



Hemoglobin interaction with formaldehyde in cigarette smoke: A DFT study

Mudar Ahmed Abdulsattar^{1,2*}, Nooruldeen Mudher Almaroof³, Tasneem H. Mahmood⁴

¹Ministry of Science and Technology, Baghdad, Iraq

²Department of Pharmacy, Al-Rasheed University College, Baghdad, Iraq

³Sheikh Zayed General Hospital, Baghdad, Iraq

⁴Department of Physics, College of Science for Women, University of Baghdad, Baghdad, Iraq

Abstract

Effect of dispersion correction on the interaction of hemoglobin with the oxygen (O₂) and formaldehyde (CH₂O) molecules using density functional theory is performed. The interaction of hemoglobin singlet and triplet states (multiplicity=1 and 3 respectively) is discussed. The dispersion correction is correlated with the induced dipole-dipole interaction between atoms or molecules. The results show that the dispersion correction with PBE theory gives the oxyhemoglobin molecule the exact ground state diamagnetic properties. The calculated negative Gibbs free energy of interaction of deoxyhemoglobin with O₂ and CH₂O is (-0.42748) and (-0.29418) eV respectively. As a result, the hemoglobin transfers O₂ and CH₂O both to human cells, causing cancer in the case of CH₂O. Raman spectra of hemoglobin can be used to determine the molecules attached to deoxyhemoglobin. Raman experimental lines difference (shift) between deoxyhemoglobin and oxyhemoglobin is 32 cm⁻¹ which is comparable to the theoretical 34 cm⁻¹.

Keywords: Hemoglobin; O₂; CH₂O; Density functional theory; Gibbs free energy

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

1. Introduction

The oxidation of hemoglobin is a vital process for human respiration. Due to this process, blood can transfer oxygen inside the human body. The oxygen afterward is distributed to cells inside the body. The process begins in the lungs, when oxygen in inhaled air is in touch with deoxygenated hemoglobin. However, air contains many other gases besides oxygen to interact with hemoglobin [1]. Usually, environmental gases such as N₂, CO₂, Ar, Ne, He, Kr, CH₄, H₂ are either inactive or found in trace amounts that do not threaten human health [2]. However, new unusual or different concentrations of usual ingredients might expose human health to danger such as cigarette smoke [3] or pollution gases [4].

Density functional theory (DFT) is one of the useful tools that can be used to predict and explain experimental findings in many branches of science such as physics, chemistry, biology, etc. [5–7]. The DFT method and its related electronic structure methods are continuously improved with new corrections [8]. One of the important contemporary corrections to DFT methods is the dispersion correction [9,10]. This correction deals with a more accurate

empirical van der Waals interaction between molecules. This correction includes two types of forces, namely dipole-dipole forces, and induced dipole-dipole forces. As a result, molecules with no permanent dipole moments can also have dispersion corrections.

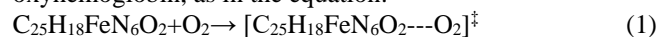
Formaldehyde (CH₂O) is chosen to make a comparison with the oxidation of deoxyhemoglobin for several reasons. CH₂O is one of the dangerous gases that exist in cigarette smoke [11]. Formaldehyde is also considered a pollution gas [12] and is also considered one of the cancerous gases [13]. CH₂O can cause leukemia especially myeloid leukemia [14,15]. The question is: how does formaldehyde reach the bone marrow to cause leukemia? The molecular weight of CH₂O is 30 (g/mol), which is comparable to oxygen molecular weight (32 (g/mol)). The similarity in molecular weight leads to other similar properties such as traveling speed, reaction cross-section, etc. We shall see later that the human body is deceived by various formaldehyde similar properties to O₂ and transported inside the human body that eventually reaches bone marrow and causes cancer.

In the present work, we evaluate the effect of dispersion corrections on several physical quantities, including bond length and Raman spectra of oxyhemoglobin and deoxyhemoglobin and the interaction of deoxyhemoglobin with formaldehyde. The thermodynamic interaction quantity Gibbs free energy is calculated for the singlet and triplet states to interpret reaction rates of deoxyhemoglobin with oxygen and formaldehyde.

2. Materials and methods

Both oxygen molecule and deoxyhemoglobin are in the triplet state [16,17]. This can be recognized from the experimental paramagnetic behavior of both molecules [18]. The oxyhemoglobin, on the other hand, is in the singlet state because of the diamagnetic behavior of this molecule [19]. Previous use of first principles of electronic structure methods using Hartree–Fock (HF), Second-order Møller–Plesset perturbation theory (MP2) [20], and other DFT methods such as B3LYP, LSDA [21] are used to investigate the electronic structure of deoxyhemoglobin and oxyhemoglobin. Dispersion correction is one of the contemporary added corrections to DFT methods to account for London dispersion correction [22,23]. This correction includes empirical instantaneous dipole-dipole forces and fluctuation of induced dipole forces. Several kinds of dispersion corrections are available in the presently used Gaussian 09 program that can be used to perform present calculations [24]. This includes GD2, GD3, and GD3BJ versions of Grimme’s dispersion correction. In the present work, we used the GD3BJ version in connection with PBE and B3LYP/6-311G** methods and basis. The vibrational Raman spectra are corrected using an empirical scale factor with the value 0.991 for the PBE method [25].

Deoxyhemoglobin interacts with oxygen to form oxyhemoglobin, as in the equation:



The deoxyhemoglobin ($\text{C}_{25}\text{H}_{18}\text{FeN}_6\text{O}_2$) is represented by a Fe atom in the center of the porphyrin molecule ($\text{C}_{20}\text{H}_{12}\text{N}_4$), which is also connected to an axial 4-Imidazoleacetate ($\text{C}_5\text{H}_5\text{N}_2\text{O}_2$) molecule [16]. The Fe atom can connect to various other molecules such as oxygen as in Fig. (1) or formaldehyde as in Fig. (2). After the interaction with O_2 , a transition state is formed, which is represented by the square brackets and a double dagger (‡) in Eq. 1. The reaction rate in Eq. 1 can be given by the equation [26]:

$$\frac{d[\text{C}_{25}\text{H}_{18}\text{FeN}_6\text{O}_2]}{dt} = -C[\text{O}_2][\text{C}_{25}\text{H}_{18}\text{FeN}_6\text{O}_2]k(T). \quad (2)$$

In the above equation $[\text{O}_2]$ and $[\text{C}_{25}\text{H}_{18}\text{FeN}_6\text{O}_2]$ represent the concentration of oxygen and deoxyhemoglobin in the reaction, respectively. C is the reaction constant that can be determined experimentally. The term $k(T)$ is called the reaction rate constant and is given by:

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

In the above equation, T is the temperature, ΔG is the change in Gibbs energy of the reaction in Eq. 1, and k_B is the Boltzmann constant. These equations apply for singlet and triplet states with different reaction constants and different Gibbs energies (ΔG). In Eq. 3, the positive values of ΔG give weak reaction rates that need external energy to be performed and are called nonspontaneous reactions. Negative values of ΔG give high reaction rates that do not need an external supply of energy and are called spontaneous reactions [27].

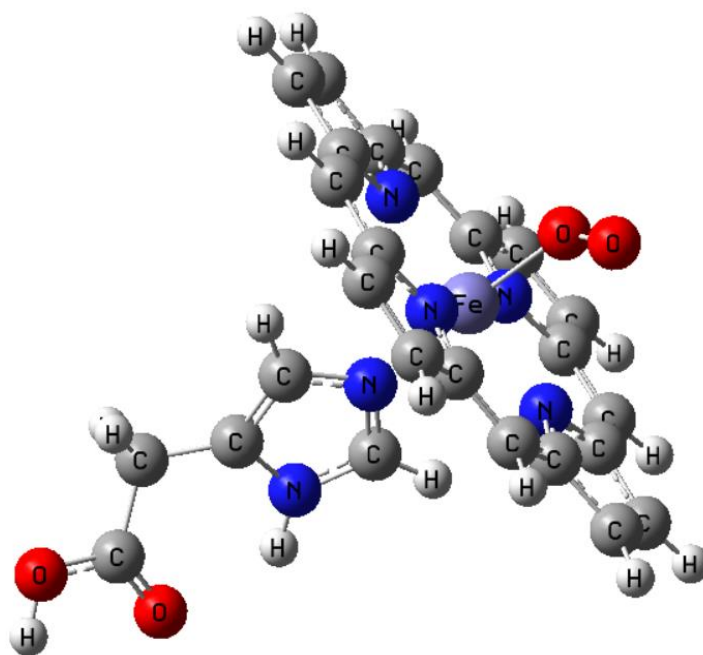


Fig. 1. Deoxyhemoglobin interaction with O_2 to form oxyhemoglobin molecule.

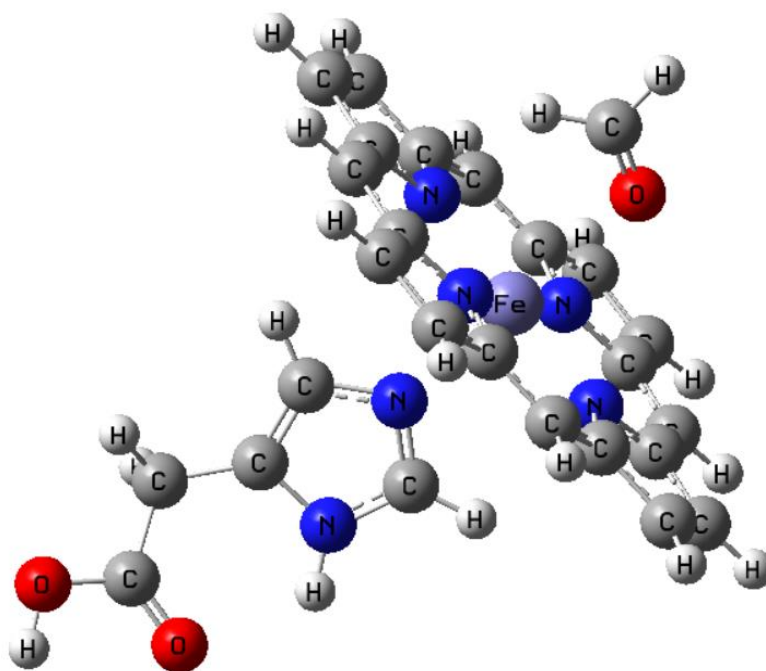


Fig. 2. Deoxyhemoglobin interaction with formaldehyde molecule.

3. Results and discussion

Table 1 shows Gibbs free energies of the different deoxyhemoglobin reactions considered in the present work in the two kinds of multiplicities 1 and 3. All the values are evaluated using B3LYP and PBE methods in density functional theory. The reactions of deoxyhemoglobin with O_2 show that the B3LYP method always gives a positive value of the Gibbs free energy of reaction with oxygen. In addition, the B3LYP always results with triplet states with lower Gibbs free energy than the singlet, which is the opposite of experimental findings. On the other hand, the PBE method gives negative values to all interactions with oxygen. However, the PBE method also gives the triplet state lower energy than the singlet without adding dispersion correction. The only method that gives the correct order of states (lower singlet state) is the PBE with dispersion correction. The value of PBE singlet state with dispersion correction (**-0.42748 eV**) is written in bold in Table 1.

Table 1 also gives the Gibbs free energy of the interaction of CH_2O with deoxyhemoglobin. Formaldehyde as a hydrocarbon with an oxygen atom is in the singlet state. The triplet state of CH_2O is higher than the singlet by 3 eV. Depending on the best results of the interaction of deoxyhemoglobin with O_2 , the correct value of CH_2O interaction with deoxyhemoglobin is the singlet state having the value (**-0.29418 eV**) for the PBE with dispersion correction. Since formaldehyde is one of the pollution and smoke contents, the negative value of the Gibbs energy indicates that deoxyhemoglobin can connect and carry CH_2O with it inside the human body during respiration or

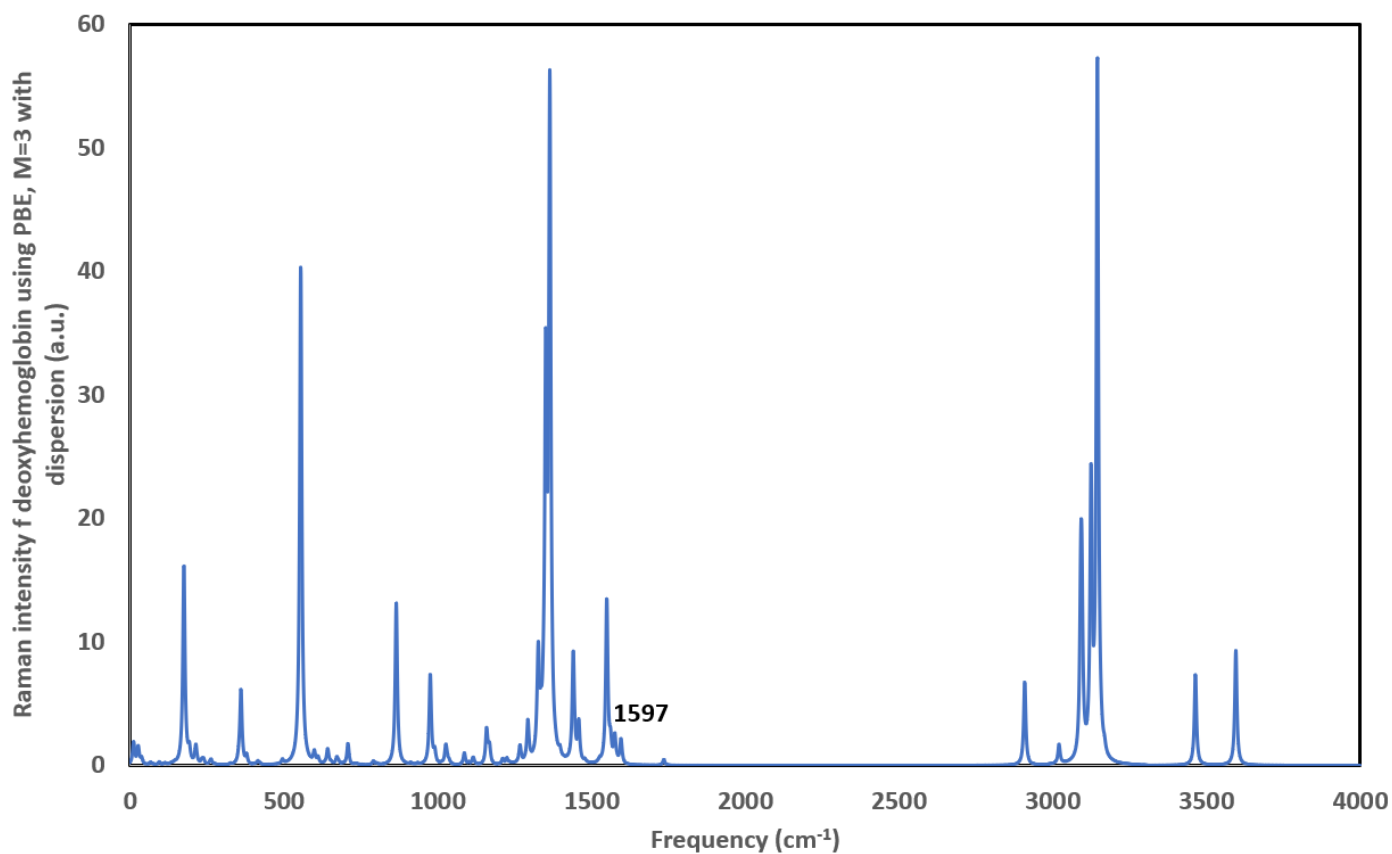
smoking in a similar way of carrying O_2 . Formaldehyde is one of the most cancerous substances in smoke [28].

The theoretical (PBE with dispersion in singlet state) bond length between iron in deoxyhemoglobin and oxygen molecule (Fe-O Bond length) is 1.755 Å compared with the experimental value of the range (1.77-1.9 Å) [29]. The theoretical (PBE with dispersion in singlet state) bond length between iron in deoxyhemoglobin and oxygen atom in formaldehyde is 1.917 Å. This indicates that the higher limit of experimental value (1.77-1.9 Å) is due to oxygen atoms in other compounds (other than oxygen molecules) that are attached to deoxyhemoglobin, such as formaldehyde or water molecules.

The experimental Raman spectra of deoxyhemoglobin and oxyhemoglobin [30] can discriminate the existence of oxygen in the blood. The last Raman peak before the frequency gap can be used for this purpose. In deoxyhemoglobin, the last peak can be found experimentally at nearly 1606 cm^{-1} , while the last peak in oxyhemoglobin can be found at 1640 cm^{-1} [30]. These results can be compared with the calculated Raman spectra in Fig (3) and Fig. (4). The last peak before the frequency gap in Fig. (3) is at 1597 cm^{-1} for the deoxyhemoglobin using PBE theory and M=3 with dispersion correction. The last peak before the frequency gap in Fig. (4) is at 1629 cm^{-1} for the oxyhemoglobin using PBE theory and M=1 with dispersion correction.

Table 1. B3LYP and PBE comparison of calculated thermodynamic Gibbs free energy of the various reactions of deoxyhemoglobin with O₂ and CH₂O in the two multiplicities (M=1 and 3).

	M	B3LYP ΔG (eV)	PBE ΔG (eV)
Deoxyhemoglobin+O ₂ without dispersion	1	0.72207	-0.27875
Deoxyhemoglobin+O ₂ without dispersion	3	0.51018	-0.29763
Deoxyhemoglobin+O ₂ with dispersion	1	0.66019	-0.42748
Deoxyhemoglobin+O ₂ with dispersion	3	0.28656	-0.39704
Deoxyhemoglobin+CH ₂ O without dispersion	1	0.02501	-0.12291
Deoxyhemoglobin+CH ₂ O without dispersion	3	0.31480	0.28430
Deoxyhemoglobin+CH ₂ O with dispersion	1	-0.12484	-0.29418
Deoxyhemoglobin+CH ₂ O with dispersion	3	0.07537	0.16471

**Fig. 3.** Raman intensity f deoxyhemoglobin using PBE, M=3 with dispersion correction in arbitrary units (a.u.). The highest frequency before the frequency gap is indicated.

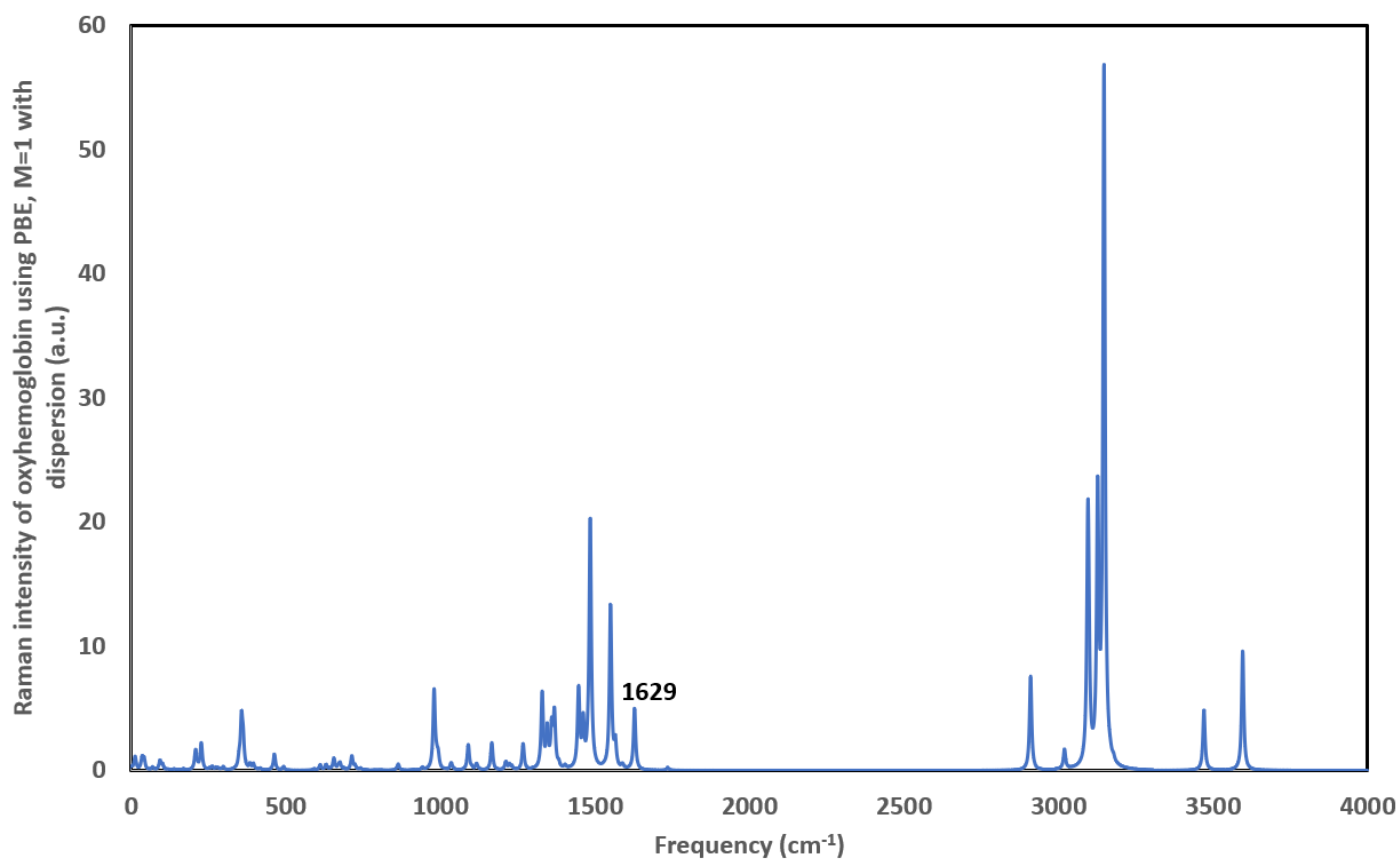


Fig. 4. Raman intensity of oxyhemoglobin using PBE, M=1 with dispersion correction in arbitrary units (a.u.). The highest frequency before the frequency gap is indicated.

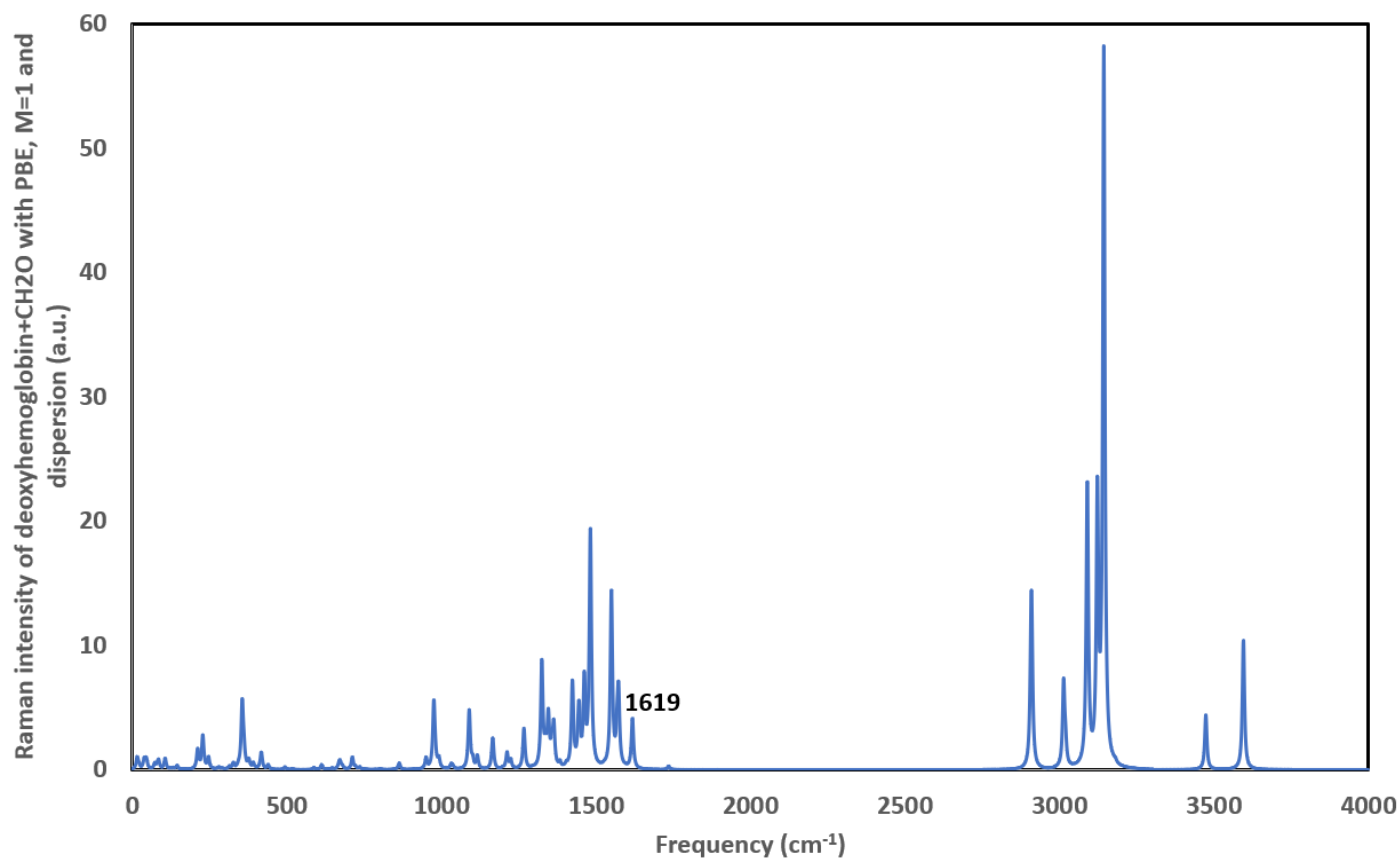


Fig. 5. Raman intensity of deoxyhemoglobin+CH₂O with PBE, M=1, and dispersion correction in arbitrary units (a.u.). The highest frequency before the frequency gap is indicated.

The theoretical difference between the two peaks is 32 cm^{-1} in comparison with 34 cm^{-1} in the experimental results mentioned above. Finally, Fig. (5) represents the interaction of formaldehyde with deoxyhemoglobin using PBE theory with $M=1$ and dispersion correction. The last peak before the frequency gap in Fig. (5) is at 1619 cm^{-1} which can be used as a signature for the interaction between deoxyhemoglobin and CH_2O . The frequency shift of the attachment of formaldehyde to deoxyhemoglobin is 22 cm^{-1} compared to 32 cm^{-1} in the case of the attachment of O_2 .

4. Conclusions

The present work proves that to reproduce the experimental magnetic properties of hemoglobin, dispersion correction should be added. The present work also proves that the expected magnetic properties are sensitive to the kind of functional used in DFT calculations even after adding dispersion correction. The PBE theory is more appropriate than B3LYP after adding dispersion correction. The PBE calculated Gibbs free energy of O_2 and CH_2O attachment to deoxyhemoglobin is negative and close in their values. As a result, deoxyhemoglobin carries O_2 and CH_2O and distributes them nearly equal to the human body, which illustrates the reason for high cancerous behavior of CH_2O . The difference (shift) in the frequency of Raman spectra of the last vibration peaks before the frequency gap is reproduced with good agreement with experimental findings for the two molecules O_2 and CH_2O .

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