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Interaction Energies and Raman Shifts of Hemoglobin with Aspirin, Paracetamol, and Ibuprofen: A DFT Study

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Abstract

The interaction of deoxyhemoglobin with antipyretics, including aspirin, paracetamol, and ibuprofen, is investigated using density functional theory with dispersion correction. The formed molecules, after the interaction, are of approximately 1.5-nanometer length, within the nanoscale range. Interaction with water and O_2 molecules is included for comparison. Objective: The discussion includes the thermodynamic interaction energies: Gibbs free energy, enthalpy, and entropy, in addition to Raman shifts. The interaction distance and vibrational-induced lines due to interaction are discussed. Results: The two strongest interactions include the interaction of the Fe ion center in deoxyhemoglobin with the carbonyl (C=O) and hydroxy group (OH) in antipyretics. Results show that the interaction distance of the carbonyl group in antipyretics is shorter than the hydroxy group. All interactions of Gibbs energies are less than O_2 interaction with ibuprofen, the nearest to O_2. Results are in good agreement with experimental results. Conclusions: The importance of this work is that: depending on attachment energy and Raman shifts, the antipyretics can reach different organs with different speeds and different delivered quantities.

Keywords: Hemoglobin; Density functional theory; Aspirin; Paracetamol; Ibuprofen; Dispersion correction.

Full length article *Corresponding Author, e-mail: mudarahmed3@yahoo.com

1. Introduction

Antipyretics, including aspirin, paracetamol, ibuprofen, and others, are an important part of daily medications. They are consumed in huge quantities all around the world. Every one of these antipyretics has its own molecular structure that determines exactly how these antipyretics interact with surrounding molecules and structures. Aspirin is known to have fever and inflammation reduction effects [1,2]. It also has the effect of thinning blood and some cancer reduction effects [3,4]. Taking aspirin every day has become a habit for many people to reduce mortality related or not related to COVID-19 [5].

Paracetamol is the most prescribed medication for pain and fever [6], especially after operations [7]. However, higher doses of paracetamol may have negative effects on hemoglobin and liver, etc. [8]. Paracetamol is inferior to ibuprofen in reducing fever which might be interpreted from its electronic structure, as can be seen in the theory and results section in the present work.

Ibuprofen in smaller quantities is more effective than paracetamol when it comes to fever and pain [9,10]. Ibuprofen also has anti-inflammation effects that are weaker than other antipyretics [11]. The stronger effects of ibuprofen can be understood from a comparison of its molecular structure and interactions, as we shall see in the present work.

The reduction of hemoglobin through interaction with antipyretics is an observed phenomenon [12]. Hemoglobin not only transports oxygen to the human body but also many other materials, such as antipyretics. The part that is responsible for such transfer is the Fe ion in the deoxyhemoglobin molecule. Fe ion has the highest positive charge in the deoxyhemoglobin molecule that attracts negative parts of other molecules, as we shall see later.

Molecular calculations with varying degrees of sophistication can be made depending on the number of atoms in the system. With a higher number of atoms, semiempirical methods are more practical in terms of the computational time needed to perform such calculations [13,14]. As the number of atoms decreases, density functional theory (DFT) becomes the obvious choice with varying sophistication depending on the number of basis states used to describe the system [15]. Unfortunately, the number of researches that apply DFT to hemoglobin interactions is limited [16–18]. The deficiency in such kinds of calculations is one of our motivations for performing the present work. The interaction of hemoglobin M with tyrosine is discussed in reference [18]. The interaction of hemoglobin with environmental and toxic gases is discussed in reference [17]. Reference [17] is the only reference that applies thermal corrections. However, no reference applies dispersion corrections, which is the case in the present work.

In the present work, the interaction of deoxyhemoglobin with antipyretics (aspirin, paracetamol, and ibuprofen) is investigated. The investigation includes the attachment distance, thermodynamic attachment energies (Gibbs free energy, enthalpy, and entropy), and vibrational Raman shifts.

Methods/Theory

When dealing with deoxyhemoglobin interactions that contain Fe ions, one must be careful in selecting the DFT method and basis sets that results in matching with experimental findings. Deoxyhemoglobin has experimental paramagnetic behavior that indicates deoxyhemoglobin is in the triplet state [19,20]. Oxygen molecules are also in the triplet state with paramagnetic behavior [21]. However, the interaction between oxygen molecules and deoxyhemoglobin ends in oxyhemoglobin, which has a singlet state and a diamagnetic behavior [22]. This combination of states cannot be satisfied easily with all kinds of methods and basis in DFT calculations. PBE method with 6-311G** results in the exact triplet ground state lower than the singlet state. This method and basis are used throughout the present work for all calculations using the Gaussian program [23]. Dispersion corrections are added to present calculations because of their importance in attachment connections [24]. GD3BJ dispersion correction is used [25]. Vibrational Raman shifts are also calculated with a scale factor of 0.991 [26].

Fig. 1 shows the deoxyhemoglobin molecule, including charges on every atom, using the natural bond order (NBO) method. As we can see from this figure, the highest charge is on the Fe ion with 1.326 atomic units of charge (au). As a result, the Fe ion will be the center of attraction to the negative part in other molecules. Fig. 2 shows the aspirin molecule, including charges on every atom, using the NBO method. As we can see from Fig. 2, the highest negative charges are on the oxygen ions in hydroxyl and carbonyl functional groups. As a result, we expect that the attachment of aspirin to the deoxyhemoglobin molecule is in one of these groups. Fig. 3 shows the paracetamol molecule, including charges on every atom, using the NBO method. The main difference between aspirin and paracetamol is that hydroxyl and carbonyl functional groups in paracetamol are on the two different ends of paracetamol that giving them more freedom to connect to deoxyhemoglobin with the angle that can satisfy higher connecting energy. However, aspirin has its hydroxyl and carbonyl functional groups near the middle of the molecule, which reduces the attachment angle. Finally, Fig. 4 shows an ibuprofen molecule in which hydroxyl and carbonyl functional groups are on one side of the end of the molecule. Depending on NBO calculations, thermodynamic energies (Gibbs free energy, enthalpy, and entropy) and vibrational spectra will be manifested in the results and discussion section.

Deoxyhemoglobin ($C_{25}H_{18}FeN_6O_2$) interacts with aspirin ($C_9H_8O_4$), forming a molecule of approximately 1.5-nanometer length as in the following equation:

$$C_{25}H_{18}FeN_6O_2 + C_9H_8O_4 \rightarrow [C_{25}H_{18}FeN_6O_2\text{---}C_9H_8O_4]^{\ddagger} \quad (1)$$

The attachment is through the weak van der Walls force between either the hydroxyl or carbonyl groups in aspirin and the Fe ion in deoxyhemoglobin. The double dagger (‡) represents the transition state that transports aspirin before its delivery to various parts of the human body. The weak bond is between the Fe ion and either the oxygen in the carbonyl group (Fig. 5) or the oxygen in the hydroxyl group.

The reaction rate between aspirin and deoxyhemoglobin in Eq. 1 can be given by the equation [27]:

$$\frac{d[C_{25}H_{18}FeN_6O_2]}{dt} = -C[C_9H_8O_4][C_{25}H_{18}FeN_6O_2]k(T). \quad (2)$$

$[C_9H_8O_4]$ and $[C_{25}H_{18}FeN_6O_2]$ are the concentration of aspirin and deoxyhemoglobin, respectively. C is the experimental reaction constant. k(T) is the reaction rate constant that is given by:

$$k(T) = T \exp^{\left(\frac{-\Delta G}{k_B T}\right)}. \quad (3)$$

T is the temperature, ΔG is the change in Gibbs energy, and k_B is the Boltzmann constant. These equations are useful to give some interpretations in the following results section.

Results and discussions

Table 1 shows the distances between the Fe ion in deoxyhemoglobin and carbonyl and hydroxyl in aspirin, paracetamol, and ibuprofen. As we can see from Table 1, the distances between carbonyl are shorter than that of hydroxyl. The reason is that the hydrogen in the hydroxyl group has a repulsive positive charge force with that of Fe. The results are also compared with the distances of the interaction of O_2 and H_2O with deoxyhemoglobin. The bond length of O_2 with deoxyhemoglobin is 1.755 Å which is slightly less than the lower end of available experimental data (1.77 Å) [28]. The interaction with H_2O shows a bond length of (2.081 Å) which is higher than all carbonyl interactions but less than all hydroxyl interactions. H_2O is the most available molecule in blood, and it may hinder the interaction of deoxyhemoglobin with some molecules, as we shall see in Table 2.

Table 2 shows the thermodynamic interaction energies (Gibbs free energy, enthalpy, and entropy) and Raman shifts. Deoxyhemoglobin (without interaction) is taken as the reference point. All energies have negative values so that they have a high reaction rate, as in Eq. 3. The biggest change in Gibbs free energy (ΔG) is for O_2 (-0.427 eV) followed by ibuprofen (-0.407 eV) in the case of carbonyl attachment (C=O). In addition, these are the only two Gibbs free energies that are higher than H_2O Gibbs free energy (-0.337 eV). The high Gibbs free energy of ibuprofen (that is nearly equal to oxygen) might explain the higher activity of ibuprofen relative to aspirin or paracetamol. The high Gibbs free energy of ibuprofen can be attributed to its high number of atoms that can attach to deoxyhemoglobin at several points, which is not the case with aspirin or paracetamol. The second column that contains the change in enthalpy energy (ΔH) represents the real heat that is absorbed by the surrounding (exothermic reaction). In the case of enthalpy change, ibuprofen and paracetamol are the highest energy producers that are followed by O_2 interaction with deoxyhemoglobin. On the other hand, the entropy energy (ΔST) reflects the effect of the number of atoms in the interacting molecule with deoxyhemoglobin in a more obvious way. The highest entropy energy is for ibuprofen, followed by aspirin, paracetamol, H_2O, and O_2, with some changes between carbonyl and hydroxyl groups. The three quantities (Gibbs free energy, enthalpy, and entropy) are connected by the following equation:

$$\Delta G = \Delta H - \Delta ST \quad (4)$$

This equation is obeyed by quantities in Table 2 with some tolerance due to the limited number of digits for numbers in the table. Experimental values that match the findings of Table 2 are not available in the literature. However, the reaction of all contents of human hemoglobin with ibuprofen (and not only deoxyhemoglobin as in the present case) is available [29].

The last column in Table 2 shows Raman shifts with respect to the deoxyhemoglobin Raman spectrum in Fig. 6. The present last calculated vibration in deoxyhemoglobin before the frequency gap is at 1597 cm^{-1} as in Fig. 6. A low-intensity frequency line in the frequency gap is usually neglected. The experimental frequency line that matches the theoretical 1597 cm^{-1} is at 1606 cm^{-1} [30]. The present theoretical Raman shift for oxygen is at 32 cm^{-1} compared to the experimental 34 cm^{-1} [30]. The Raman shift serves as an indicator of the kind of antipyretic that exists in the blood. The Raman shifts of C=O groups are higher than that of OH groups. In addition, ibuprofen Raman shifts are higher than aspirin and paracetamol. However, another difference between the Raman shifts of C=O groups and OH groups in Figs. 7 and 8 for aspirin. Both deoxyhemoglobin and aspirin have C=O groups in their structure, as we can see in Fig. 5. When aspirin is attached to deoxyhemoglobin through the C=O group, the vibrations of C=O in the final molecule (in the attachment region) are suppressed, and the frequency gap continues to have a small intensity in the 1700-1800 cm^{-1} region as in Fig. 7. The 1700-1800 cm^{-1} region peaks are found experimentally in aspirin, paracetamol, and ibuprofen [31–33]. However, if the attachment is with the OH group, the Raman spectra of the combined molecule will have a non-negligible intensity of C=O in the 1700-1800 cm^{-1} region, as in Fig. 8. This difference can be used to discriminate between C=O and OH group attachments. This is also applied to paracetamol and ibuprofen.

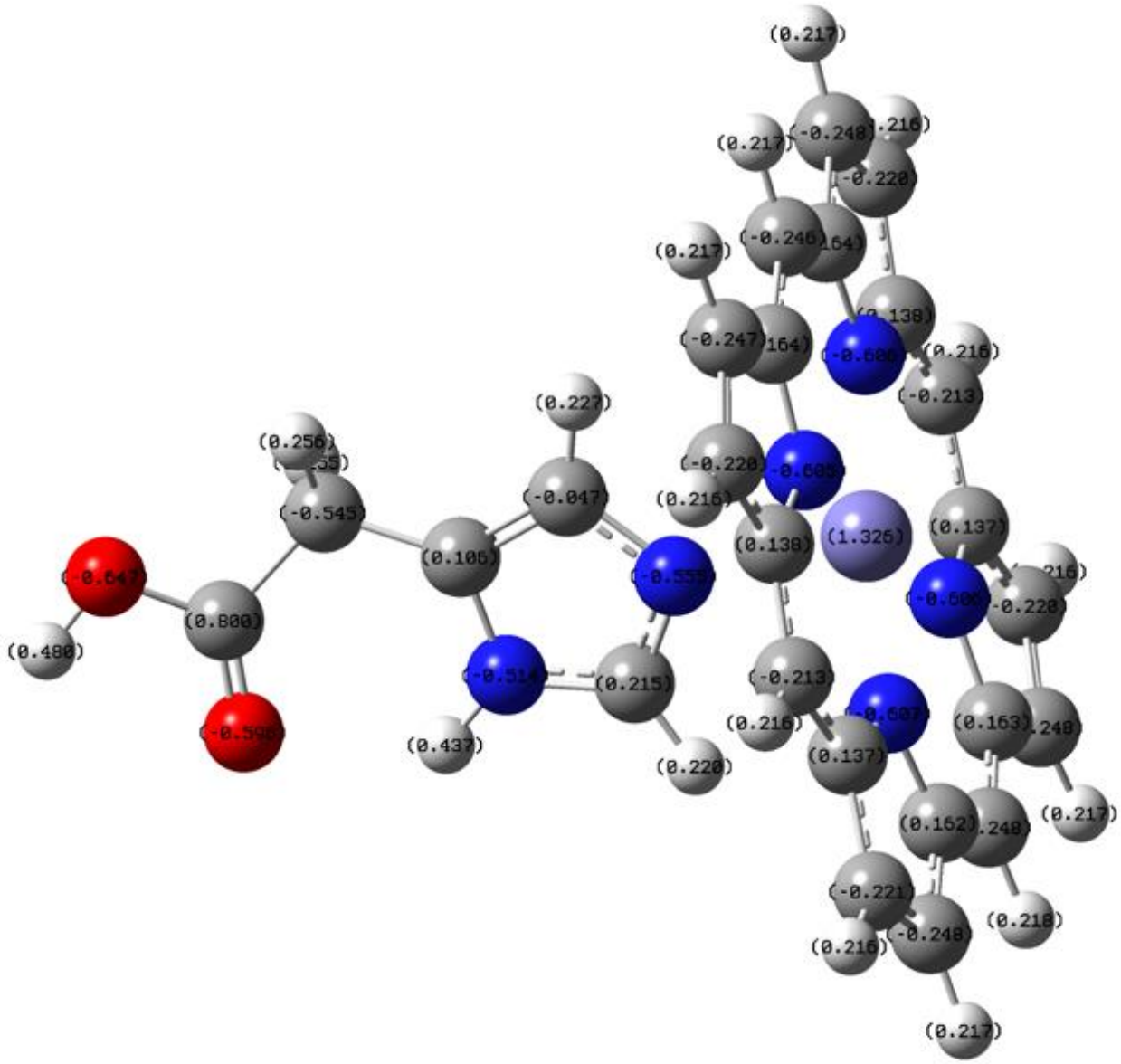

Fig. 1. Deoxyhemoglobin with charges on each atom using the NBO method. White, gray, blue, red, and purple balls represent hydrogen, carbon, nitrogen, oxygen, and iron atoms, respectively.

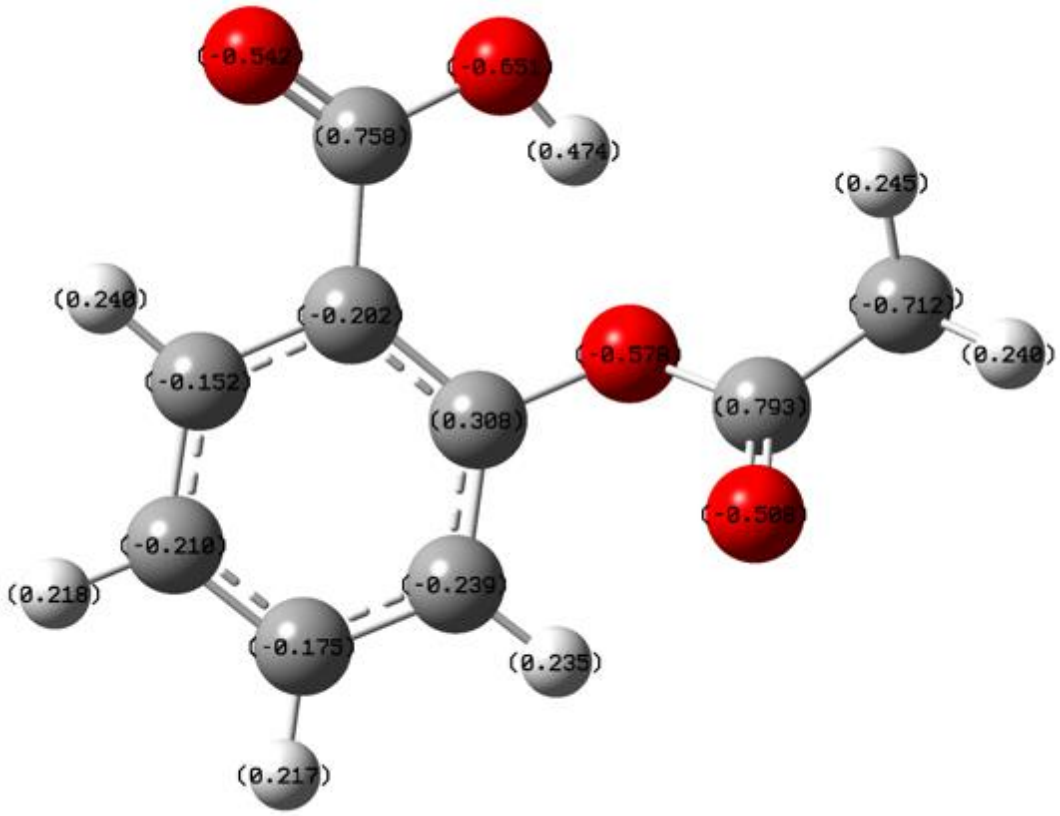

Fig. 2. Aspirin molecule with charges on each atom using the NBO method.

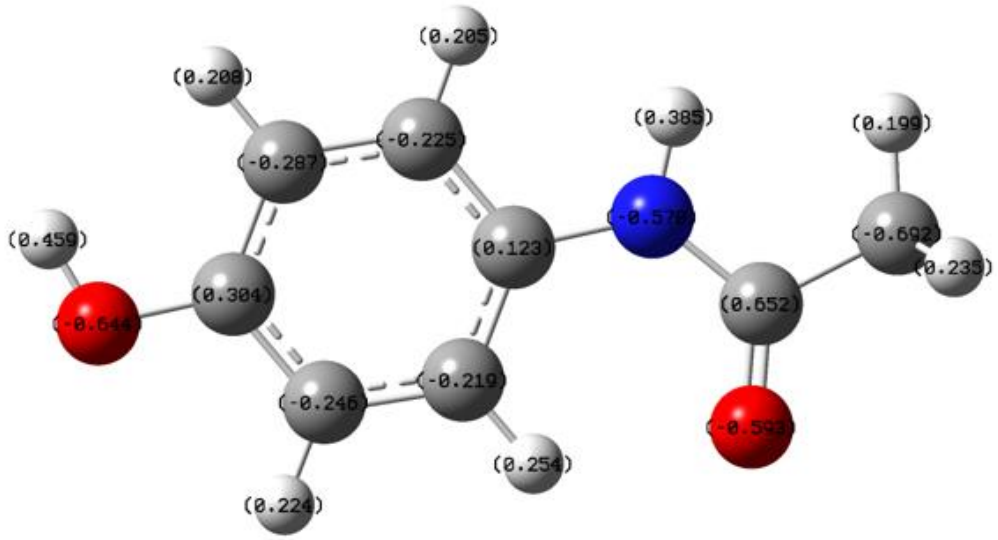

Fig. 3. Paracetamol molecule with charges on each atom using the NBO method.

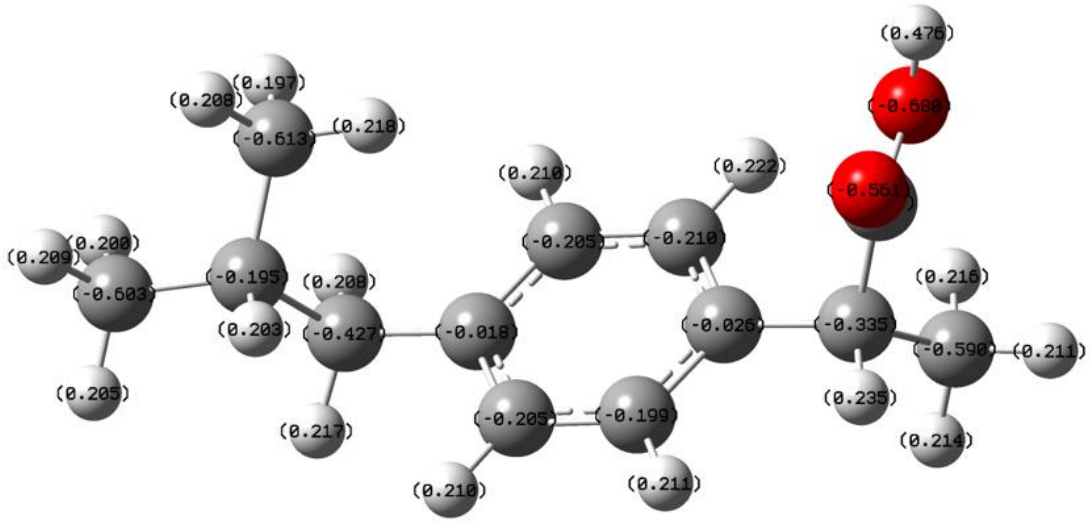

Fig. 4. Ibuprofen molecule with charges on each atom using the NBO method.

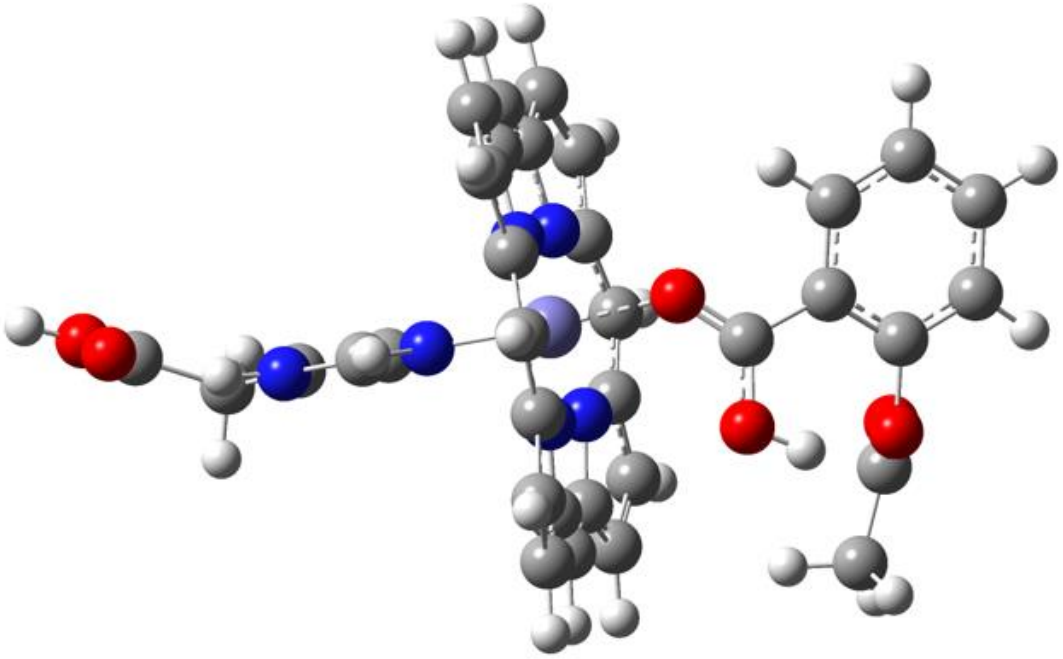

Fig. 5. The attachment of the C=O group in aspirin to deoxyhemoglobin (dashed single bond).

Table 1. distances between deoxyhemoglobin and C=O and OH groups in antipyretic molecules. Distances between deoxyhemoglobin and O_2 and H_2O are added for comparison.

Interaction	Distance (Å) (C=O)	Distance (Å) (OH)
Deoxyhemoglobin + aspirin	1.990	2.423
Deoxyhemoglobin + paracetamol	1.999	2.402
Deoxyhemoglobin + ibuprofen	2.011	2.456
Deoxyhemoglobin + O_2	1.755	
Deoxyhemoglobin + H_2O	2.081	

Table 2. Thermodynamic energies (Gibbs free energy, enthalpy, and entropy) of the attachment of antipyretics to deoxyhemoglobin. O_2 and H_2O energies are added for comparison. The last column represents the Raman shift of the last Raman line before the frequency gap. All quantities are taken with reference to oxyhemoglobin value.

Interaction	ΔG (eV)	ΔH (eV)	ΔST (eV)	Δν (cm^{-1})
Deoxyhemoglobin	0	0	0	0
Deoxyhemoglobin + aspirin (C=O)	-0.178	-0.882	-0.704	54
Deoxyhemoglobin + aspirin (OH)	-0.181	-0.959	-0.778	20
Deoxyhemoglobin + paracetamol (C=O)	-0.309	-1.012	-0.703	35
Deoxyhemoglobin + paracetamol (OH)	-0.244	-0.908	-0.664	8
Deoxyhemoglobin + ibuprofen (C=O)	-0.407	-1.184	-0.777	58
Deoxyhemoglobin + ibuprofen (OH)	-0.151	-0.869	-0.717	22
Deoxyhemoglobin + O_2	-0.427	-0.976	-0.548	32
Deoxyhemoglobin + H_2O	-0.337	-0.929	-0.593	20

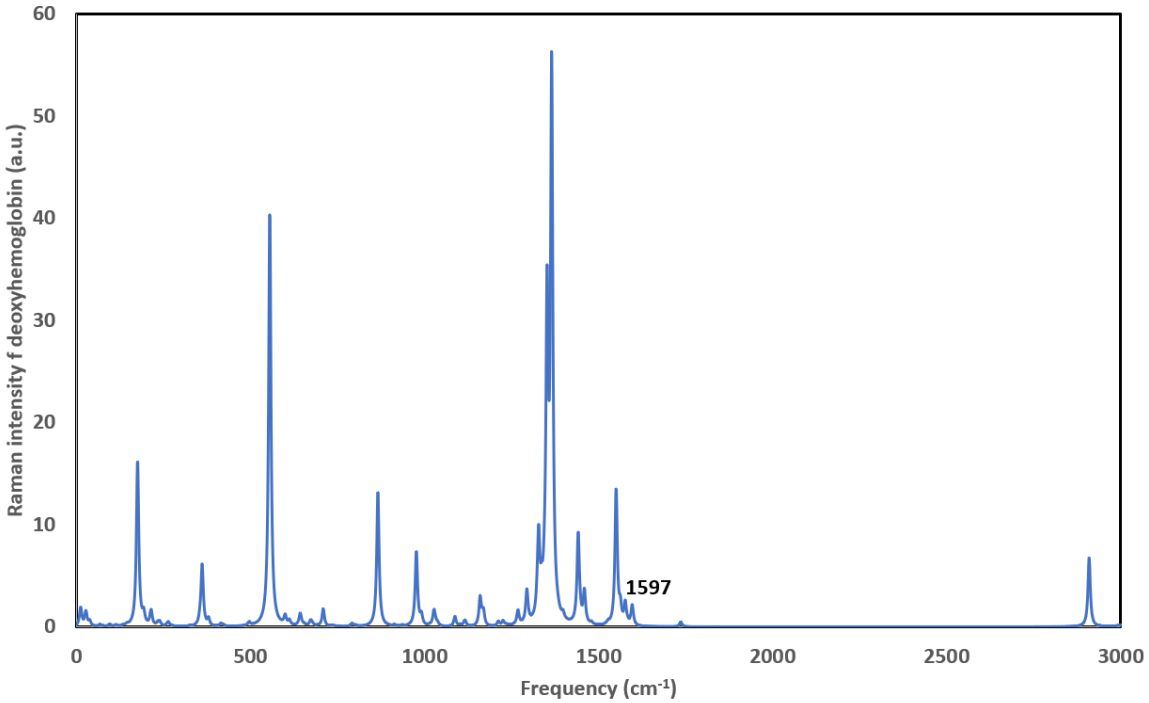

Fig. 6. Raman intensity of deoxyhemoglobin in arbitrary units (a.u.). The highest frequency before the frequency gap is indicated.

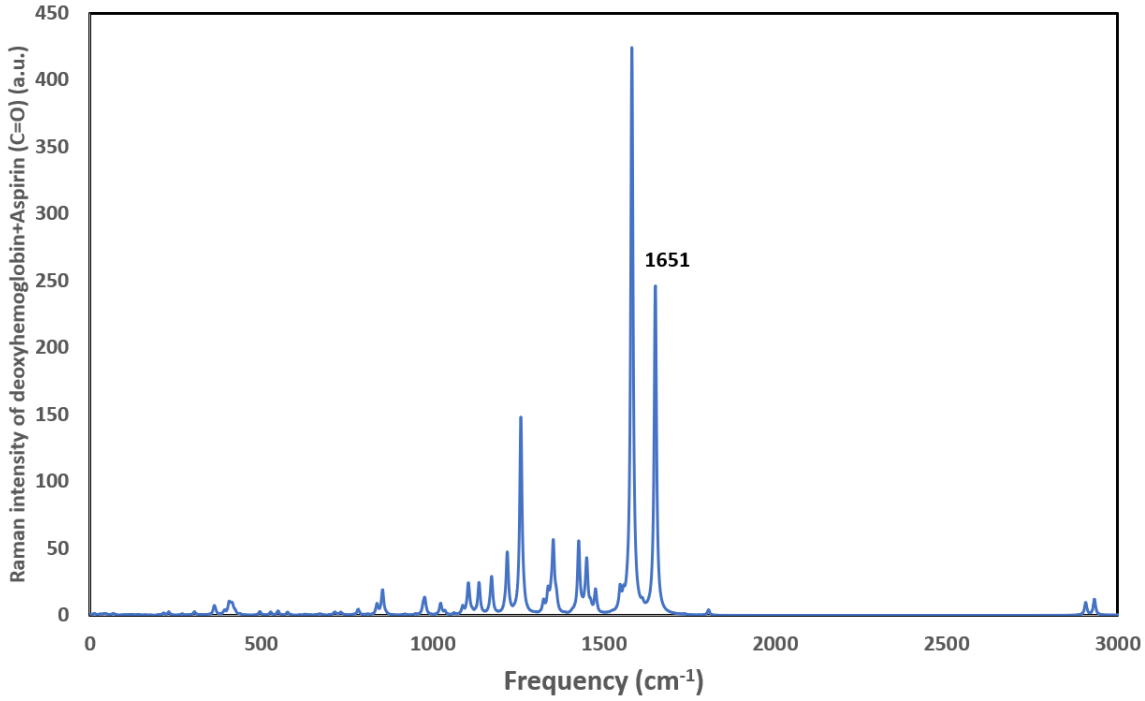

Fig. 7. Raman intensity of deoxyhemoglobin + aspirin (C=O group attachment) in arbitrary units (a.u.). The highest frequency before the frequency gap is indicated.

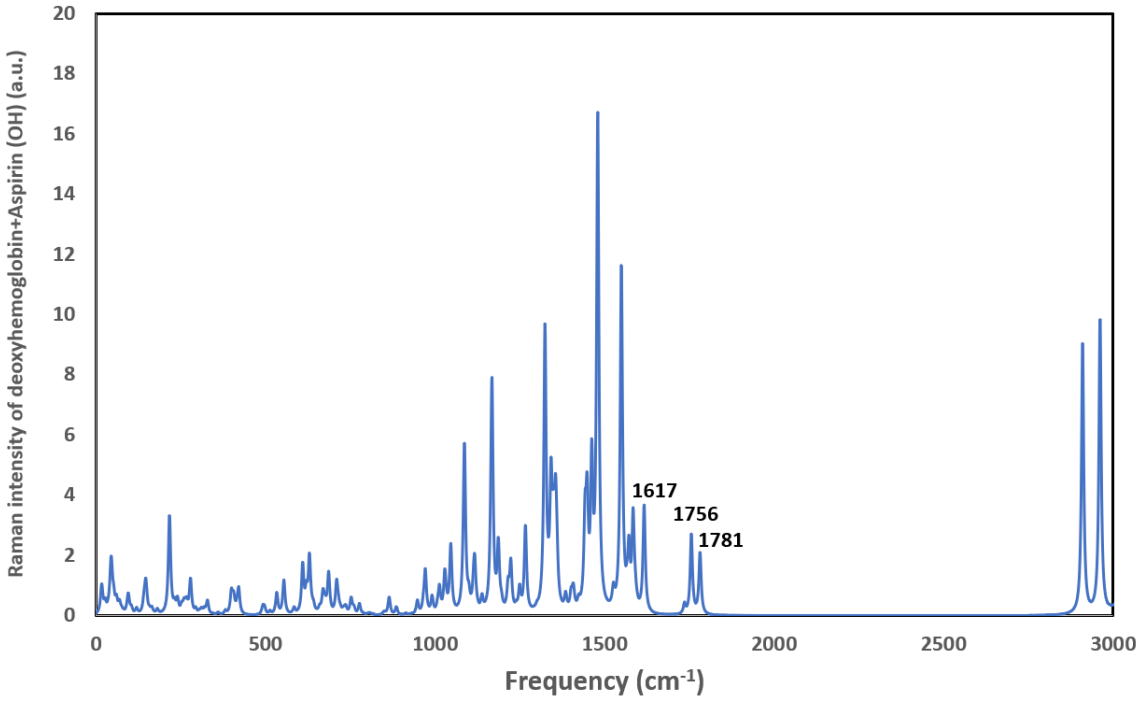

Fig. 8. Raman intensity of deoxyhemoglobin + aspirin (OH group attachment) in arbitrary units (a.u.). The highest frequency before the frequency gap is indicated.

We can summarize the above discussion by the following: The interaction between deoxyhemoglobin and antipyretics is mainly by attaching oxygen or oxygen groups in the antipyretics to the Fe ion in the deoxyhemoglobin. This is confirmed by the NBO calculations that investigate the highest positive and negative charges on both of the two interacting molecules. The calculated thermodynamic energies can discriminate the antipyretics that can reach more deeply into tissues which turned out to be ibuprofen. This discrimination is also reflected in the shift or Raman line before the frequency gap. The transition state theory can be applied to calculate the reaction rate between aspirin and deoxyhemoglobin or any other molecule. However, since no experimental data is available, this part is postponed to future work.

4. Conclusions

The interaction of antipyretics (aspirin, paracetamol, and ibuprofen) with hemoglobin, represented by its active part, deoxyhemoglobin, is performed. Results show that the interaction is mainly between Fe ions in deoxyhemoglobin and C=O or OH groups in antipyretics. The reactions are compared with that of O_2 and H_2O to manifest the reaction strength compared with commonly known reactions. The reaction distances between carbonyl (C=O group) are shorter than that of hydroxyl (OH group). The highest Gibbs free energy interaction for antipyretics is for ibuprofen, followed by paracetamol and aspirin. The interaction of ibuprofen (C=O group) is comparable to that of oxygen, and it can replace H_2O connected to deoxyhemoglobin. The Raman spectra of the interaction of antipyretics with deoxyhemoglobin can be used to distinguish these antipyretics from each other. Further, it can distinguish between the C=O and OH groups' interaction by the intensity of the C=O group vibration at the 1700-1800 cm^{-1} region.

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