic Ibuprofen with Water. They reported the shift of vibrational wavenumbers in the combined state, charge transfer between the molecules, and variation of electron density in the combined state. Zhang [7] and his group carried out the interaction mechanism of Ibuprofen with ethanol and water molecules using molecular dynamics simulation. They observed the strength of newly formed intermolecular hydrogen bonds and the charge transfer paths between the molecules at different temperatures. Ouafy *et al*. [8] used the DFT technique to investigate the quantum chemical properties and vibrational spectra of Ibuprofen, Paracetamol, and their interacting state, Ibuprofen + Paracetamol. They applied the B3LYP / 6-311G (d, p) basis set under the DFT framework for optimization of the molecule. The absorption behavior of Ibuprofen drug on aluminum nitrate Nano cage was reported by Wei [9]. The DFT study by Wei [9] showed the depletion of the HOMO-LUMO gap of the interacting state compared to the individual states. Oyeneyin *et al*. [10] carried out the quantum chemical and molecular docking study of Ibuprofen and its derivatives using density functional theory. They reported the drug's likeness as well as the pharmacokinetic properties of Ibuprofen's derivatives. The experimental and computational study on the dimer state of Ibuprofen is performed by Vueba *et al.* [11]. The formation of intermolecular hydrogen bonds between the molecular units of Ibuprofen is confirmed by their spectral assignments (both Raman and IR) and natural bond orbital analysis. The DFT study on the interactions of Ibuprofen with other biological molecules (propionic acids) and metal complexes is performed by Shahawy *et al*. [12]. They utilized experimental and computational methods to explain the interacting states' electron affinities, ionization potential, and electron transfer nature.

The literature survey reveals that a limited study has been carried out on the interaction of Ibuprofen and biological water molecules using DFT and spectroscopic techniques. However, an in-depth study has been required to understand their interaction mechanism at the fundamental atomic level. In the present study, the combined DFT and spectroscopic study (Raman, SERS, FTIR, and UV-Vis) on the interaction between neutral Ibuprofen and Water are carried out, which will provide new insights into the molecular interaction. The spectral characterization (both theoretical and experimental) is performed using Raman, SERS (Surface Enhanced Raman Spectroscopy), and FTIR techniques and compared to the reported individual wavenumbers of the molecules. The quantum chemical parameters of

the interacting state, such as dipole moment, HOMO-LUMO gap, electrophilicity index, chemical potential, electron affinity, etc., are reported. The calculated molecular parameters may help to understand the interaction mechanism of Ibuprofen with Water and develop new hybrid molecules further.

2. Materials and Methods

2.1. *Experimental*

The drug ibuprofen is bought from Abbott India Limited (Pharmaceutical Company). The FTIR spectrum (resolution 1 cm^{-1}) of the physical mixtures (Ibuprofen + water) is recorded on an IRAffinity-1 spectrophotometer designed by Shimadzu, Japan (spectral resolution 1 cm^{-1}) in the spectral range 400-4000 cm^{-1}. KBr pellet technique is employed to collect the FTIR spectra [13,14]. The Raman and SERS spectra of the physical mixture (Ibuprofen + Water) are recorded on XPlora ONE Raman microscope manufactured by HORIBA Scientific, Japan, having a spectral resolution of 1.1 cm^{-1}, embedded with a 785 nm diode laser that works as an excitation source. The Raman and SERS spectra are recorded in the range 100 cm^{-1} to 3500 cm^{-1}.

2.2. *Computational methods*

The molecular structure of the interacting state, Ibuprofen + water, is optimized in Gaussian 09W software at DFT-B3LYP/6-31G (d, p) model [15]. The Potential Energy Distribution (PED) of some important vibrational modes of the optimized structure is calculated using the Vibrational Energy Distribution Analysis (VEDA) program and visualized by Gauss view 5.0 [16]. The charge transfer (intra and intermolecular) mechanism of Ibuprofen + water is scrutinized through the NBO 5.0 program in Gaussian 09W software. The computed wavenumbers are scaled down by the factor of 0.9627 to reduce anharmonicity [17].

3. Results and Discussion

3.1. *Structural parameters*

The optimized molecular structure of the interacting state (Ibuprofen + water) is shown in Fig. 1, and its computed bond lengths are listed in Table 1. A molecule's bond lengths and wavenumbers are directly correlated, so to determine how water affects the medication, the computed bond lengths of Ibuprofen + water are compared to Ibuprofen, and any notable changes in bond lengths are noted. The computed bond length in the interacting state of Ibuprofen + water is found to be altered as compared to the individual state of Ibuprofen. The C15=O2 and C15-O1 bond lengths of the combined state are calculated at 1.21 and 1.35 Å, which are observed to be elongated by 0.1 and 0.5 Å as compared to Ibuprofen alone [18].

Similarly, a change in C-C bond distances is observed in the interacting state. The computed C7-C15, C7-C14, C5-C11, and C6-C12 bond lengths of optimized Ibuprofen + Water are altered by 0.01 and 0.02 Å in comparison to the single state of Ibuprofen (Table 1). The O-H bond lengths (0.96 Å) are found to be intact in the individual as well as the combined state. The C-H bond lengths of Ibuprofen + water are also observed to be altered by 0.01 and 0.02 Å when compared to the reported bond lengths of Ibuprofen (Table 1). Some of the C-H bond lengths of the interacting state are contracted, while some of the bond lengths are elongated in comparison to the reported bond distances of Ibuprofen. The C8-H20 bond distance of Ibuprofen + water shows a maximum deviation of 0.03 Å in comparison to the corresponding C-H bond length of Ibuprofen. The elongation and the contraction of bond lengths in Ibuprofen + water clearly indicate the interaction of Ibuprofen with water molecules. There will likely be some charge transfer between the Ibuprofen molecule and the water, as evidenced by the formation of two new intermolecular hydrogen bonds (O34-H36---O1 and O34-H35---O2) [19,20]. The Ibuprofen molecule interacts with water through its carboxylic group, and its corresponding intermolecular hydrogen bond lengths are observed to be 2.58 Å and 2.08 Å, respectively (Table 1). The transfer of charges between the molecular units may alter the structural parameters discussed in the natural bond analysis of the combined state.

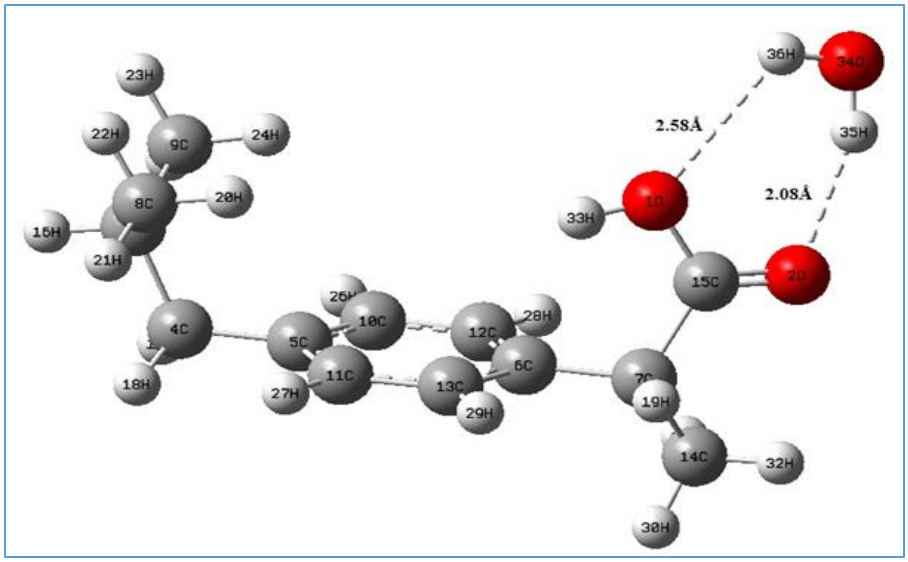

Fig. 1. Optimized molecular structure of Ibuprofen + water.

Table 1. Bond lengths of optimized Ibuprofen + water.

Serial No	Bond	Bond Length [Å]	Reference [18]
1	C13-H29	1.08	1.10
2	C12-H28	1.08	1.07
3	C11-H27	1.08	1.07
4	C10-H26	1.08	1.10

5	C4-H18	1.09	1.08
6	C4-H17	1.09	1.10
7	C9-H24	1.09	1.09
8	C3-H16	1.10	1.08
9	C8-H20	1.09	1.06
10	C15=O2	1.21	1.20
11	C15-O1	1.35	1.30
12	O34-H35	0.96	0.96
13	O34-H36	0.96	0.96
14	**O34-H36---O1**	**2.58**	
15	**O34-H35---O2**	**2.08**	
16	C7-C15	1.52	1.50
17	C7-C14	1.51	1.50
18	C5-C11	1.51	1.49
19	C6-C12	1.53	1.52
20	O1-H33	0.96	0.96

3.2. *Analysis of charge transfer mechanism*

The Natural Bond Orbital (NBO) analysis provides a picture of the hyper-conjugative interaction of molecules. It is a powerful tool at the atomic level to understand the intra as well as intermolecular charge transition of molecules and their interacting state [21]. The charge transfer from Lewis to non-Lewis orbital can be interpreted from NBO analysis. The second-order perturbation theory is used to investigate the interaction between the donor and the acceptor orbital of a molecule, which provides information on the stabilization energies of orbital interaction [22].

In the present work, the study of charge transfers between the molecular units, i.e., Ibuprofen and Water, was performed by employing the NBO 5.0 program embedded with Gaussian 09w software. The orbital interaction (donor and acceptor) of Ibuprofen + water and its corresponding stabilization energies are computed using the following equation.

$$E^{(2)q} = \Delta E_{ij} = q_i \frac{F(i,j)^2}{\varepsilon_j - \varepsilon_i}$$

Where the donor and acceptor orbitals are indicated by i and j, and their diagonal elements are specified by ϵ_i and ϵ_j. The terms q_i, F (i, j), and $E^{(2)}$ represent donor orbital occupancy, off-diagonal Fock matrix elements, and stabilization energy, respectively [23]. The stabilization energies of interaction indicate the strength of interaction. Strong interactions are correlated with high stabilization energy, while weak interactions are correlated with low stabilization energy. The computed NBOs of Ibuprofen + water are shown in Table 2.

Table 2. Second-order perturbation theory analysis of Fock matrix in NBO basis for Ibuprofen + water.

Donor (i)	Acceptor (j)	$E(^2)$ (kcal/mol)	E(j)–E(i) (a.u.)	F_{ij} (a.u.)
σ(O1-H33)	π* (O2-C15)	3.84	0.72	0.049
σ(C3-C4)	π* (C5-C10)	2.61	0.62	0.037
π(C5-C10)	π*(C6-C12)	11.85	0.30	0.053
π(C5-C10)	π*(C11-C13)	10.67	0.30	0.050

σ(C6-C7)	σ*(O1-C15)	4.02	0.81	0.052
σ*(C6-C12)	π*(C5-C10)	9.80	0.32	0.050
n_1(O1)	σ*(O2-C15)	6.09	0.61	0.055
n_2(O2)	σ*(O1-C15)	17.93	0.53	0.088
π(C6-C12)	π*(C11-C13)	11.08	0.30	0.052
σ(O1-C15)	σ*(O34-H36)	3.02	1.57	0.063
n_1(O1)	σ*(O34-H36)	30.75	1.38	0.185
n_2(O1)	σ*(O34-H36)	18.26	1.08	0.126
n_2(O2)	σ*(O34-H35)	35.32	0.95	0.167
σ(O34-H35)	σ*(O34-H36)	5.53	1.29	0.077

a.u.: arbitrary unit, NBO: Natural Bond Orbital, $E^{(2)}$ represents stabilization energy, E(j)−E(i) indicates the energy difference between the i and j NBO orbitals, F(i,j) is the off-diagonal Fock matrix elements

In the NBO analysis of ibuprofen + water, stabilization energies of more than 2 kcal/mol are enlisted. Both intra- and inter-molecular charge transfers are observed in the NBO calculation. The transfers of charges between the O1-H33 bonding orbital and the O2-C15 antibonding orbital lead to a stabilization energy of 3.84 kcal/mol. Some strong interactions are found between π(C5-C10), and π*(C6-C12) orbitals, π(C5-C10) and π*(C11-C13) orbitals, and their corresponding stabilization energies are found to be 11.85 and 10.67 kcal/mol, respectively. The lone pair orbital also takes part in the charge transfer process. The lone pair orbitals are denoted by n_1 and n_2, respectively. In Ibuprofen's carboxylic group, the highest stabilization energy of 17.93 kcal/mol is obtained between the n_2 (O2) lone pair and σ*(O1-C15) orbital. The transfer of charges between the two molecular units, i.e., Ibuprofen and Water, is observed through the newly formed intermolecular hydrogen bonds (O34-H36---O1 and O34-H35---O2), which is mentioned in structural analysis. The interaction of lone pair orbital n_1(O1) and σ*(O34-H36), n_2 (O1) and σ*(O34-H36), and n_2(O2) and σ*(O34-H35) shows stabilization energies of 30.75, 18.26, and 35.32 kcal/mol respectively. Some other interactions between the molecular orbital of ibuprofen and water (σ(O1-C15) and σ*(O34-H36) orbitals, σ(O1-H33) and σ*(O34-H36) orbitals) are observed through the new O-H---O bonds (Table 2). The stabilization energy of orbital interaction is associated with bond lengths. The higher the bond length, the lower the stabilization energy. Therefore, it can be summarized that the orbital interaction involving n_2(O2) and σ*(O34-H35) orbital (bond distance 2.08 Å) shows the highest stabilization energy as compared to n_1(O1) and σ*(O34-H36), n_2(O1) and σ*(O34-H36) orbital (bond distance 2.58 Å) interaction [24].

3.3. *Analysis of frontier molecular orbital, molecular electrostatic potential, and quantum chemical parameters*

The Frontier Molecular Orbital (FMO) of a molecule includes HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital). Usually, FMOs of a molecule are measured in electron volts (eV), and their energy difference is called the HOMO-LUMO energy gap. The molecules of low band gap have a greater probability of charge transfer; hence, they are highly reactive and very responsive to electric fields [25-27]. In the current work, the HOMO-LUMO energy gap and the parameters associated with

HOMO-LUMO, such as chemical reactivity, electron affinity, ionization potential, electrophilicity index, hardness, etc., are calculated using B3LYP/ 6-31G + (d, p) model. The quantum chemical parameters are presented in Table 3. The HOMO-LUMO energy gap of Ibuprofen + water is calculated as 5.90 eV (Table 3). In the experimental UV-Vis spectrum of the physical mixture (Fig. 3), an absorption peak is observed at 216.59 nm, which is equivalent to 5.72 eV. The experimental energy gap of 5.72 eV is found close to the computed energy gap (5.90 eV) of Ibuprofen + water. The HOMO-LUMO energy diagram is shown in Fig. 2.

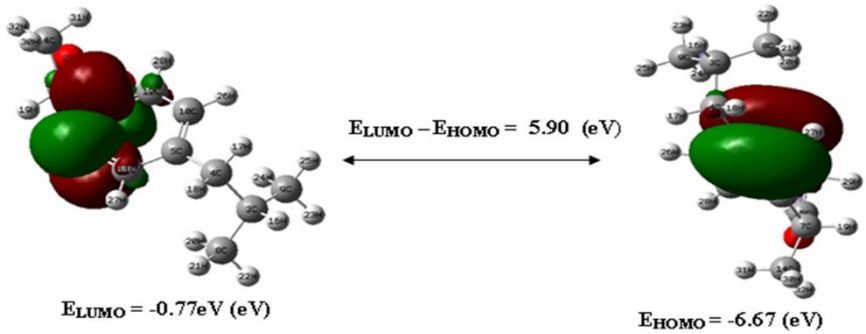

Fig. 2. Frontier Molecular Orbital diagram of Ibuprofen + water.

It is found that the computed HOMO-LUMO gap of Ibuprofen + water is less than the Ibuprofen's reported HOMO-LUMO gap (6.14eV) [10]. The depletion of the HOMO-LUMO gap in the interacting state compared to the individual state of Ibuprofen indicates that the combined state is highly reactive and less stable. Ibuprofen+water has a higher chemical potential (-3.72 eV) than the reported chemical potential of Ibuprofen (-3.30 eV) [10]. The increase of chemical potential in the associated state clearly indicates the highly reactive nature of the compound state. The dipole moment is another physical parameter used to identify the reactive nature of a material.

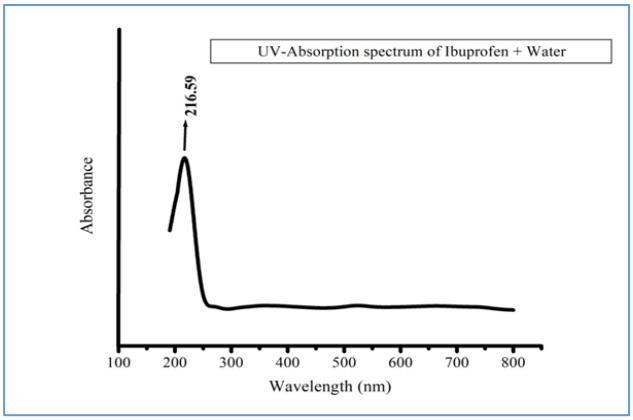

Fig. 3. Experimental Ultraviolet-Visible spectrum of Ibuprofen + water.

Table 3. Quantum chemical parameters of Ibuprofen + water.

Parameters	Ibuprofen +water
SCF energy (Hartree)	-733.30
Total energy (thermal) (Kcal mol^{-1})	206.01
Zero point Vibrational energy (Kcal mol^{-1})	193.88
Rotational Constants (GHz) A	0.81
B	0.23
C	0.20
Dipole moment (Debye) μ	7.85
E_{LUMO}	-0.77eV
E_{HOMO}	-6.67eV
E_{HOMO}- E_{LUMO}	5.90eV
Hardness(η) = 1/2(E_{LUMO}- E_{HOMO})	2.95 eV
Chemical potential(μ) = 1/2(E_{HOMO}+E_{LUMO})	-3.72eV
IE = -E_{HOMO}	6.67 eV
EA=-E_{LUMO}	0.77 eV
Global electro-philicity index(ω) = $\mu^2/2\ \eta$	2.34

SCF: Self-Consistent Field, E_{LUMO}: Energy of the lowest unoccupied molecular orbital, E_{HOMO}: Energy of the highest occupied molecular orbital, IE: Ionization Energy, EA: Electron Affinity.

The molecules having high dipole moments show a speedy response to an electric field. In the present work, the dipole moment of Ibuprofen (7.85 Debye) is found to be higher in comparison to the reported dipole moment of Ibuprofen (2.21 Debye) [12]. The E_{HOMO} profile of Ibuprofen + water represents the massive electron-donating nature of the compound. The E_{HOMO} (-6.67 eV) of Ibuprofen + water is found to be more than the Ibuprofen individual molecule (-6.37 eV) [10]. The computed hardness of ibuprofen + Water is less than the reported hardness of Ibuprofen alone (Table 3).

Comparing the quantum chemical parameters of Ibuprofen + water to individual Ibuprofen reveals that the interacting state is less stable and more reactive than Ibuprofen alone. A molecule's electrophilic, nucleophilic, and reactive nature can be picturized using one more effective tool called the MEP (Molecular Electrostatic Potential) surface. The MEP profile of a molecule of biological importance helps in the prediction of reactive sites as well as drug-receptor interactions [28]. In this work, The MEP surface of Ibuprofen + water (Fig. 4) is computed using the same basis set, i.e., B3LYP/ 6-31 G (d, p).

The colors in the MEP diagram indicate various reactive sites. The red and blue colors signify positive and negative electrostatic potential, while the neutral region is represented by green. In the MEP surface of Ibuprofen + water, positive and negative potentials are observed near hydrogen and oxygen atoms, respectively (Fig. 4).

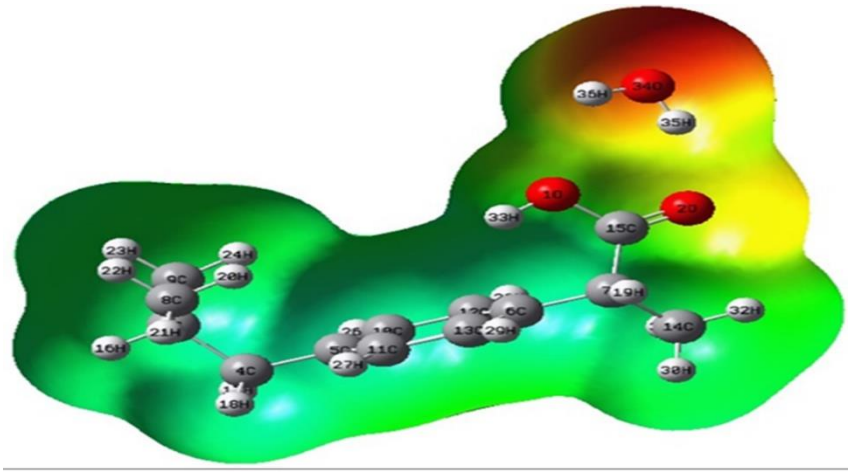

Fig. 4. Molecular Electrostatic Potential surface of Ibuprofen + water.

3.4. *Quantum theory of atom in molecule analysis*

Bader's quantum theory of atoms in molecules is an important tool that has been widely used for studying the nature and strength of hydrogen bonding interactions [29]. The existence of hydrogen bonding depends on the values of electron density (0.002–0.040 a.u.) and its Laplacian (0.024–0.139 a.u.) at BCPs (bond critical points) as suggested by Koch and Popelier [30].

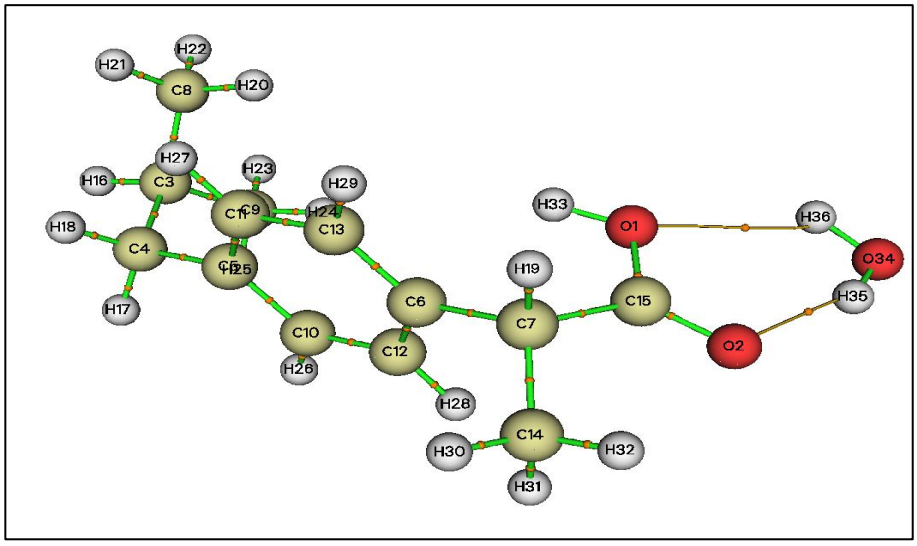

Fig. 5. Molecular graph of Ibuprofen + Water showing bond critical points (small orange spheres represent bond critical points).

The AIM molecular graph of Ibuprofen + Water at BCPs is generated using Multiwfn software [31] and presented in Fig. 5. The topological parameters, such as electron density $\rho(r)$, Laplacian of electron density $\nabla^2(r)$, kinetic energy density G(r), potential energy density V(r) and energy density H(r) evaluated at BCPs of the system (Table 4) reveal that both $\rho(r)$ and $\nabla^2\rho(r)$ values lie inside the boundary values, indicating the presence of intermolecular hydrogen bonding interaction between Ibuprofen and water molecule. Usually, a higher $\rho(r)$ value indicates stronger interaction, and thus, O34−H35···O2 is more intense as compared to O34−H36···O1.

Table 4. Topological parameters of the hydrogen bonds at the bond critical points of Ibuprofen + water.

Hydrogen bonds	ρ_{BCPs}	$\nabla^2 \rho_{BCPs}$	H(r)	G(r)	V(r)
O34−H35···O2	0.0154	0.0686	−0.0002	0.0173	−0.0175
O36−H36···O1	0.0059	0.0297	0.0009	0.0065	−0.0055

ρ_{BCPs}: electron density; $\nabla^2 \rho_{BCPs}$: Laplacian of electron density; H(r): Energy density; G(r): kinetic energy density, V(r): potential energy density.

Moreover, Rozas *et al*. [32] suggest that a strong hydrogen bond with covalent character has $\nabla^2(r) < 0$ and $H(r) < 0$, for a medium hydrogen bond with partially covalent nature: $\nabla^2\rho(r) > 0$ and $H(r) < 0$, and for a weak and electrostatic nature: $\nabla^2\rho(r) > 0$ and $H(r) > 0$. It is obvious from Table 4 that O34−H35···O2 has positive $\rho(r)$ and negative H(r), revealing its moderately strong nature with partially covalent characteristics. On the other hand, with positive $\rho(r)$ and H(r) values, the O34−H36···O1 bond shows its weak and electrostatic nature.

The energy of the hydrogen bonds (E_{bond}) O34−H35···O2 and O34−H36···O1 is calculated using the following formula [33] and found to be 5.49 kcal/mol and 1.72 kcal/mol, respectively.

$$E_{bond} = -\frac{V(r)}{2} \times 627.51 \text{ kcal/mol}$$

The greater bond energy is associated with the shorter bond distance of O34−H35···O2 (2.08 Å) compared to the O34−H36···O1 (2.58 Å) bond, representing stronger intermolecular interaction [34].

3.5. *Spectral analysis*

Spectral analysis is considered a paramount tool to identify compounds and molecules. The spectral signature carries information about the constituent functional groups of a molecule [35]. In the present work, the Raman, SERS (Fig. 6a), and FTIR (Fig. 6b) spectra of the interacting state (Ibuprofen + Water) are computed for the first time and compared with the experimental findings. Furthermore, the wave numbers of Ibuprofen + water are compared with the individual state of Ibuprofen (reported), and the effect of intermolecular hydrogen bonding is discussed. The interacting state is composed of 36 atoms. Therefore, it shows 3N-6, i.e., 103 modes of vibration; however, in this paper, some important vibrational

modes are presented (Table 5). The PED of some modes is also calculated using the VEDA [16].

The organic compounds show O-H stretching mode in the range 3400-3600 cm^{-1} [23]. In ibuprofen + water, the O-H wavenumbers are computed at 3601.06, 3598.70, and 3562.39 cm^{-1} that correspond to the Raman (experimental) and SERS peaks observed at 3501.23 cm^{-1} and 3471.63 cm^{-1} (Fig 6a, Table 5). In the FTIR spectrum (experimental) of ibuprofen + water, the O-H wavenumbers are assigned at 3637.02 and 3428.13 cm^{-1}. The calculated O-H wavenumbers are close to those reported by M. Zhang et al. Both stretchings and symmetric vibration modes are observed in the Ibuprofen + water interacting state.

In organic compounds, the C=O stretching vibration appears at 1550-1850 cm^{-1} [35]. In Ibuprofen + Water, the C=O wavenumber is found at 1755.56 cm^{-1} (PED of 77 %), and its corresponding Raman and FTIR peaks (experimental) are observed at 1733.20 and 1711.25 cm^{-1}, respectively. In the SERS spectrum of the interacting state, the C=O stretching mode is found at 1710.37 cm^{-1}. The C=O wave numbers are detected to be blue-shifted compared to the reported C=O wave numbers of individual Ibuprofen (1765 cm^{-1}) [11].

The C-H stretching vibrations of organic molecules fall in the range of 2900-3100 cm^{-1} [23]. The C-H stretching vibration modes in Ibuprofen + water are calculated between 2900-3100 cm^{-1}. The direct stretching (C-H), symmetric (CH_2), and asymmetric stretching modes are noticed (Table 5) in the experimental and computed vibrational spectrum of the compound. The CH_2 asymmetric vibrations are calculated at 3060.34 and 2929.13 $cm^{-1,}$ and their corresponding experimental FTIR absorptions are found at 3097.12 and 2895.57 cm^{-1}. In the Raman spectrum (experimental) of Ibuprofen + Water, the asymmetric CH_2 vibration is detected at 2912.12 cm^{-1} (Fig. 6a). The symmetric CH_3 vibrational wavenumber is computed at 2936.52 cm^{-1}. The symmetric CH_3 vibration is observed at 2974.53 and 2963.06 cm^{-1} in the experimental SERS and FTIR spectrum of the compound. An overtone band is observed in the compound's experimental and computed spectra, which is assigned to symmetric CH stretching. It is calculated at 3212.20 cm^{-1}.

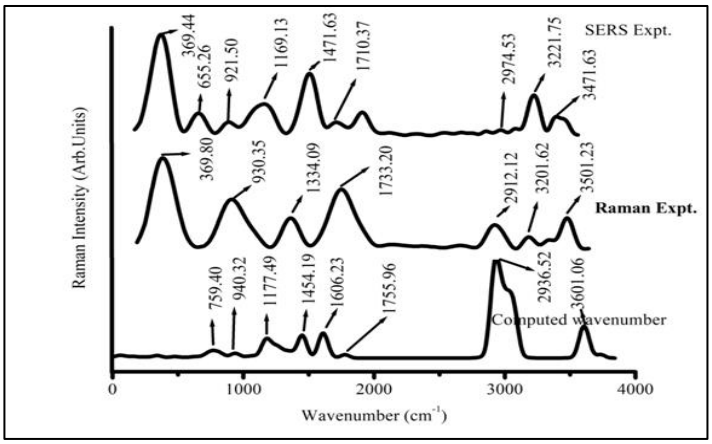

Fig. 6a. Raman and Surface Enhanced Raman spectra of Ibuprofen + water (0-4000 cm^{-1}).

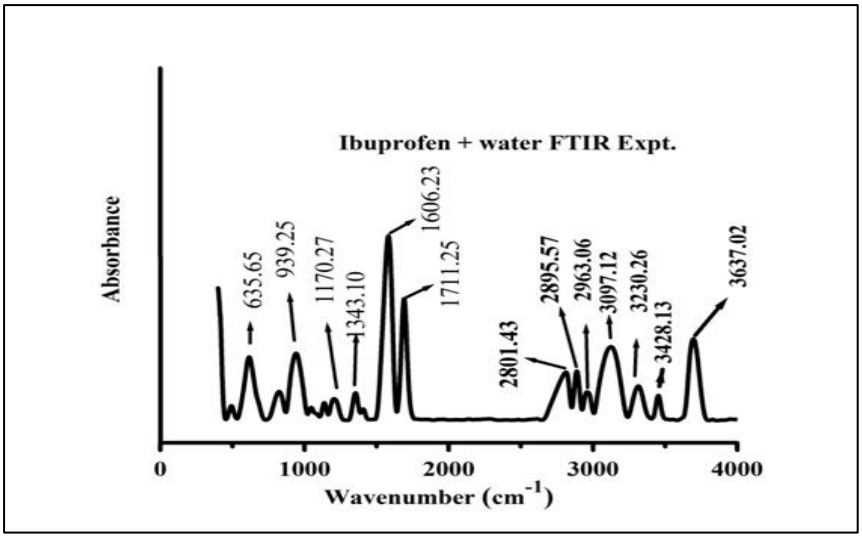

Fig. 6b. Experimental Fourier Transformed Infrared spectrum of Ibuprofen + water (0-4000 cm^{-1}).

Table 5. Vibrational assignments of Ibuprofen + water.

Mode	DFT wave numbers	Raman (Expt.)	SERS (Expt.)	FTIR (Expt.)	Vibrational Assignments
1	3601.06			3637.02	υ (O34-H36) 90
2	3598.70			3428.13	υ (O1-H33) 98
3	3562.39	3501.23	3471.63		$\upsilon_s(O^{34}H_2)$ 88
4	3212.20	3201.62	3221.75	3230.26	$\upsilon_s(C^{11}H_{27})$, $\upsilon_s(C^{12}H_{28})$, 89
5	3060.34			3097.12	$\upsilon_{as}(C^{14}H_3)$ 72
6	2936.52		2974.53	2963.06	$\upsilon_s(C^9H_3)$, $\upsilon_s(C^8H_3)$, 76
7	2929.13	2912.12		2895.57	υ_{as}(C7-H19) 80
8	1755.56	1733.20	1710.37	1711.25	υ (C15=O2) 77
9	1606.23			1606.23	$\delta_{as}(C^{13}H_2)$,
10	1511.12				$\beta_{as}(C^{14}H_3)$ 50
11	1454.19		1471.63		υ(C13=C1),υ(C6=C12),$\beta_{as}(C^7H_3)$,$\beta_{as}(C^8H_3)$
12	1319.24	1334.09		1343.10	β(C^9-C^3-C^4), β(H^{17}-C^4-H^{18}),
13	1177.49		1169.13	1170.27	$\beta_{as}(C^7H_3)$ 45
14	1067.06				υ (C15-O1) 67
15	1001.46				$\beta_s(C^7H_3)$ 52, δ (C6-H9) 14
16	940.32	930.35	921.50	939.25	$\beta_s(C^9H_3)$ 50, $\beta_s(C^8H_3)$, $\beta_s(C^{14}H_3)$40,
17	865.42				δ (C12-H28), δ (C8-H21), δ (C14-H32) 52
18	802.71				β(H^{33}-O^1-C^{15}) 67, β(H^{35}-O^2-C^{15})
19	659.40		655.26	635.65	β(H^{27}-C^{11}-C^5), β(H^{28}-C^{12}-C^6) 40,
20	398.05	369.80	369.44		β(C^4-C^3-H^{16}) 43, β(C^9-C^8 -C^4), γ(C^5-C^4-C^3-H^{16}), τ (C^6-C^7-C^{15}-O2), τ (C^6-C^7-C^{15}-O1)

ν – stretching, ν_s – symmetric stretching, ν_{as} – asymmetric stretching, τ – torsion, β – in-plane bending, γ – out-of-plane bending.

In the FTIR, Raman (experimental), and SERS spectra of the compound, the overtone band is observed at 3230.26, 3201.62, and 3221.75 cm^{-1}, respectively (Table 5). The

overtone/combinational mode band is found close to the reported wavenumber of Ibuprofen, i.e., 3215 cm^{-1} [11]. The in-plane CH_3 bending modes with different PED distributions are listed in Table 5. The CH_3 bending mode is found at 940.32 cm^{-1} in the computed spectrum of Ibuprofen + Water (Table 5), while it is observed at 930.95 and 939.25 cm^{-1} in the Raman, SERS, and FTIR (experimental) spectra of the physical mixture (Ibuprofen + Water). The C-O stretching wavenumber is computed at 1067.06 cm^{-1}, which is decreased compared to the reported C-O stretching of Ibuprofen. The decreased C-O stretching wave number in Ibuprofen + water could be attributed to the expansion of the C-O bond length compared to the individual C-O bond length of Ibuprofen (Table 5). Other vibrations found in the vibrational spectra of Ibuprofen + water include deformation, wagging, out-of-plane bending, in-plane bending, and torsion modes (Table 5). However, only some selected vibrational modes are discussed here. The low wavenumber modes are found to be mixed with such vibrations.

4. Conclusion

The DFT and spectroscopic study on interactions of Ibuprofen with Water are carried out using the B3LYP/ 6-31G (d, p) level of theory. The computed vibrational spectra (Raman, SERS, and FTIR) correlate well with the compound's experimental spectra. The computed quantum chemical descriptors of the interacting state and their comparison with the individual state infer the bioactivity of the compound. The compound's HOMO-LUMO gap (5.90 eV) is close to the energy gap obtained from its UV-Vis spectrum. Two intermolecular hydrogen bonds, O34-H36---O1 (2.58 Å) and O34-H35---O2 (2.08 Å), are observed between Ibuprofen and a water molecule, and the transfer of charges through the newly formed hydrogen bonds are validated from NBO analysis of the compound. AIM analysis reveals the existence of a moderate (O34−H35···O2) and a weak hydrogen bonding (O34−H36···O1) having bond energies of 5.49 kcal/mol and 1.72 kcal/mol, respectively, between the two monomers. The newly formed intermolecular hydrogen bonds are responsible for the deviation in bond parameters, spectral shift, and change in quantum chemical parameters of the compound state when compared to individual Ibuprofen.

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