International Journal of Chemical and Biochemical Sciences
(ISSN 2226-9614)

Journal Home page: www.iscientific.org/Journal.html

Hemoglobin interaction with amoxicillin, cefepime, and penicillin G: A DFT and Raman shift Study

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Abstract

The interaction of hemoglobin represented by its active part deoxyhemoglobin with antibiotics, including amoxicillin, cefepime, and penicillin G, is investigated using dispersion corrected density functional theory. The interaction is in its strongest bonding between Fe in deoxyhemoglobin and O in antibiotics. Bonding length, thermodynamic quantities such as Gibbs free energy, enthalpy, and entropy of reaction are evaluated. Two positions of interaction are chosen for each antibiotic to illustrate the bonding strength with deoxyhemoglobin. Results show that the interaction bonding length of Fe-O is 2.005-2.378 Å near the high end of Fe-O bond theoretical and experimental values. All Gibbs free energy, enthalpy, and entropy of reaction are negative so that they are all exergonic, exothermic, with decreased disorder reaction. Raman spectral shift of the interaction for the last peak before the frequency gap is always positive with respect to deoxyhemoglobin. This shift depends on the kind of antibiotic and the position of interaction in the antibiotic.

Keywords: Haemoglobin; Density functional theory; Amoxicillin; Cefepime; Penicillin; Dispersion correction.

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1. Introduction

Antibiotics are one of the most used medications for humans. The use of antibiotics is in many times the only choice to save life. Although antibiotics effects were known from antient civilizations, their use was revolutionized in the twentieth century by Alexander Fleming by the discovery of penicillin in 1928. New antibiotics are continuously manufactured and improved [1–3]. Three antibiotics are considered in the present work namely: amoxicillin, cefepime, and penicillin. These antibiotics belong to different classes. Penicillin is the first antibiotic that was in wide use from a long time ago. It is still in use although some bacteria developed resistance to it [4,5]. Penicillin includes many kinds of purified antibiotics from which we choose penicillin G to discuss in the present work. Amoxicillin was discovered in 1958 by the Beecham Group. It is widely used especially for children [6,7]. Cefepime is a fourth generation of cephalosporin antibiotics. Its bacterial spectrum is wider than the previous two antibiotics. It is reserved for use in severe infections for bacteria that developed resistance to older antibiotics [8,9]. Density functional theory (DFT) is a computational method that is widely used to solve quantum mechanical problems in atoms, molecules, chemistry, biology, solid state, and even nuclear physics [10–12]. Dispersion corrections are important in many cases in density functional calculations including biomolecules [13,14] as in the present work. Hemoglobin (Hb) is a human protein that is responsible mainly to transport oxygen from lungs to body tissues. Hb can also transport other materials such as CO_2 from body tissues to lungs. When Hb is oxygenated, it is called oxyhemoglobin (oxyHb), and when losses its oxygen, it is called deoxyhemoglobin (deoxyHb). Iron (Fe) is the vital ingredient that allows such transport. In the present work, we shall use DFT to simulate the reaction of deoxyHb with the three antibiotics amoxicillin, cefepime, and penicillin. The simulation includes bond length, thermodynamic interaction energy

between a deoxyHb and the three mentioned antibiotics including Gibbs free energy, enthalpy, and entropy. Two positions in each antibiotic are chosen that illustrate the strong attraction between the antibiotic and deoxyHb. Raman spectra and shifts due to the interaction between deoxyHb and antibiotics is illustrated.

2. Materials and Methods

Molecular orbital theory is the starting point in much research that aims to simulate problems in physics, chemistry, and biology [11,15,16]. DFT is the most accepted current method in molecular orbital theory. This theory is continuously refined and corrected to better match with experimental findings. Some corrections to DFT proved their importance such as dispersion corrections [17–19]. Some methods in DFT gained exceptional popularity such as B3LYP method [20–22]. However, even when we use the best available methods in molecular orbital theory, problems continue to appear as we proceed in calculations. As an example, basis functions must be chosen carefully to match the size of the considered system of atoms or molecules. In the present case we are considering the interaction of deoxyHb ($C_{25}H_{18}FeN_6O_2$) [11] with amoxicillin ($C_{16}H_{19}N_3O_5S$) [23], cefepime ($C_{19}H_{24}N_6O_5S_2$) [24], and penicillin G ($C_{16}H_{18}N_2O_4S$) [25] as in figures 1-3. In figures 1-3, deoxyHb is the molecule that is at the left side of the figures while the antibiotics are at the right side of these figures. DeoxyHb consists of two parts, porphyrin molecule with an Fe ion in its center and 4-Imidazole acetate axial part that is also connected to the Fe ion at the center of porphyrin molecule. The investigated antibiotics amoxicillin, cefepime, and penicillin all contains one or two sulfur (S) atoms. In addition, the antibiotics also contain four or five oxygen (O) atoms. Gaussian 09 program is used to perform density functional theory calculations for the interaction between deoxyHb with antibiotics [26]. The number of atoms in the interaction cases is around 100 atoms. Initially we used 6-311G** basis to perform calculations. The size of memory required to perform such calculations exceeded the Gaussian 09 program allowed memory of 2 Gb. As a result, we were obliged to use 6-31G basis for the present calculations. 6-31G basis are used whenever such high number of atoms are encountered [27,28].

The interaction between deoxyHb and antibiotics such as amoxicillin can be written as follows:

$$C_{25}H_{18}FeN_6O_2 + C_{16}H_{19}N_3O_5S \rightarrow [C_{25}H_{18}FeN_6O_2\text{---}C_{16}H_{19}N_3O_5S]^{\ddagger} \quad (1)$$

In Eq. (1) the square brackets and double-dagger symbol represent a transition state that are in equilibrium with the reactants. The bonding usually occurs between the Fe ion in deoxyHb and the carbonyl (C=O) or hydroxy (OH) groups in antibiotics. Fe and O ions in deoxyHb and antibiotics have the highest positive and negative charges respectively. At a given temperature (T), the reaction rate of Eq. (1) can be given by [29,30]:

$$\frac{d[C_{25}H_{18}FeN_6O_2]}{dt} = -C[C_{16}H_{19}N_3O_5S][C_{25}H_{18}FeN_6O_2]k(T). \quad (2)$$

In the above equation $[C_{25}H_{18}FeN_6O_2]$ and $[C_{16}H_{19}N_3O_5S]$ are the concentration of deoxyHb and amoxicillin respectively. C is an experimental fitting constant and k(T) is the reaction rate constant which is given by:

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

In the above equation ΔG is the change in Gibbs energy of the reaction, and k_B is the Boltzmann constant. From Equations 2, and 3 we can see that the reaction rate depends on temperature and concentration of the reactants in addition to the change in Gibbs free energy. If the value of ΔG is positive (endergonic) the reaction will be weak and if it is negative (exergonic) the reaction will increase exponentially. Dispersion corrections are important for the present calculations because of weak van der Waals forces between the interacting molecules. GD3BJ dispersion correction version are added [31]. Vibrational Raman shifts are calculated with the use of the usual scale factor of 0.962 suitable for the kind of used method and basis set [32].

3. Results and discussion

DeoxyHb is known to be paramagnetic with weak attracting force to magnets [33]. Being paramagnetic means that its ground state has uncoupled electrons. In our theoretical results, DeoxyHb triplet ground state (two uncoupled electrons) is lower than its singlet state (no uncoupled electrons) which agrees with experiment. In addition, experimental last peak before the frequency gap is at 1606 cm^{-1} [34]. This value is in good agreement with our theoretical result at 1661 cm^{-1} as shown in figure 4. Table 1 shows the bond lengths between Fe in deoxyHb and two chosen points in every antibiotic. The bond lengths ranges between 2.005 to 2.378 Å. These values are near or greater than previous theoretical or experimental Fe-O bond lengths [35,36]. The highest Fe-O bond length in Table 1 is for penicillin as shown in figure 2. This long bond length is due to the connection to the hydroxy (OH) group in penicillin. Positive proton charge in hydroxy group repulses the positive charge in Fe ion that elongate the bond length. This is not the case for the oxygen in carbonyl group (C=O) in which the carbon atom is far enough from the Fe ion as in figure 1 and figure 3.

Table 2 shows thermodynamic interaction energies between deoxyHb and antibiotics. The energies are evaluated at two different points for each antibiotic (p1 and p2). The thermodynamic energies Gibbs (ΔG), enthalpy ΔH, and entropy (ΔST) energies are connected through the equation:

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

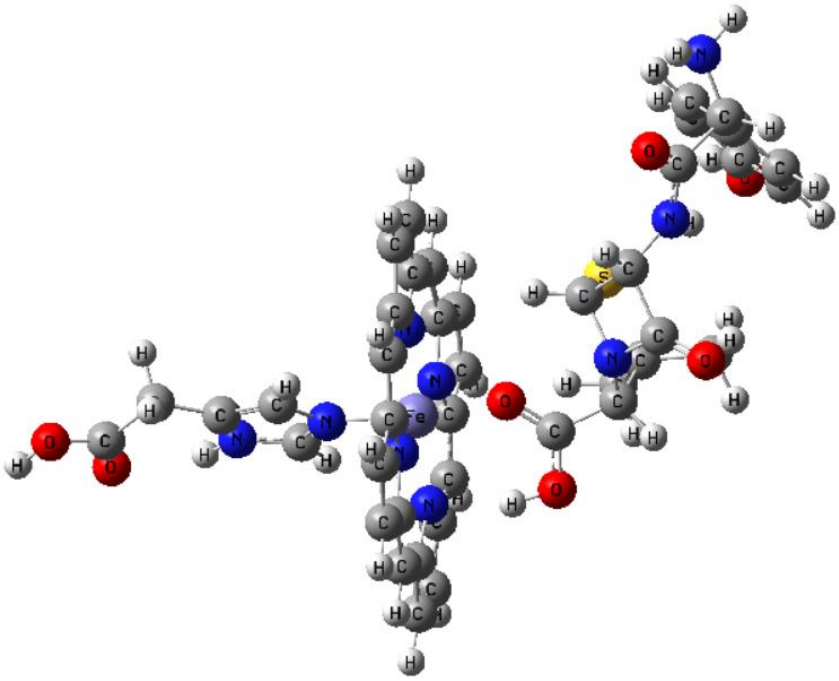

Figure 1. DeoxyHb bonding to amoxicillin (first position).

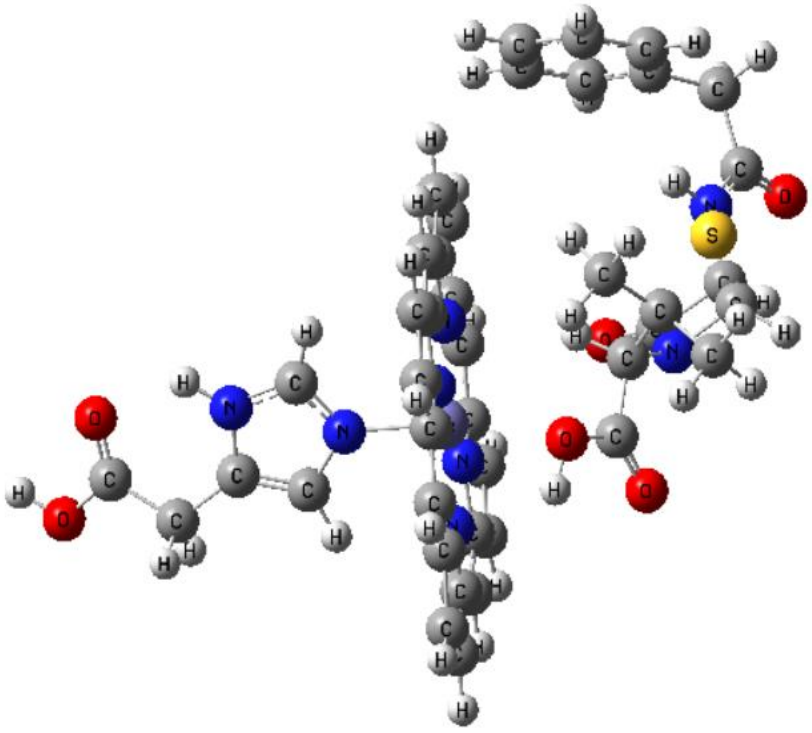

Figure 2. DeoxyHb bonding to penicillin (first position).

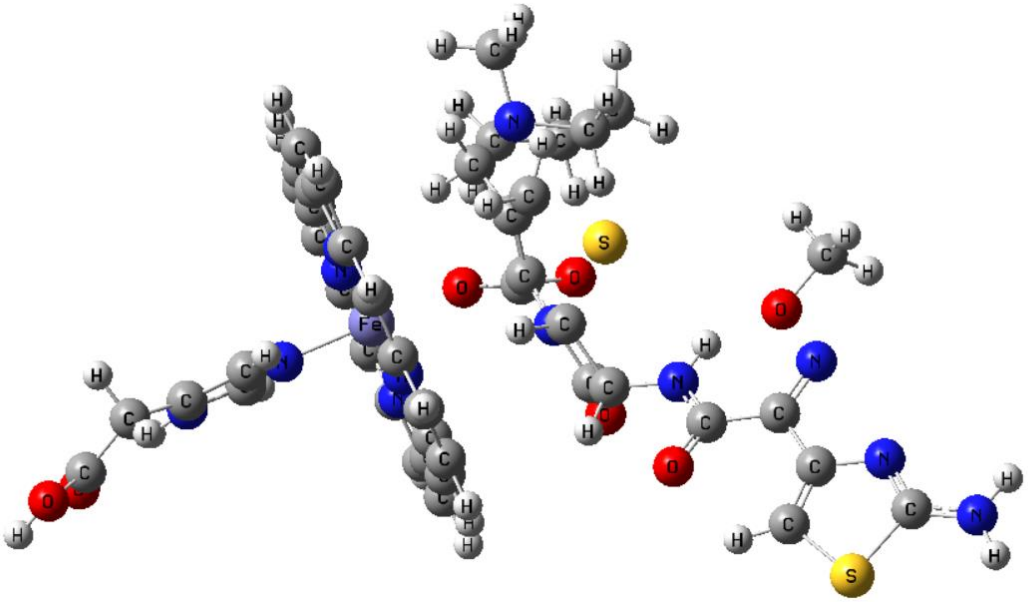

Figure 3. DeoxyHb bonding to cefepime (first position).

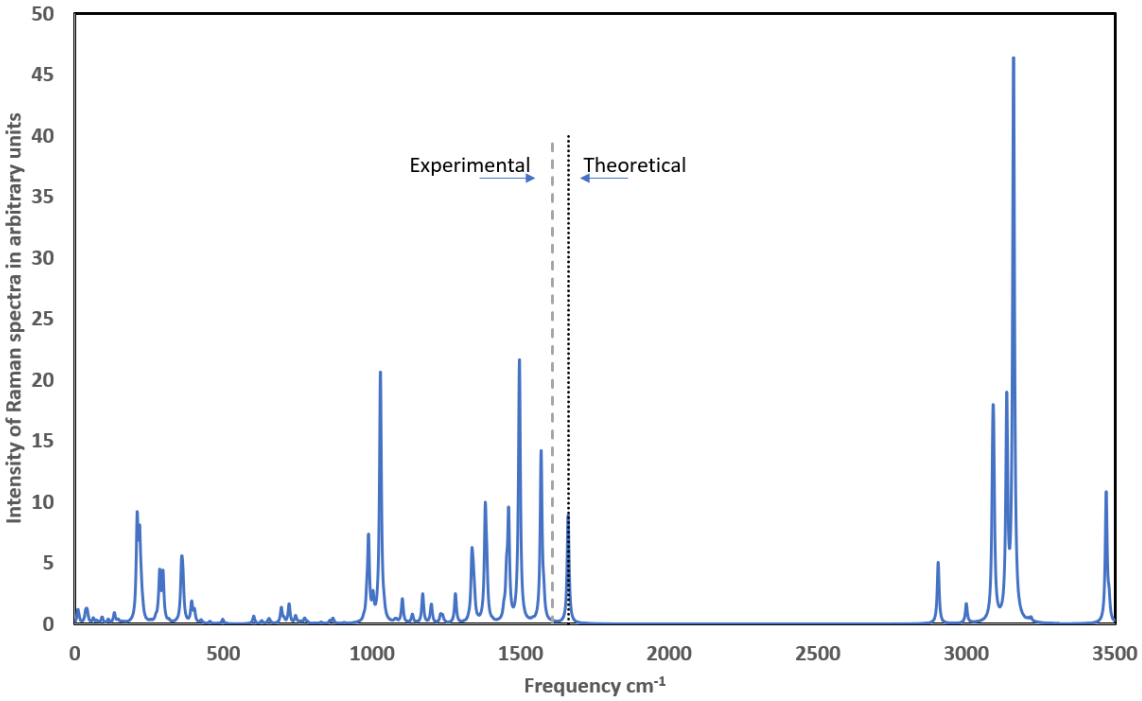

Figure 4. Raman intensity of deoxyHb in arbitrary units. Theoretical and experimental [34] last peaks before the frequency gap are shown.

Table 1. distances between deoxyHb and oxygen atom in antibiotics amoxicillin, cefepime, and penicillin. Two interaction points (p1 and p2) are chosen for each antibiotic.

Interaction	P1 Distance (Å)	P2 Distance (Å)
Deoxyhemoglobin---amoxicillin	2.116	2.005
Deoxyhemoglobin---cefepime	2.024	2.024
Deoxyhemoglobin---penicillin	2.129	2.378

Table 2. Gibbs free energy, enthalpy, and entropy of the interaction of antibiotics with deoxyHb. The last column shows the Raman interaction shift of the last Raman peak before the frequency gap referenced to that of deoxyHb.

Interaction	ΔG (eV)	ΔH (eV)	ΔST (eV)	Δν (cm^{-1})
DeoxyHb (no interaction)	0	0	0	0
DeoxyHb---amoxicillin p1	-0.281	-0.714	-0.721	78
DeoxyHb---amoxicillin p2	-0.424	-0.985	-0.850	74
DeoxyHb---cefepime p1	-0.867	-1.509	-0.642	89
DeoxyHb---cefepime p2	-0.565	-1.117	-0.552	54
DeoxyHb---penicillin p1	-0.440	-0.982	-0.542	47
DeoxyHb---penicillin p2	-0.542	-1.190	-0.648	48

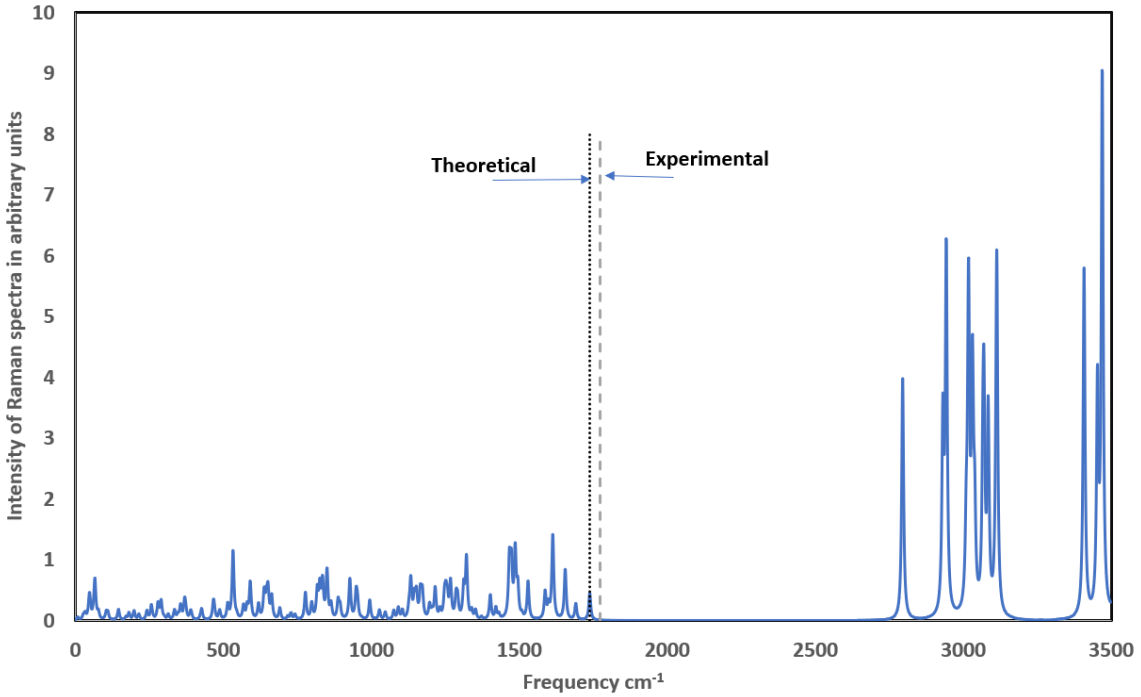

Figure 5. Raman spectra of amoxicillin. The last theoretical peak before the frequency gap is at 1739 cm^{-1}.

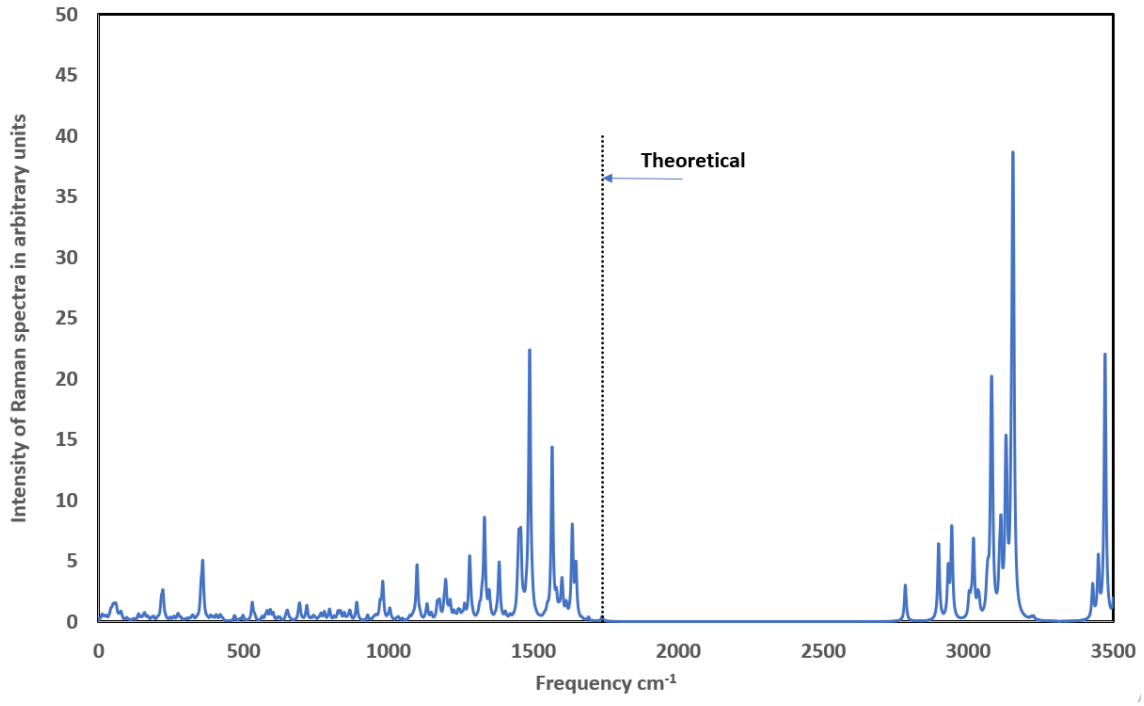

Figure 6. Raman intensity of deoxyhemoglobin interacting with amoxicillin (p1) in arbitrary units (a.u.). The highest frequency before the frequency gap is indicated.

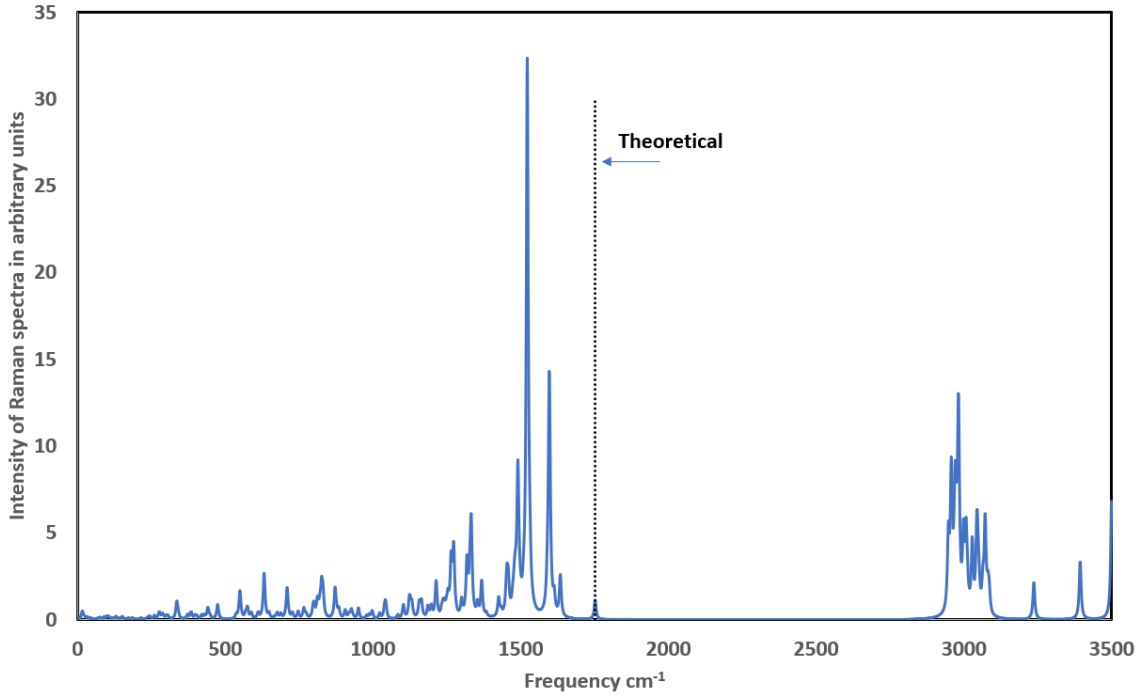

Figure 7. Raman intensity of cefepime in arbitrary units (a.u.). The highest frequency before the frequency gap is indicated.

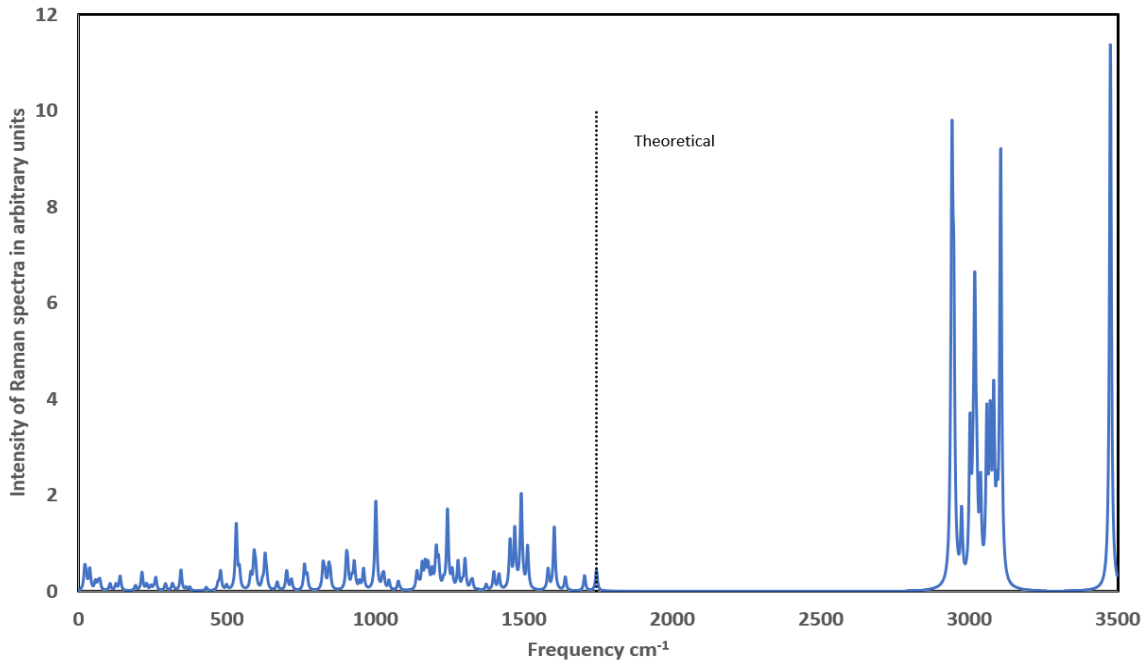

Figure 8. Raman intensity of penicillin G in arbitrary units (a.u.). The highest frequency before the frequency gap is indicated.

As we can see from table 2 that all Gibbs free energies of interaction are negative that means all interactions are (exergonic) interactions. The highest Gibbs energy is for cefepime while the lowest is for amoxicillin. Enthalpy represents the heat absorbed or produced by the interaction. All enthalpies in table 2 are negative and the reactions are called exothermic reactions. As in the case of Gibbs energy of reaction, the highest enthalpy of rection is for cefepime while the lowest is for amoxicillin. The entropy energy (ΔST) in table 2 shows the same negative trend of Gibbs and enthalpy energies. The entropy is related to the concept of disorder or randomness [37] so that the more strong the connection between the two molecules the more the reduction in entropy. The three antibiotics amoxicillin, cefepime, and penicillin have higher reduction of entropy respectively as shown in table 2.

The last column in table 2 shows the Raman shift of deoxyHb due to interaction with antibiotics. Pristine amoxicillin Raman spectra is shown in figure 5 with a comparison between theoretical and experimental results for the last peak before the frequency gap [38]. The last theoretical peak before the frequency gap in amoxicillin for the chosen positions p1 is at 1739 cm^{-1} compared to the experimental value at 1774 cm^{-1} as in figure 5. In the case of interaction of deoxyHb with amoxicillin, the value of last theoretical peak before the frequency gap of deoxyHb is shifted from the value of deoxyHb at 1661 cm^{-1} by 78 cm^{-1} to 1739 cm^{-1} as in table 2 and figure 6. This value is the same value for amoxicillin without interaction as in figure 5. However, for the interaction of deoxyHb with amoxicillin at the second point (p2) the frequency shift is slightly less at 74 cm^{-1}. For the interaction of deoxyHb with cefepime, the two shifts for the two points p1 and p2 are 89 and 54 cm^{-1} respectively. The reason of such difference between the two points is due to the fact that p1 is interaction of carbonyl group (C=O) while p2 is for double carbonyl group i.e., two oxygen atoms attached to the same carbon atom (O=C=O). Finally, the interaction of deoxyHb with penicillin G results with nearly the same shifts at 47 and 48 cm^{-1}.

The Raman spectra of pristine amoxicillin, cefepime, and penicillin in figures 5, 7, and 8 show that the last frequency peak before frequency gap is always higher than deoxyHb last frequency peak. This shows that the existence of these antibiotics in the blood stream will cause a positive shift of last frequency peak before frequency gap of Raman spectra as in table 2. Every antibiotic has its unique frequency shift that can be used to distinguish it from others and depends on what position it was attached to deoxyHb. We can also suggest that the concentration of these antibiotics can be found by calibrating the height of the last frequency peak with the experiment. The Raman spectra of the interacting molecules are nearly the sum of the Raman of individual molecules.

4. Conclusions

The interaction of antibiotics amoxicillin, cefepime, and penicillin G with deoxyHb is investigated. The most probable interaction point is between the Fe atom in deoxyHb (highest positive charge point) and various oxygen atoms in antibiotics (highest negative charge points). Two points in each antibiotic is chosen to investigate the interaction. Results show that the bond length between Fe and nearest O atom in the antibiotics is in the range 2.005-2.378 Å which is near the high end of Fe-O theoretical and experimental results. The bond length depends on the neighbouring atoms of oxygen in Fe-O. All Gibbs free energies of interaction are negative with

exergonic reaction. All enthalpies are exothermic negative interactions, and all entropy energies are negative that means decreasing disorder of the interaction system. All Raman spectra of studied antibiotics are characterized by a frequency peak before the frequency gap that are greater than the same peak in deoxyHb. The interaction between deoxyHb and antibiotics conserve these peaks with a shift depending on the interaction position point of the antibiotic.

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