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STUDY OF THE STRUCTURES AND PROPERTIES OF THE MOLECULES PYRIMETHAMINE AND SULFADOXINE USING AB INITIO AND DFT METHODS

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ABSTRACT

Density functional theory (DFT) and ab- initio Quantum Mechanical calculations have been used to study the structures and properties of the Molecules Pyrimethamine and Sulfadoxine. Their molecular stabilities, structures, dipole moments, charges transfer, polarizability tensors, average polarizability anisotropy, energies, IR and Raman vibrational frequencies have been predicted. Tentative assignments for their intense IR active frequencies have been carried out and represented. We have used the Restricted Hartree-Fock (RHF) and density functional Becke3LYP (B3LYP) theories by employing 6-311++G** basis set for inclusion of electron correlation. From our results we observe that the molecules are more stable at the RHF level of theory than at the B3LYP level of theory. The frequency calculations obtained at the B3LYP level are closer to some experimental values than those obtained at the RHF level due the effect of electron correlation. The magnitude of the dipole moment is higher in the RHF level and the polarizability tensor components, the average polarizability and the anisotropy are greater at the B3LYP level. This implies that the inclusion of electron correlation decreases the dipole moment and increases the polarizability tensors, the average polarizability and the anisotropy. The IR and Raman spectra of the molecules have also been presented and the IR spectrum of Pyrimethamine lies in the same range as that given by some experimental results.

Keywords: DFT, RHF, pyrimethamine, sulfadoxine, ab-initio quantum mechanical calculations.

INTRODUCTION

Daraprim, also called Pyrimethamine, was first developed in 1952 by Crud, Davy and Rose from the synthesis of the antifolate drug Paludrine or Proguanil (chlorguamide Hydrochloride) (Kakkilaya, 2008). It is an antiparasitic compound and a hydrofolate reductase inhibitor essential for the synthesis of Folic acid (Winstanley, 2006; Alexis, 2006). It is essential for the synthesis of folic acid. Pyrimethamine possesses blood schizonticidal and some tissue schizonticidal activity against malaria parasite in human (Marina *et al*., 2005). Its inhibition activity leads to either killing a pathogenic organism (malaria parasite) or to modify some aspects of metabolism of the body that are functioning dormally. Daraprim interferes with the biosynthesis of the parasite by inhibiting the enzyme dihydrofolate reductase of plasmodia thereby blocking the biosynthesis of purine and pyrimidine which are essential for DNA synthesis and cell multiplication (http://www.Drug bank showing Pyrimethamine (DB002050).mht). This leads to failure of nuclear division at the time of schizont formation in the erythrocytes and liver. Daraprim is a weak basic drug and sparingly soluble in water. It has a half life of 4.2days (Alexis, 2006). The resistance of Pyrimethamine is due to its long half life. Pyrimethamine is the most widely used anti malarial antifolate drug. For almost three quarters of a century, Daraprim is used as one of the anti malaria resistance drug in some countries or places where Quinine and its derivatives failed to treat malaria. It is recommended to patients infected in areas where susceptible plasmodia exist (Michelle and Qin Cheng, 2006). Although the drug has antimalarial activity when used alone, parasitological resistance can develop rapidly (Winstanley *et al*., 2004). When used in combination, it produces a synergistic effect on the parasite and can be effective even in the presence of resistance to individual component. Pyrimethamine is usually used in combination with Sulfadoxine [4-amino-N-(5, 6-dimethoxy-Pyrimidin-4-yl) benzenesulfoamide] and Sulfalene (Alexis, 2006).

The structure of Pyrimethamine and its derivatives have been studied by Clare E. Samsom et al using modeling techniques (Clare *et al*., 1989). Molecular dynamics calculations have been carried out in order to understand the resistance of Pyrimethamine (Giulio *et al*., 2005 and Reinaldo *et al*., 2002). X-ray analysis of Pyrimethamine and its hydrochloride salt was carried out by Rumiko Tanaka *et al*. (2004). Onyeji *et al*. (2009) studied the powder X-ray diffraction analysis and Fourier transformation infrared spectroscopy of Pyrimethamine

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Onyeji *et al*. (2009) and Maitarad *et al*. (2009) carried out comparative field analysis (CoMFA) while Phornphimon *et al*. (2009) carried out some ab intio quantum chemical calculations on some derivative of Pyrimethamine.

Sulfadoxine [4-amino-N-(5, 6-dimethoxy-Pyrimidin-4-yl) benzenesulfoamide or 4,5 dimethoxy-6-Sulfanilamidopyrimidine] was first synthesized by the standard scheme from 4-acetylaminobenzenesulfonyl chloride and 4-amino-5,6-dimethoxypyrimidine. Sulfadoxine is similar to other Sulfanilamides however, but it possesses very prolonged action. It has a half life of 120 to 200hours (Ruben and Victor, 2006). It is an antiparasitic agent, anti protozoan agent, anti-infective agent and an anti malaria agent. It is also a hydrofolate reductase inhibitor. Sulfadoxine also inhibits the production of an enzyme involved in the synthesis of folic acid within the parasite. Although this drug has antimalaria activity when used alone, parasitological resistance can also develop (Winstanley *et al*., 2004). It is more effective when used in combination with other drugs for example Pyrimethamine.

Sulfadoxine and Pyrimethamine are both antifolate drugs. They both inhibit the production of enzymes involved in the synthesis of folic acid within the parasites. Sulfadoxine-Pyrimethamine combination act synergistically to inhibit two enzymes important in the parasite's folate biosynthetic pathway; dihydrofolate reductase (DHFR) and dihydropteroate synthetase (DHPS). Michelle and Qin Cheng (Michelle and Qin Cheng, 2006) have shown that the DHFR gene confer resistance to Pyrimethamine while the DHPS gene confer resistance to Sulfadoxine. Although some works have been done on these molecules, yet detail works are required to improve the understanding of their electronic structures and physico-chemical properties.In this work, ab initio calculations have been performed in order to predict the molecular stabilities, structures, dipole moments, atomic charges, polarizability tensors, average polarizability, anisotropy, energies, IR and Raman vibrational frequencies of Daraprim and Sulfadoxine. The computational methodology and the results of our calculations are reported in this article.

MATERIALS AND METHODS

Computational Method

Theoretical frame work

This section gives a brief outline of the theoretical methods that are performed in this work.

The Hartree-Fock (FH) Method

The HF method is used to solve the time independent Schrödinger equation for a multi-electron atom or molecule as described in the Born-Oppenheimer approximation (Colin, 1992). In the HF theory, each electron is assigned to a molecular orbital, and the wave function is expressed as a single Slater determinant (Slater, 1974) in terms of the molecular orbitals. For a system with n electrons, the wave function ψ is given as:

$$\psi(\chi_1,\chi_2,\ldots,\chi_n)=\frac{1}{\sqrt{n!}}\begin{vmatrix}\phi_1(\chi_1) & \phi_2(\chi_2) & \ldots & \phi_n(\chi_1)\\ \phi_1(\chi_2) & \phi_2(\chi_2) & \ldots & \phi_n(\chi_2)\\ \ldots & \ldots & \ldots & \ldots\\ \phi_1(\chi_n) & \phi_2(\chi_n) & \ldots & \phi_n(\chi_n)\end{vmatrix} \quad (1)$$

ϕ_i represent a molecular orbital and χ_i designates the spatial and the spin coordinates of the electron i. If we define two spin functions α and β as follows $\alpha(\uparrow)=1 \quad \alpha(\downarrow)=0$ $\beta(\uparrow)=1 \quad \beta(\downarrow)=0$, we can build a closed shell wave function by defining n/2 molecular orbital for a system with n-electrons and then assigning electrons to these orbitals in pairs of opposite spin as follows:

$$\psi(\vec{r})=\frac{1}{\sqrt{n!}}\begin{vmatrix}\phi_1(\vec{r}_1)\alpha(1) & \phi_1(\vec{r}_1)\beta(1) & \ldots & \phi_{\frac{n}{2}}(\vec{r}_1)\alpha(1) & \phi_{\frac{n}{2}}(\vec{r}_1)\beta(1)\\ \phi_1(\vec{r}_2)\alpha(2) & \phi_1(\vec{r}_2)\beta(2) & \ldots & \phi_{\frac{n}{2}}(\vec{r}_2)\alpha(2) & \phi_{\frac{n}{2}}(\vec{r}_2)\beta(2)\\ \ldots & \ldots & \ldots & \ldots & \ldots\\ \phi_1(\vec{r}_n)\alpha(n) & \phi_1(\vec{r}_n)\beta(n) & \ldots & \phi_{\frac{n}{2}}(\vec{r}_n)\alpha(n) & \phi_{\frac{n}{2}}(\vec{r}_n)\beta(n)\end{vmatrix}$$

(2)

From the case of the closed-shell, the spin coordinates can be eliminated so that we can formulate the equations in terms of spatial orbitals.

The molecular orbitals are expressed as a linear combination of atomic orbtals φ_μ

$$\phi_i(r)=\sum_{\mu}^{n}C_{\mu i}\varphi_\mu(r) \quad (3)$$

Expressing the nonrelativistic time-independent Schrödinger's equation using a wave function of this form yields a generalized eigenvalue problem, the (Roothaan, 1951) equations.

$$\sum_{v=1}^{N}\left(F_{\mu v}-\varepsilon_i S_{\mu v}\right)C_{vi}=0\ , \qquad \mu=1, 2,\ldots..N \quad (4)$$

This equation can be rewritten in matrix form as:

$$FC=SC\varepsilon \quad (5)$$

In which F represent the Fock matrix, S is the overlap matrix, C is the molecular orbital coefficients matrix with elements C_{vi} and ε is diagonal matrix of orbital

energies. The Fock matrix can be expressed as a sum of one-electron part H^{core} (the core Hamiltonian) and a two-electron part G, and its elements are given as follows in the atomic orbital basis (Janssen and Neilsen, 2008).

$$F_{\mu\nu} = H_{\mu\nu}^{core} + G_{\mu\nu} \quad (6)$$

$$F_{\mu\nu} = H_{\mu\nu}^{core} + \sum_{\rho\lambda} P_{\rho\lambda}\left[(\mu\nu/\rho\lambda) - \frac{1}{2}(\mu\lambda/\rho\nu)\right] \quad (7)$$

The elements $P_{\rho\lambda}$ of the density matrix p are computed from the molecular orbital coefficients (assumed to be real).

$$P_{\rho\lambda} = 2\sum_{i}^{n/2} C_{\rho i} C_{\lambda i} \quad (8)$$

where the sum runs over all occupied molecular orbitals i. The electronic contribution of the Hartree-Fock energy can be computed as follows:

$$E_{el} = \frac{1}{2}\sum_{\mu\nu} P_{\mu\nu}\left(H_{\mu\nu}^{core} + F_{\mu\nu}\right) \quad (9)$$

And the total Hartree-Fock energy is the sum of the electronic energy and the nuclear repulsion energy $E_{HF} = E_{el} + E_{nuc}$.

$$H^{core}(1) = -\frac{1}{2}\nabla_1^2 - \sum_{\alpha}\frac{Z_\alpha}{r_1\alpha} \quad (10)$$

is the one-electron core Hamiltonian.

The term $(\mu\nu/\rho\lambda)$ in equation (7) signifies the two-electron repulsion integrals. Under the Hartree-Fock treatment, each electron sees all of the other electrons as an average distrubtion, there is no instantaneous electron – electron included in the Schrödinger's equation.

Density Functional Theory (DFT)

It is a quantum mechanical theory used in physics and chemistry to investigate the electronic structure (principally the ground state) of many body systems, in particular atoms, molecules, and the condensed phases. DFT is among the most popular and versatile methods available in condensed-matter physics, computational physics and computational chemistry. DFT has its conceptual roots from the Thomas – Fermi model and Slater's fundamental work in quantum chemistry in 1950. DFT approach is based upon a strategy of modeling electrons via general functional (functions of functions) of the electron density. DFT was put on a firm theoretical footing by the Hohenberg – Kohn theorem (Hohenberg and Kohn, 1964) which shows the existence of a unique functional which determines the ground state energy and density of a system exactly. The theorem does not provide the form of the functional.

Following on the work of Kohn and Sham (Kohn and Sham, 1965), the approximate functional employed by the current DFT method partition the electronic energy into several terms.

$$E = E^T + E^v + E^j + E^{xc} \quad 11$$

E^T = kinetic energy (arising from motion of electrons)
E^v = potential energy of the nuclear–electron attraction and of the repulsion between pairs of nuclei.
E^{xc} = exchange – correlation term and includes the remaining part of the electron–electron interaction. The exchange correlation functional used is the Becke-style three – parameter functional generally known as Becke3LYP (B3LYP) which in build in the Gaussian computer code. The exchange correction potential which is the functional derivative of the exchange correction energy functional with respect to the density is approximated. The approximations used are the local density approximation and the generalized gradient approximations (Leeuwen and Baerends, 1995). The exchange correction potential determines the Kohn-Sham orbitals ϕ_i and their one-electron energies. It also determine the density, which is obtained from the squares of occupied Kohn-Sham orbitals times their occupation number f_i;

$$\rho(r) = \sum_{i}^{N_{occ}} f_i \left|\phi_i(r)\right|^2 \quad (12)$$

The exact exchange correction potential which is unique yields the exact density of the system. After having iteratively found the exchange correction potential which generates the accurate target density, we immediately obtain Kohn-sham orbitals and the one electron energies to very good accuracy.

COMPUTATIONAL METHODOLOGY

The molecular structures and geometries of Daraprim and Sulfadoxine were completely optimized by using ab-initio quantum mechanical calculations at the Restricted Hartree-Fock (RHF) level of theory without using any symmetry constraints. Initial geometry optimizations were performed using the ab-initio RHF method with 3-21G basis set. Subsequently, its results were utilized to the 6-31G basis set and final calculation were carried out with 6-311++G** basis set. The structures were refined further using Density Functional Theory which is a cost effective method for inclusion of electron correlations with the three-parameter density functional generally known as Becke3LYP (B3LYP), which includes Becke's gradient exchange corrections (Becke, 1988) the Lee *et al*. (1988) correlation functional and Vosko *et al*. (1980) with a 6-311++G** basis set. At the first step, geometry optimizations were carried out then, the IR and Raman frequencies were calculated using the Hessian which is

the matrix of second derivatives of the energy with respect to geometry.

The optimized molecular structures were tested by computing the second derivatives and checking that all the harmonic vibrational frequencies are found to be real at all level of calculations. All calculations in the present work were performed using Windows version of Gaussian 03 (Gaussian 03, 2004) suit of ab initio quantum chemical program.

RESULTS AND DISCUSSION

Molecular structures and Geometries

The geometry of a molecules or system gives more information on its physical and chemical properties. The geometric optimization of any system gives the ground state geometry of that system. The total ground state energy of a system is as a function of the coordinates of the nuclei from Born-Oppenheimer (BO) approximation. The ground state geometry corresponds to the minimum total ground state energy whereas a first order saddle point on the BO surface gives the transition state geometry.

The geometric parameters of Daraprim molecule are listed in table 1, while the molecular structure is shown by figure 1. The calculated bond lengths at RHF/6-311++G** level are slightly (0.01Å to 0.04Å) smaller than the corresponding values obtained at the DFT/B3LYP/6-311++G** level. The bond angles vary from 0.1 to 2 degree in both RHF and DFT levels of theories with the 6-311++G** basis set except for the angle A_{21}. Its RHF value is greater than its corresponding B3LYP value by approximately 4 degree. The six member carbon ring (Phenyl) and the other ring with two of the carbon atom replaced by Nitrogen atoms (pyrimidine) possibly gives added stability to the molecule. The Nitrogen atoms (N11, N12, N14 and N17) play a major role in the electron density configuration. Appreciable changes in bond angles are noted both at RHF/6-311++G** and B3LYP/6-311++G** levels, but no significant change in the bond length is noticed.

Table 1. Optimized geometrical parameters of Daraprim molecule obtained at RHF and B3LYP methods by employing 6 311++G** basis sets. Bond Lengths are given in Armstrong (Å) and Bond Angles are in degrees (˚).

Geomet. Parameters	RHF/ 6311++G**	B3LYP/ 6311++G**	Experiment (a,b,c)
R(C1C2)	1.4676	1.4419	1.399
R(C1C6)	1.5191	1.5084	
R(C1C7)	1.3529	1.3909	
R(C2C3)	1.3312	1.3592	1.386
R(C3C4)	1.4600	1.4411	1.402
R(C4C5)	1.3161	1.3397	
R(C5C6)	1.4999	1.4900	
R(C7C8)	1.4836	1.4645	
R(C7C10)	1.4947	1.4891	
R(C20C21)	1.5302	1.5348	
R(C4Cl13)	1.7454	1.7604	1.725
R(C5H30)	1.0749	1.0834	
R(C2H28)	1.0683	1.0794	
R(C3H27)	1.0742	1.0832	
R(C6H29)	1.0848	1.1032	1.082
R(C20H22)	1.0873	1.0969	
R(C20H23)	1.0814	1.0902	
R(C21H24)	1.0858	1.0931	
R(C21H25)	1.0813	1.0895	
R(C21H26)	1.0855	1.0931	
R(C8N11)	1.2712	1.3002	
R(C8N20)	1.5198	1.5226	1.40
R(C9N11)	1.3892	1.3865	1.360
R(C9N12)	1.2761	1.3006	
R(C9N17)	1.3479	1.3611	
R(C10N12)	1.3866	1.3870	1.391
R(C10N14)	1.2599	1.2937	
R(N14H16)	1.0046	1.0221	1.036
R(N17H18)	0.9919	1.0065	
R(N17H19)	0.9928	1.0071	
A(C4C5H30)	120.989	121.0876	119.60
A(C1C2H28)	119.4443	119.4605	
A(C3C2H28)	117.7976	117.5702	
A(C2C3H27)	120.1191	120.0862	
A(C4C3H27)	118.1486	118.5468	
A(C6C5H30)	116.9048	117.6603	
A(C8C20H22)	108.2771	108.5762	109.46
A(C1C6H15)	108.0402	108.2218	
A(C1C6H29)	109.9126	109.6664	
A(C5C6H15)	108.4750	109.1419	
A(C5C6H29)	109.4080	111.3224	
A(C8C20H23)	109.7684	109.9217	
A(C21C20H22)	109.0559	108.7757	
A(C21C20H23)	109.4436	109.5586	
A(C20C21H24)	109.4153	109.8469	
A(C20C21H25)	111.3222	111.1172	
A(C20C21H26)	110.9702	110.9170	
A(C3C4Cl13)	116.9139	117.4104	119.80
A(C2C1C6)	116.0590	116.2501	
A(C2C1C7)	122.3605	122.0668	
A(C6C1C7)	121.5044	121.5384	
A(C1C2C3)	122.6049	122.7434	
A(C3C4C5)	120.888	120.8603	
A(C5C4Cl13)	122.1929	121.7226	
A(C4C5C6)	122.0977	121.2497	
A(C1C6C5)	116.5419	117.4778	
A(C1C7C8)	125.528 0	124.5085	
A(C1C7C10)	123.0658	122.1469	
A(C8C7C10)	111.2219	113.2535	
A(C7C8C20)	122.8700	122.7951	
A(C8C20C21)	112.6834	112.8448	
A(C2C3C4)	121.7085	121.3239	
A(C7C8N11)	120.5857	121.5168	
A(N11C8C20)	116.2653	115.3545	

Geomet. Parameters	RHF/ 6311++G**	B3LYP/ 6311++G**	Experiment (a,b,c)
A(N11C9N12)	126.3676	126.3414	
A(N11C9N17)	113.0728	113.7140	113.9
A(N12C9,17)	120.5194	119.9025	
A(C7C10N12)	115.6151	117.2364	
A(C7C10N14)	121.8607	121.4397	
A(N12C10N14)	122.4825	121.2770	122.3
A(C8N11C9)	117.5250	117.1495	114.4
A(C9N12C10)	117.4445	117.8609	
A(C10N14H16)	109.0621	107.7203	
A(C9N17H18)	117.9875	117.8709	113.90
A(C9N17H19)	117.7085	117.8803	
A(H18N17H19)	118.9561	119.0952	
A(H22C20H23)	107.4679	106.9812	109.01
A(H24C21H25)	108.7557	108.7960	
A(H24C21H26)	108.0855	108.0803	
A(H25C21H26)	108.2063	107.9960	
A(H15C6H29)	103.6641	99.4445	

a= (Hellwege *et al.,* 1976) b=(Roussy *et al.,* 1986) c=(Herzberg, 1966).

The geometric parameters of Sulfadoxine molecule are listed in table 2, while its molecular structure is shown by figure 2. The calculated bond lengths at RHF/6-311++G** level are slightly (0.01Å to 0.04Å) smaller than the corresponding values obtained at the B3LYP/6-311++G** level. The bond angles vary from 0.1 to 2 degrees at both levels of theories except for the angles A_6 and A_9. For the angle $A_{6,}$ its RHF value is greater than its corresponding B3LYP value by approximately 9 degrees while for the angle $A_{9,}$ its RHF value is less than its corresponding B3LYP value by approximately 10 degrees. The Phenyl group and the pyrimidine possibly give added stability to the molecule. The Nitrogen atoms (N4, N17, N18 and N32) and the oxygen atoms (O6, O7, O20 and O21) play a major role in the electron density configuration. Appreciable changes in bond angles are noted both at RHF/6-311++G** and B3LYP/6-311++G** levels of theory, but no significant change in the bond length is noticed.

In both molecules, the RHF/6-311++G** and B3LYP/6-311++G** bond lengths and bond angles are approximately equal to the experimental values determined by Hellwege *et al*. (1976), Roussy *et al*. (1986) and Herzberg (1966). The B3LYP/6-311++G** theoretical calculated values are in better accord to the experimental values than their corresponding RHF/6-311++G** theoretical calculated values.

Table 2. Optimized geometrical parameters of Sulfadoxine molecule obtained at RHF and B3LYP methods by employing 6- 311++G** basis sets. Bond Lengths are given in Armstrong (Å) and Bond Angles are in degrees (˚).

Geomet. Parameters	RHF/ 6311++G**	B3LYP/ 6311++G**	Experiment (a,b,c)
R(C1-C2)	1.3906	1.4012	1.392
R(C2-C8)	1.3827	1.4015	
R(C22-C23)	1.3881	1.3956	
R(C22-C24)	1.3862	1.3947	
R(C23-C25)	1.3765	1.3855	
R(C24-C27)	1.3778	1.3855	
R(C25-C29)	1.3975	1.4069	
R(C27-C29)	1.3958	1.4065	
R(C3-H5)	1.0755	1.0857	1.084
R(C9-H10)	1.0814	1.0907	
R(C9-H11)	1.0795	1.0882	
R(C9-H12)	1.0813	1.0906	
R(C13-H14)	1.0858	1.0942	
R(C13-H15)	1.0807	1.0889	
R(C13-H16)	1.0823	1.0902	
R(C24-H28)	1.0723	1.0814	
R(C25-H30)	1.0755	1.0848	
R(C27-H31)	1.0755	1.0848	
R(C23-H26)	1.0740	1.0827	
R(C1-O6)	1.3173	1.3445	1.364
R(C2-O7)	1.3543	1.3687	
R(O6-C9)	1.4166	1.4385	
R(O7-C13)	1.4151	1.4407	1.364
R(C1-N4)	1.3163	1.3312	
R(C3-N4)	1.3175	1.3337	1.431
R(C3-N18)	1.3073	1.3257	
R(C8-N17)	1.3781	1.3848	1.391
R(C8-N18)	1.3251	1.3396	
R(N32-H33)	0.9943	1.0079	1.036
R(N32-H34)	0.9943	1.0079	
R(N17-H35)	0.9970	1.0139	
R(N17-S19)	1.6583	1.7155	1.764
R(S19-O20)	1.4262	1.4622	1.485
R(S19-O21)	1.4192	1.4554	
R(S19-C22)	1.7516	1.7771	1.799
A(C2-C1-N4)	122.0420	122.1251	
A(C2-C8-N17)	118.6527	118.3754	
A(C2-C8-N18)	122.4360	122.3286	
A(C25-C29-N32)	120.3621	120.5146	
A(C27-C29-N32)	120.4731	120.5838	
A(N4-C1-O6)	120.0894	119.9435	
A(C2-C1-O6)	117.8659	117.9303	
A(C1-C2-O7)	123.8872	125.3592	124.5
A(O7-C2-C8)	120.3521	118.6734	
A(C1-C2-C8)	115.6604	115.8060	
A(C23-C22-C24)	120.2114	120.7773	120.64
A(C22-C23-C25)	120.0296	119.5987	
A(C23-C25-C29)	120.294	120.5735	
A(C24-C27-C29)	120.4646	120.7318	
A(C25-C29-C27)	119.1143	118.8467	
A(C22-C23-H26)	119.9901	119.9711	119.88
A(C1-C2-H14)	117.7478	108.6403	
A(C8-C2-H14)	104.2631	114.1031	
A(C25-C23-H26)	119.9746	120.4233	
A(C22-C24-H27)	119.8824	119.4706	119.88
A(C22-C24-H28)	119.6725	119.6918	
A(H27-C24-H28)	120.4451	120.8367	
A(C23-C25-H30)	119.8702	119.7538	
A(C29-C25-H30)	119.8271	119.6671	
A(C24-C27-H31)	119.7763	119.6580	
A(C29-C27-H31)	119.7575	119.6094	

Geomet. Parameters	RHF/ 6311++G**	B3LYP/ 6311++G**	Experiment (a,b,c)
A(O7-C2-H14)	50.7482	50.8964	
A(O6-C9-H10)	110.7581	110.7862	
A(O6-C9-H11)	105.2635	104.9192	
A(O6-C9-H12)	110.6851	110.6751	
A(O7-C13-H14)	110.5706	110.3087	
A(O7-C13-H15)	106.4787	105.6954	
A(O7-C13-H16)	110.7179	110.7691	
A(N4-C3-H5)	116.2226	116.2719	
A(N4-C3-N18)	127.2166	127.1283	
A(N17-C8-N18)	118.8764	119.2504	
A(H5-C3-N18)	116.5587	116.5974	
A(C1-N4-C3)	116.5062	116.4994	114.4
A(C1-O6-C9)	119.2710	117.6077	
A(C2-O7-C13)	116.3092	116.8824	
A(H10-C9-H11)	110.4156	110.6829	
A(H10-C9-H12)	109.3575	109.1557	
A(H11-C9-H12)	110.3109	110.5784	
A(H14-C13-H15)	109.5910	109.7055	
A(H14-C13-H16)	109.8328	110.1695	
A(H15-C13-H16)	109.5887	110.1021	
A(C2-H14-C13)	63.1271	63.9766	
A(C8-N17-S19)	127.3534	126.2279	
A(S19-N17-H35)	112.7488	111.5772	
A(C3-N18-C8)	116.1111	116.0613	
A(N17-S19-O20)	101.7478	101.4478	
A(N17-S19-O21)	109.3153	109.4086	
A(N17-S19-C22)	106.7402	105.4150	
A(O20-S19-O21)	120.6094	121.4704	121.25
A(O20-S19-C22)	108.7478	108.8046	106.5
A(O21-S19-C22)	108.7671	109.0257	
A(S19-C22-C23)	119.57	00	119.2582
A(S19-C22-C24)	120.2075	119.9573	
A(C8-N17-H35)	116.8378	115.8576	
A(C29-N32-H33)	116.4304	117.4914	114.92
A(C29-N32-H34)	116.4674	117.4960	114.92
A(H33-N32-H34)	113.1870	114.0313	113.90

a=(Hellwege *et al*., 1976) b=(Roussy *et al*., 1986)
c= (Herzberg, 1966)

Energies and Dipole moments

The dipole moments (in Debye) and total electronic energies (a.u) without zero point correction (E_1), with zero point correction (E_2), with thermal energy correction (E_3) and with enthalpy correction (E_4) for the molecule are listed in table 3. The scaling factor for the zero-point vibrational energy is 0.9877 for the 6-311++G** basis set (Andersson and Uvdal, 2005). The zero point energy is a correction of electronic energy to account for the effects of molecular vibrations which persist at 0K. It is the minimum energy due uncertainty principle. Dipole moment is the first derivative of the energy with respect to the applied electric field. It is a measure of symmetry in molecular charge distribution. The dipole moment of a molecule gives the strength of the polarity of the molecule. The magnitude of the dipole moments obtained at B3LYP/6-311++G** level of theory is smaller as compared to the corresponding values of the dipole moment at RHF/6-311++G** level of theory for both Daraprim and Sulfadoxine molecules. This is due to the effect of electron correlation at the B3LYP/6-311++G** level of theory. The difference in the dipole moments between the two methods is 23.25 percent for Pyrimethamine and 4.47 Percent for Sulfadoxine. Nitrogen atoms draw more electrons from their neighboring carbon atoms, become highly electronegative in these molecules and attract electrons more strongly than the other atoms.

Table 3. Dipole moments and Total electronic energies without and with zero point energy corrections, with thermal energy correction and with enthalpy correction of Daraprim and Sulfadoxine molecules obtained using RHF and B3LYP methods by employing 6-311++G** basis set. All energies are given in Kilocalories/Mol.

	Methods/Basis Set			
	Daraprim		Sulfadoxine	
	RHF/ 6-311++G**	B3LYP/ 6-311++G**	RHF/ 6-311++G**	B3LYP/ 6-311++G**
μ	3.1524	2.4189	6.0206	5.7513
E_1	-714990.50	-718172.66	-864401.87	-868487.65
E_2	-714891.82	-718078.38	-864222.55	-868321.18
E_3	-714882.40	-718068.33	-864210.72	-868308.44
E_4	-714881.81	-718067.74	-864210.13	-868307.85

μ =Dipole moment
E_1=Total Electronic Energy without Zero point correction, E_2=Total Electronic Energy with Zero point correction, E_3=Total Electronic Energy with Thermal energies, E_4=Total Electronic Energy with enthalpies

Atomic Charges and Polarizability

The electrostatic potential derived charges using the CHelpG scheme of Breneman on at different atomic positions of Daraprim and Sulfadoxine molecules at RHF/6-311++G** and B3LYP/6-311++G** levels of theories are given in Table 4 and 5 respectively. The Mulliken population analysis partitions the charges among the atoms of the molecule by dividing orbital overlap evenly between two atoms. Whereas the electrostatic potential derived charges assign point charges to fit the computed electrostatic potential at a number of points on or near the Van der Waal surface. Hence, it is appropriate to consider the charges calculated by CHelpG scheme of Breneman instead of Mulliken population analysis. Within a molecular system, atoms can be treated as a quantum mechanical system. On the basis of the topology of the electron density, the atomic charges in the molecule can be explained.

From table 4 it is clear that the amount of charges on C2,C3, C7, C12, H15, H23, H29, N11 N12, N14 N17 and C13 atoms is negative while C1, C4, C6, C8, C9, H16, H18, H19,C20, H22,H24,H25H26, H27,H28, H30 atoms are positive at RHF/6-311++G** level of theory and at B3LYP/6-311++G** level of theory for the Daraprim

Table 4. Electrostatic Potential Derived Charges on different atomic positions of Daraprim.

S. No. Atom	RHF/ 6-311++G**	B3LYP/ 6-311++G**	S. No. Atom	RHF/ 6-311++G**	B3LYP/ 6-311++G**
1 C	0.192053	0.134847	16 H	0.395010	0.345307
2 C	-0.245038	-0.180216	17 N	-1.086988	-0.969737
3 C	-0.057188	-0.025741	18 H	0.436246	0.399691
4 C	0.159353	0.082126	19 H	0.437308	0.406305
5 C	-0.358067	-0.232976	20 C	0.051870	0.026295
6 C	0.422854	0.302053	21 C	-0.154424	-0.088515
7 C	-0.605130	-0.468105	22 H	0.033451	0.038177
8 C	0.700480	0.538939	23 H	-0.008479	-0.010396
9 C	1.268641	1.096434	24 H	0.044388	0.027084
10 C	1.002893	0.872279	25 H	0.047563	0.025608
11 N	-0.891348	-0.767659	26 H	0.034966	0.021404
12 N	-1.046270	-0.921292	27 H	0.121116	0.102252
13 Cl	-0.170415	-0.141227	28 H	0.099245	0.082839
14 N	-0.953443	-0.837950	29 H	-0.017111	-0.011049
15 H	-0.021981	-0.004421	30 H	0.168444	0.135547

Table 5. Electrostatic Potential Derived Charges on different atomic positions of Sulfadoxine.

S. No. Atom	RHF/ 6-311++G**	B3LYP/ 6-311++G**	S. No. Atom	RHF/ 6-311++G**	B3LYP/ 6-311++G**
1 C	0.829167	0.664160	19 S	1.358718	1.109000
2 C	-0.346762	-0.223034	20 O	-0.656988	-0.560633
3 C	0.654243	0.519349	21 O	-0.617873	-0.524356
4 N	-0.815720	-0.688231	22 C	-0.220339	-0.092523
5 H	0.043688	0.035156	23 C	0.013868	-0.055445
6 O	-0.321893	-0.270138	24 C	0.071994	-0.033149
7 O	-0.398941	-0.377867	25 C	-0.363883	-0.257738
8 C	0.879255	0.754729	26 H	0.118861	0.116012
9 C	-0.000386	-0.037434	27 C	-0.406594	-0.277854
10 H	0.075553	0.074989	28 H	0.132097	0.129016
11 H	0.076619	0.085538	29 C	0.574641	0.449034
12 H	0.062655	0.065823	30 H	0.166902	0.138133
13 C	0.221497	0.229324	31 H	0.171939	0.143852
14 H	0.019746	0.010558	32 N	-0.902917	-0.832951
15 H	0.034284	0.030178	33 H	0.368124	0.351824
16 H	-0.006662	-0.018385	34 H	0.360857	0.350497
17 N	-0.791444	-0.739795	35 H	0.423783	0.402920
18 N	-0.808861	-0.670559			

molecule. From table 5, the amount of charges on C2, N4, O6, O7, H16, N17, N18, O20, O21, C22, C25, C27 and N32 atom are negative while on the C1, C3, H5, C8, C9, H10, H11, H12, C13, H14, H15, S19, C23, C24, H26, H28, C29, H30, H31, H33, H34, H35 atoms is positive in the case of Sulfadoxine molecule.

Polarizability is a property which depends on the second derivative of the energy with respect to the applied electric field. It gives information about the distribution of electrons in the molecule. The rotational excitation of a polyatomic molecule by electron collision is considered as caused by the polarization interaction as well as by the electrostatic interaction (Yukikazu, 1971). The polarizability tensor components, the average polarizability and the anisotropy of Daraprim and Sulfadoxine obtained at RHF/6-311++G** and B3LYP/6-311++G** level of theories are listed in table 6. All the six polarizability tensor components of Daraprim and Sulfadoxine molecules α_{xx}, α_{xy}, α_{yy}, α_{xz} α_{yz} and α_{zz} components changes significantly at both level of theory considered here. But they do not follow any regular pattern. For Pyrimethamine, only the α_{yz} component is negative while for Sulfadoxine α_{xy}, α_{xz}, and α_{yz}

Table 6. Polarizability tensors, average polarizability and anisotropy of Daraprim and Sulfadoxine using RHF and B3LYP methods by employing 6-311++G** basis set.

	Methods/Basis set			
	Daraprim		Sulfadoxine	
Tensor component	RHF/ 6-311++G**	B3LYP/ 6-311++G**	RHF/ 6-311++G**	B3LYP/ 6-311++G**
α_{xx}	266.054	334.059	228.290	277.071
α_{XY}	7.639	9.782	-14.833	-15.615
α_{YY}	165.501	188.045	182.697	209.664
α_{XZ}	5.719	9.684	-6.978	-10.415
α_{YZ}	-15.555	-17.344	-14.318	-15.950
α_{ZZ}	121.812	126.994	145.186	156.648
$<\alpha>$	184.456	216.033	205.391	214.461
$\Delta\alpha$	115.883	184.287	72.114	104.373

Table 7. IR intense vibrational frequencies and their approximate description of Daraprim molecule obtained using B3LYP methods by employing 6-311++G** basis set.

No.	Freq theory	expt (a)	Approximate descrition
1	219.81		Symmetrical bending of Pyrimidine and phenyl rings
2	223.00		Rings distortion+stretching of N17-H10, 18+C21-H24,25,26 (CH_3) vibration
3	349.60		N-H Waging of NH2 (N17-H18, H19)+ pyrimidine ring breathing
4	367.52		Rings distortion
6	608.65		Rings distortion +Breathing of CH_3
7	634.85		Do as above
8	652.99		Rings distortion + waging of C-H bond of phenyl group (C6- H15,H29)
9	677.18		Rings breathing
10	723.25		Do as above
11	895.92		C-H bond rotations
12	958.15		N-H bond Rotation of NH_2 (N14-H16) group
13	968.35		Do as above
14	1169.12		Distortion of CH_2-CH_3 group
15	1466.27	1280	C-N stretching vibrations
16	1483.03		C-H bond symmetrical stretching of the CH_3 group
17	1485.55		C-H bond symmetrical bending of the Phenyl group (C5-H15,29)
18	1513.71		C=C-H bond waging of the phenyl group (H28C2=C3H27)
19	1555.56		C-H bond bending of the CH_2 group (C28-H22,23)
20	1558.42		C-H bond asymmetrical stretching of the CH_3 group
21	1571.47	1394	C-H bond symmetrical bending of CH_3
22	1674.26		N-H bond symmetrical bending of NH_2 group
23	1680.24	1400	C=C bond symmetrical stretching of the Carbons binding the two rings
24	1728.12		N-H bond symmetrical bending of NH_2 group +C=C stretching of benzene ring
25	1775.29		C=N bond symmetrical stretching of Pyrimidine ring
26	1788.79	1649	C=N-H bond stretching +C=C-H bond stretching of benzene ring
27	1802.45		Benzene ring distortion + C=N stretching of the NH group
28	3070.44	2931	C-H bond symmetrical stretching of CH_3 and CH_2 group
29	3073.95		Do as above
30	3099.34		C-H bond symmetrical stretching of benzene ring
31	3118.62		C-H bond asymmetrical stretching of benzene ring
32	3125.89		C-H bond asymmetrical stretching of the CH_3 group
33	3146.13		C-H bond asymmetrical stretching of CH_3 and CH_2 group
34	3170.79		Do as above
35	3238.38	3149	C-H bond stretching of benzene ring (C5-H30)
36	3246.57		C-H bond stretching of benzene ring (C3-H27)
37	3300.72		C-H bond stretching of benzene ring (C2-H28)
38	3606.60		N-H bond stretching of NH group
39	3707.02	3467	N-H bond symmetrical stretching of NH_2 group
40	3836.31		N-H bond asymmetrical stretching of NH_2 group

a = Onyeji *et al*. 2009

components are negative. From the table, we can see that the tensor α_{xx} is responsible for the greatest contribution both in the average polarizability and the anisotropy for the two molecules at all levels of theory. We can also see

Table 8. IR intense vibrational frequencies and their approximate description of Sulfadoxine molecule obtained using B3LYP methods by employing 6-311++G** basis set.

No.	Freq	Approximate descrition
1	347.742	N-H waging of the NH_2 group (N32-H33,34) + breathing of phenyl ring.
2	438.036	D0 as in above.
3	484.362	N-H bond rotation of NH group + breathing of phenyl ring + twisting of the pyrimidine ring.
4	553.061	N-H bond rotation of NH group.
5	563.264	Twisting of the pyrimidine ring.
6	601.55	C-O-H bond angle bending.
7	647.33	Twisting of the phenyl ring.
8	1012.44	C-O bond stretching of the mehoxyl group (C13-O7).
9	1020.54	C=C bond symmetrical and asymmetrical stretching of phenyl ring.
10	1072.97	S=O bond symmetrical stretching of SO_2 (S19=O20,21).
11	1127.25	S-C bond stretching (S19-C22) and O=S=O bond angle bending.
12	1206.4	C-H bond symmetrical bending of phenyl ring.
13	1293.89	N-H bond rotation of NH group + twisting of the pyrimidine ring.
14	1346.6	C-H bond rotation of the pyrimidine ring (C3-H5).
15	1443.04	C-H bond bending of methoxyl group (C9-H10,11,12) + C-H bond rotation of pyrimidine.
16	1481.11	C-H bond rotation of methoxyl group (C9-H10,11,12).
17	1498.74	H-C-H bond angle bending methoxyl group (C-H10,12).
18	1601.23	C-N bond symmetrical stretching of pyrimidine group (C1,8-N4,18).
19	3049.51	C-H bond symmetrical stretching of methoxyl group (C9-H10,11,12).
20	3109.66	C-H bond symmetrical and asymmetrical stretching of methoxyl group (C13-H14,15,16).
21	3123.12	C-H bond asymmetrical stretching of methoxyl group (C9-H10,12).
22	3143.06	C-H bond symmetrical stretching of methoxyl group (C13-H15,16).
23	3151.41	C-H bond symmetrical and asymmetrical stretching of methoxyl group (C9-H10,11,12).
24	3165.9	C-H bond asymmetrical stretching of the phenyl ring (C25,27-H30,31).
25	3166.51	C-H bond asymmetrical stretching of the phenyl ring (C25,27-H30,31) and C-H bond rotation (C3-H5).
26	3203.12	C-H bond stretching of phenyl ring (C23-H26).
27	3587.29	N-H bond symmetrical stretching of NH_2 group.
28	3691.5	N-H bond symmetrical stretching of NH_2 group.

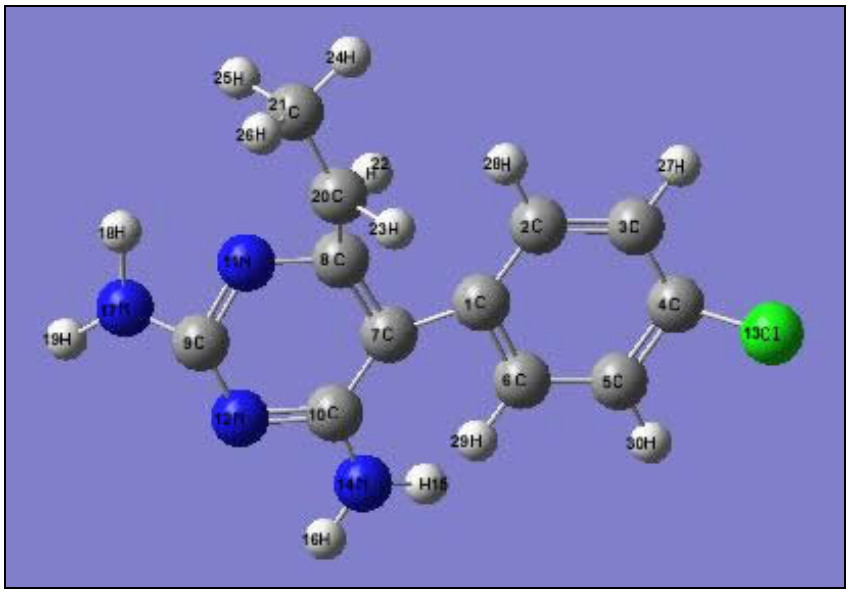

Fig. 1. DAraprim.

that the inclusion of electron correlation affect the average polarizability $< \alpha >$ and the anisotropy $\Delta\alpha$. We equally observe that the effect of inclusion of electron correlation increases $< \alpha >$ by 17.1 percent and $\Delta\alpha$ by 59 percent for Pyrimethamine and increases α by 4.4 percent and $\Delta\alpha$ by 44.7 percent for Sulfadoxine molecule.

Vibrational Frequencies and Assignments

The vibrational frequencies, IR intensities and Raman activities for pyrimethamine and Sulfadoxine molecules at RHF and B3LYP levels with 6-311++G** basis set have been calculated. This was done by calculating the matrix of second derivative of energy (the Hessian or Force constant matrix) which upon diagonalization yields the

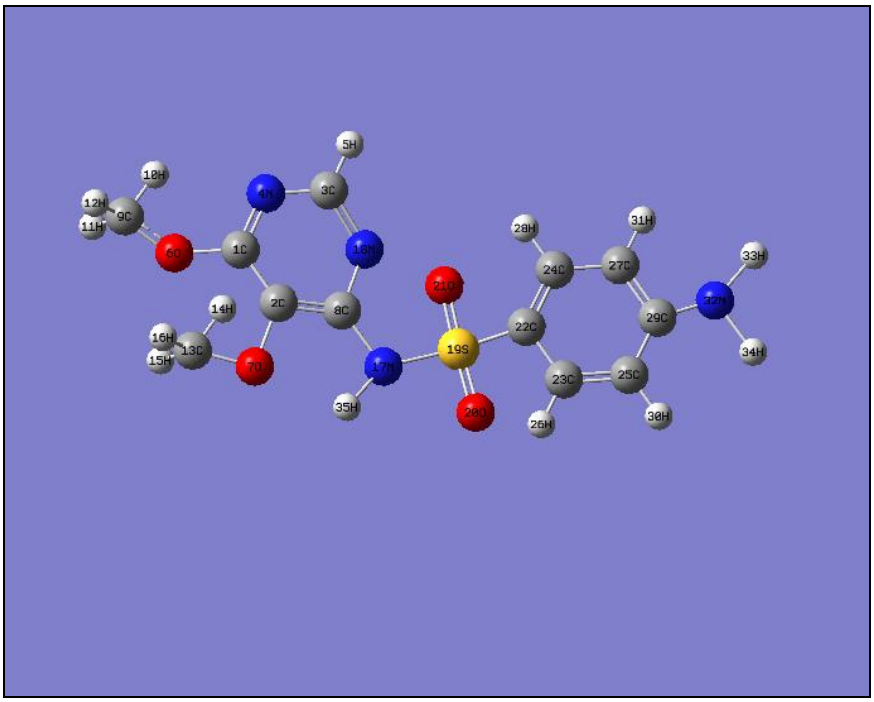

Fig. 2. Sulfadoxine.

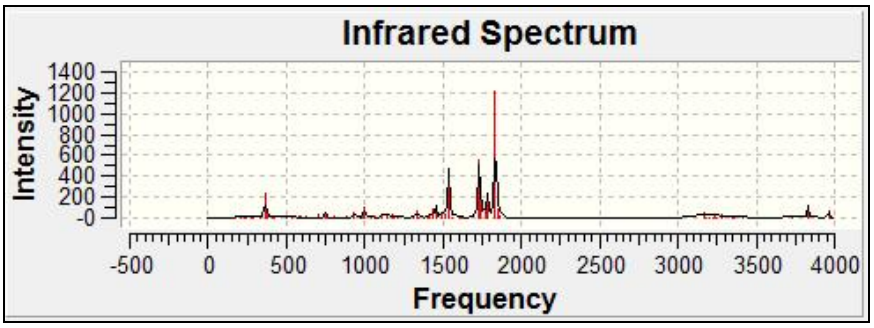

Fig. 3. Infra Red spectrum of Daraprim at RHF/6-311++G**

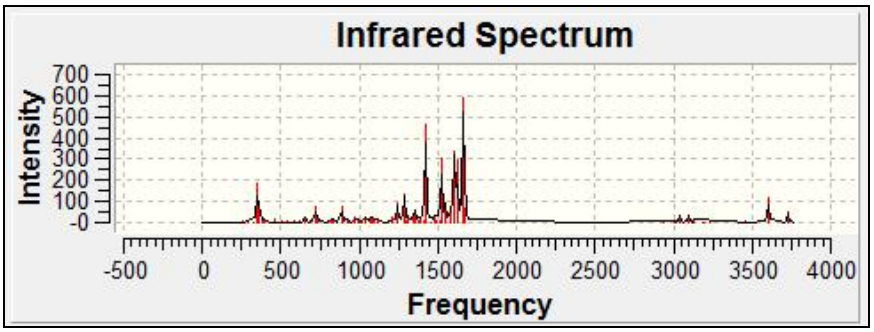

Fig. 4. Infra Red spectrum of Daraprim at B3LYP/6-311++G**

harmonics vibrational frequencies. The frequencies reported were scaled so as compare them with other results. The scaling factor for the vibrational frequencies is 0.9679 and 1.0100 for low-frequency vibrations (Andersson and Uvdal, 2005) for the 6-311++G** basis set. The B3LYP results show significant lowering in magnitude of the calculated frequencies bringing them in better accord with other theoretical and experimental results (Barbara *et al*., 2010; Onyeji *et al*., 2009). No experimental values were obtained for Sulfadoxine. The B3LYP results for Sulfadoxine showed significant lowering in magnitude of the calculated vibrational frequencies bringing them in better accord with results obtained from Barbara *et al*. (2010).

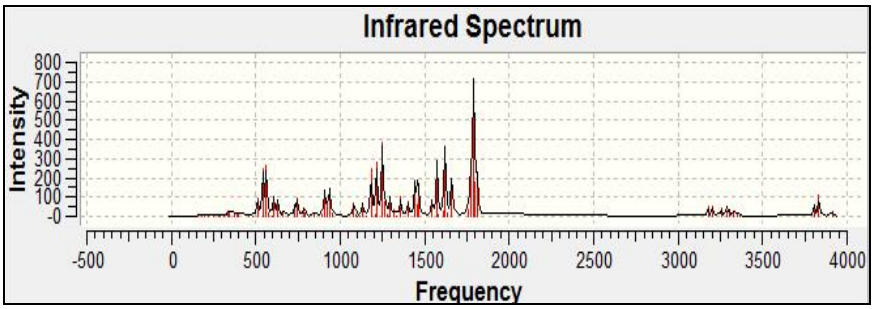

Fig. 5. Infra Red spectrum of Sulfadoxine at RHF/6-311++G**

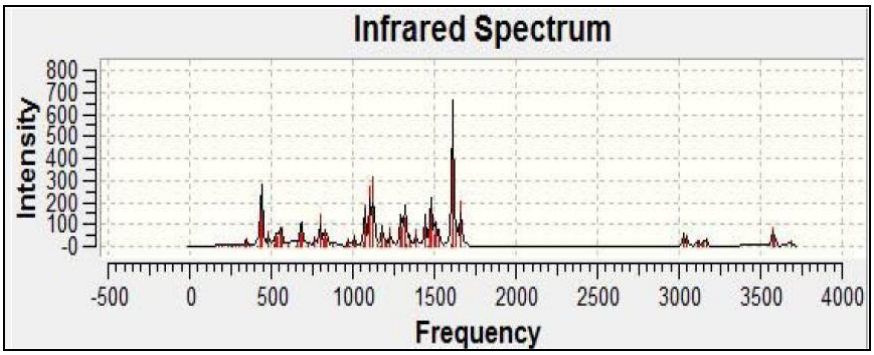

Fig. 6. Infra Red spectrum of Sulfadoxine at B3LYP/6-311++G**

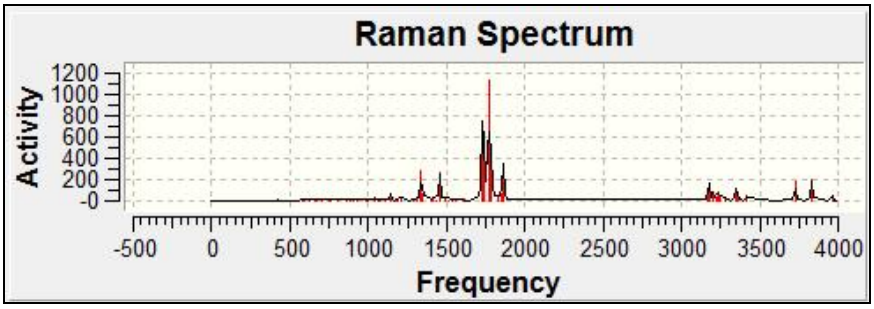

Fig. 7. Raman spectrum of Daraprim at RHF/6-311++G**

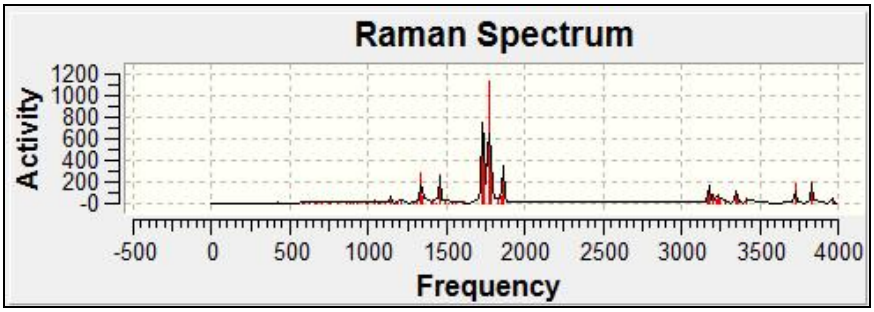

Fig. 8. Raman spectrum of Daraprim at B3LYP/6-311++G**

Table 7 and 8 gives the more prominent vibrational frequencies values and their tentative assignment for Pyrimethamine and Sulfadoxine molecules respectively which have been made on the basis of the relative displacements of the atom associated with different calculated frequencies. Onyeji *et al*. (2009) have carried out a spectroscopic study of Daraprim and presented some assignments for the observed spectra in the region 1400-3500 cm^{-1}. Some of more prominent vibrational frequencies values given by Onyeji are reported in table 7. From table 7, it is clear that our theoretical values are closed to the experimental values of Onyeji *et al*. (2009).

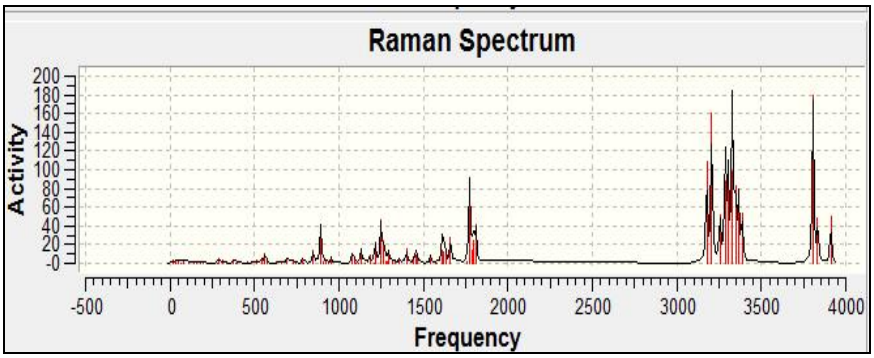

Fig. 9. Raman spectrum of Sulfadoxine at RHF/6-311++G**

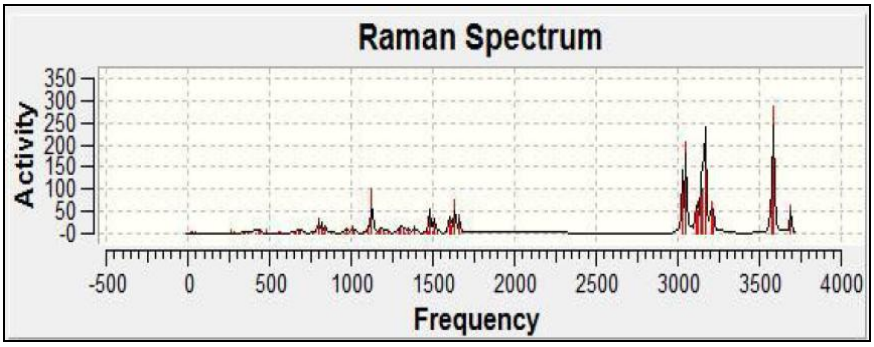

Fig. 10. Raman spectrum of Sulfadoxine at B3LYP/6-311++G**

The agreement between our theoretical and experimental values is within 10-15 percent. This may be due anharmocity effects. The theoretical obtained vibrational spectra for RHF/6-311++G** level of thoery are shown in figure 3, 5, 7, 9 and at B3LYP/6-311++G** level of thoery are shown in figure 4, 6, 8, 10 for Pyrimethamine and Sulfadoxine. The infrared spectra at both levels of theory are with the range 400-4000cm^{-1} which lies within the same range as that of the FT-IR spectrum obtained by Oneyeji *et al*. (2009), and generated using KBr dish method for Pyrimethamine molecule. The B3LYP results of the calculated vibrational frequencies were in better accord with experimental values as given by Colin (1992) and Onyeji *et al*. (2009) for Daraprim molecule.

CONCLUSIONS

In this paper we have studied the structure, energy, charges and vibrational frequencies of Pyrimethamine and Sulfadoxine molecules. We have seen that the charges on the same label atoms have same sign both in RHF and B3LYP levels of theories. The molecules are more stable at the B3LYP level of theory than at the RHF level of theory due to the low electronic energies obtained at the B3LYP level of theory. The frequency calculations obtained at the B3LYP level are closer to the experimental value than those obtained at the RHF level due the effect of electron correlation. The magnitude of the dipole moment is higher in the RHF level and the polarizability tensor components are greater at the B3LYP level. This implies that the inclusion of electron correlation decreases the dipole moment and increases the polarizability tensors, the average polarizability and the anisotropy. The IR and Raman spectra of the molecules have also been presented and the IR spectrum of Pyrimethamine lies in the same range as that given by experiment.

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