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Investigation of the Effects of Solvents on the Structural, Electronic and Thermodynamic Properties of Rosiglitazone Based on Density Functional Theory

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Authors' contributions

This work was carried out in collaboration among all authors. Author RAI performed calculation of structural properties and sourced some relevant journals for the review. Author ABS performed calculations of vibrational frequencies and thermodynamic properties. Author ASG initiated the work and performed stability check of the molecule. Author AL carried out total energy calculations and writing the theoretical background. Author AM carried out calculations on global quantities and HOMO-LUMO energy. All authors took part in the compilation of results, proof reading and effecting all corrections. All authors read and approved the final manuscript.

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ABSTRACT

Rosiglitazone ($C_{18}H_{19}N_3O_3S$) is an anti-diabetic drug that reduces insulin resistance in patients with type 2 diabetes. The parameters (bond lengths and bond angles), HOMO, LUMO, HOMO-LUMO energy gap, dipole moment, thermodynamic properties, total energy and vibrational frequencies and intensities of the Rosiglitazone molecule in gas phase and in solvents (Water, Ethanol, DMSO and Acetonitrile) were calculated based on Density Functional Theory (DFT) using standard basis sets: B3LYP/6-31G(d,p), B3LYP/6-31+G(d,p) and B3LYP/6-31++G(d,p). Windows version of Gaussian 09 was used for all the calculations. From the results obtained, the solvents have little influence on the optimized parameters of the molecule. The highest HOMO value of -5.433 eV was found in gas phase showing that the molecule will best donate electron in the gas

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phase, followed by ethanol in comparison with other solvents. The values of the HOMO were observed to increase with the decrease in dielectric constants of the solvents across all the basis sets used. The lowest LUMO energy of -1.448 eV was found to be in ethanol which shows that the molecule will best accept electron in ethanol compared to the gas phase and other solvents. The largest HOMO-LUMO gap of 4.285 eV was found in water which shows its higher kinetic stability and less chemical reactivity compared to other solvents and in the gas phase. The chemical softness of the molecule was found to decrease as the dielectric constants of the solvents increased namely from ethanol to water. The chemical hardness was found to slightly increase with the increase in dielectric constants of the solvents. The highest value of the dipole moment of 4.6874 D was found in water indicating that the molecule will have the strongest intermolecular interactions in water compared to other solvents and in the gas phase. The total energy increased as the dielectric constants of the solvents decreased from water to ethanol. The vibrational frequencies and intensities increased as the dielectric constants of the solvents increased from ethanol to water. The results confirmed the effects of solvents on the structural, electronic and thermodynamic properties of the studied molecule and will be useful in the design and development of rosiglitazone as an anti-diabetic drug.

Keywords: DFT; diabetes; gaussian 09; rosiglitazone; solvents effects.

1. INTRODUCTION

Diabetes mellitus is a group of complex metabolic disorders characterized by deficient insulin secretion, impaired insulin action, or a combination of both resulting in hyperglycemia. People with diabetes have an increased risk of developing a number of serious life-threatening health problems resulting in highly medical care costs, reduced quality of life and increased mortality [1]. Persistently high blood glucose levels cause generalized vascular damage affecting the heart, eyes, kidneys, nerves as well as resulting in various complications [1]. Diabetes is now one of the most common diseases that cause sudden death in most of the African countries and cause most of the severe heart disease and stroke, kidney damage, nerve damage, amputation and vision loss. Rosiglitazone is an antihyperglycemic agent that reduces insulin resistance in patients with Type 2 diabetes which represents a disability of the pancreas related to the secretion of insulin and peripheral insulin resistance. Rosiglitazone belongs to the thiazolidinedione class of oral antidiabetic agents [2]. A Molecular modeling study of Rosiglitazone and its metabolites by using the PM6 method have been reported [3]. Similarly, Geometry optimization and the calculation of electronic properties such as HOMO, LUMO, HOMO-LUMO energy gap, dipole moment, the total energy in gas phase and solvents of Rosiglitazone and Pioglitazone using DFT method were also reported [4]. Physical and chemical properties of a molecule depend on the structure and various kinds of the molecule. Chemical reactions of a molecule in solution are affected by the nature of the solvent not only in terms of the energies of HOMO and LUMO of the molecule but also their other properties [5].

The purpose of this work is to investigate the influence of solvation media upon the structural, electronic and thermodynamic properties of rosiglitazone based on DFT employing three basis sets B3LYP/6-31G(d,p), B3LYP/6-31+G(d,p) and B3LYP/6-31++G(d,p). The solvents used in this work included Water, Ethanol, Dimethyl sulfoxide (DMSO) and Acetonitrile with the following dielectric constants at 25°C: Water ($\varepsilon = 79$), Ethanol ($\varepsilon = 25$), Dimethyl sulfoxide (DMSO) ($\varepsilon = 47$) and Acetonitrile ($\varepsilon = 38$).

1.1 Theoretical Background

1.1.1 Density functional theory (DFT)

Density functional theory (DFT) is a computational quantum mechanical method used in physics, chemistry, and materials science to investigate the electronic structure (principally the ground state) of many body systems, in particular atoms, molecules, and the condensed phases. Using this theory, the properties of many- electron systems can be determined. DFT comes from the functional (function of a function) of electron density [6]. Within DFT the ground state energy can be determined by the relationship given as [7]:

$$\rho(r) = \sum_{i=1}^{n} \left|\psi_{i\,(r)}\right|^2 \quad (1)$$

Where $\rho(r)$ is electron density and $\psi_{i\,(r)}$ is the wave function of the electrons. This relation was

employed here to, determine the ground state energy of the molecules.

1.1.2 Local density approximation (LDA) of the electrons. This relation was employed here to determine

The local density approximation (LDA) is the basis of all approximate exchange-correlation functional. At the center of this model is the idea of a uniform electron gas. This is a system in which electrons move on a positive background charge distribution such that the total ensemble is neutral. The central idea of LDA is the assumption that we can write E_{XC} in the following form [8]:

$$E_{XC}^{LDA}[\rho] = \int \rho(\vec{r}) E_{XC}(\rho(\vec{r}))d\vec{r} \quad (2)$$

where $E_{XC}(\rho(\vec{r}))$ is the exchange-correlation energy per particle of a uniform electron gas of density $\rho(\vec{r})$. This energy per particle is weighted with the probability $\rho(\vec{r})$ that there is an electron at this position. The quantity $EXC(\rho(\vec{r}))$ can be further split into exchange and correlation contributions given by [8]:

$$E_{XC}(\rho(\vec{r})) = E_X(\rho(\vec{r})) + E_C(\rho(\vec{r})) \quad (3)$$

The exchange part, E_X, which represents the exchange energy of an electron in a uniform electron gas of a particular density, was originally derived by Bloch and Dirac in the late 1920s.

$$E_X = -\frac{3}{4}\left(\frac{3\rho(\vec{r})}{\pi}\right)^{1/3} \quad (4)$$

1.1.3 Generalized gradient approximation (GGA)

Despite its simplicity, the LDA has been found to be inadequate for some problems and for this reasons extensions of LDA have been developed [6]. The logical steps in this regard are the use of the information not only about the density $\rho(\vec{r})$ at a particular point, $\vec{r}$ but also the gradient of the charge density, $\nabla\rho(\vec{r})$ so as to account for the non-homogeneity of the true electron density distribution in the real system. Thus, we may write the exchange-correlation energy in a form known as Generalized Gradient Approximation (GGA) [6]

$$E_{XC}^{GGA}[\rho(\vec{r})] = \int f^{GGA}[\rho(\vec{r}), \nabla\rho(\vec{r})]d\vec{r} \quad (5)$$

Where *f* is the function of electron densities and their gradients [6]. E_{XC}^{GGA} is usually split into the exchange and correlation parts, which are modeled separately

$$E_{XC}^{GGA} = E_X^{GGA} + E_C^{GGA} \quad (6)$$

1.1.4 Frontier molecular orbitals (FMOs) energy and chemical indices

To explain several types of reaction and for predicting the most reactive position in conjugated systems, molecular orbitals and their properties such as energy are used [9]. The energies of the Highest Occupied Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO) are the most important orbitals in a molecule. HOMO can be through the outermost orbital containing electrons tends to give these electrons such as an electron donor. On the other hand, LUMO can be through the innermost orbital containing free places to accept electron [10]. The Energy of the HOMO is directly related to the ionization potential and LUMO Energy is directly related to the electron affinity [11]. The Energy difference between HOMO and LUMO orbital is called an energy gap which is an important parameter that determines the stability of the structures. The energy gap is also used in determining molecular electrical transport properties [12].

The HOMO and LUMO energies are used for the determination of global reactivity descriptors. It is important that Ionization potential (I), Electron affinity (A), Electrophilicity (ω), Chemical potential (μ), Electronegativity (χ), Hardness (η) and Softness (S) to be put into a Molecular Orbital's framework [12]. We focus on the HOMO and LUMO energies in order to determine the interesting molecular/atomic properties and chemical quantities. In simple molecular orbital theory approaches, the HOMO energy is related to the ionization potential (I) and the LUMO energy has been used to estimate the electron affinity (A) respectively by the following relations [12]:

$$I = -E_{HOMO} \quad (7)$$

$$A = -E_{LUMO} \quad (8)$$

$$(\mu) = -\frac{I+A}{2} \quad (9)$$

$$(\eta) = \frac{I-A}{2} \quad (10)$$

$$(S) = \frac{1}{\eta} \quad (11)$$

$$(\chi) = \frac{I+A}{2} \quad (12)$$

$$(\omega) = \frac{\mu^2}{2\eta} \quad (13)$$

In addition, according to Koopmans' theorem the energy gap, E_{gap}, defined as the difference between HOMO and LUMO energy [13].

$$E_{gap} = (E_{LUMO} - E_{HOMO}) \approx IP - EA \quad (14)$$

2. COMPUTATIONAL METHODS

The geometry optimization of Rosiglitazone molecule was performed based on Density Functional Theory (DFT) in Becke's three-parameter hybrid functional [14] combined with Lee-Yang-Parr correlation [15] functional (B3LYP) method together with the standard 6-31G(d,p), 6-31+G(d,p) and 6-31++G(d,p) basis sets utilizing gradient geometry optimization. The geometries were fully optimized without any constraint with the help of analytical gradient procedure implemented in Gaussian 09 package [16]. Prior to the geometry optimization, stability check was performed. All the parameters were allowed to relax and all calculations converged to an optimized geometry which corresponds to a true energy minimum, and revealed by absent of imaginary values in the frequency values. For the study of solvation effects a self-consistent reaction field (SCRF) approach based on Polarizable Continuum Model (PCM) were employed. The effects of four solvents (water, ethanol, DMSO, and acetonitrile) were investigated by means of the SCRF method based on PCM which is default in Gaussian 09 developed by Tomasi and Coworkers [17]. The optimized parameters were evaluated with vibrational frequencies and intensities values. The frontier molecular orbital's calculation has been carried out to explain the charge transfer within the molecule. The energy gap which is the difference between HOMO and LUMO was calculated and used in obtaining chemical hardness, chemical softness, chemical potential, electronegativity, and electrophilicity index. The total energy, thermodynamic properties and dipole moment of the molecule were calculated. All computation were carried out in gas phase and in solvents using windows version of Gaussian 09 software [16]. IR pal 2.0 was used for interpretation of the vibrational frequencies.

3. RESULTS AND DISCUSSION

3.1 Optimized Bond Lengths (Å) in the Gas phase and in Solvents

The bond length is a measurable distance between two atoms covalently bonded together. It is worth noting that the shorter the bond length, the greater the value of bond energy and bond strength [18]. The optimized bond lengths of rosiglitazone in the gas phase and in solvents are shown in Tables 1, 2 and 3.

The results obtained show that the lowest value was 1.013Å in the gas phase. In water, ethanol, DMSO and acetonitrile it was observed that the lowest value was 1.0143Å for B3LYP/6-31G(d,p) as shown in Table 1. This indicates that the values are a bit higher in solvents than in the gas phase which implies that the bonds will be slightly stronger in the gas phase than in solvents. The bond R(5,13):N5-H13 between Nitrogen and Hydrogen atoms at the indicated positions have the lowest values of bond lengths. These are the strongest bonds and a large amount of energy is needed to break them.

Also, from the results of bond length obtained the highest value 1.8472Å for B3LYP/6-31G(d,p), 1.8494Å for B3LYP/6-31+G(d,p) and 1.8495Å B3LYP/6-31++G(d,p) was exactly the same in both gas phase and solvents. The bonds R(1,2):S1-C2 between sulphur and carbon atoms at the specified positions have the highest values of bond lengths. From the results obtained increasing or decreasing the dielectric constants of the solvents has little influence on the bond lengths particularly the shorter bond lengths.

Table 1. Bond lengths of Rosiglitazone for 6-31G(d,p)

Bond lengths (Å)	Gas phase	Solvents			
		Water	Ethanol	DMSO	Acetonitrile
R(1,2)	1.8472	1.8472	1.8472	1.8472	1.8472
R(1,3)	1.7996	1.795	1.7952	1.795	1.7951
R(2,6)	1.5442	1.5437	1.5438	1.5437	1.5437
R(24,25)	1.5295	1.5276	1.5278	1.5277	1.5277
R(2,7)	1.5322	1.5303	1.5304	1.5303	1.5303
R(5,13)	1.013	1.0143	1.0143	1.0143	1.0143
R(34,40)	1.0826	1.0821	1.0821	1.0821	1.0821
R(16,21)	1.0832	1.0831	1.0831	1.0831	1.0831
R(41,44)	1.0842	1.0841	1.0841	1.0841	1.0841
R(17,22)	1.0848	1.0852	1.0852	1.0852	1.0852

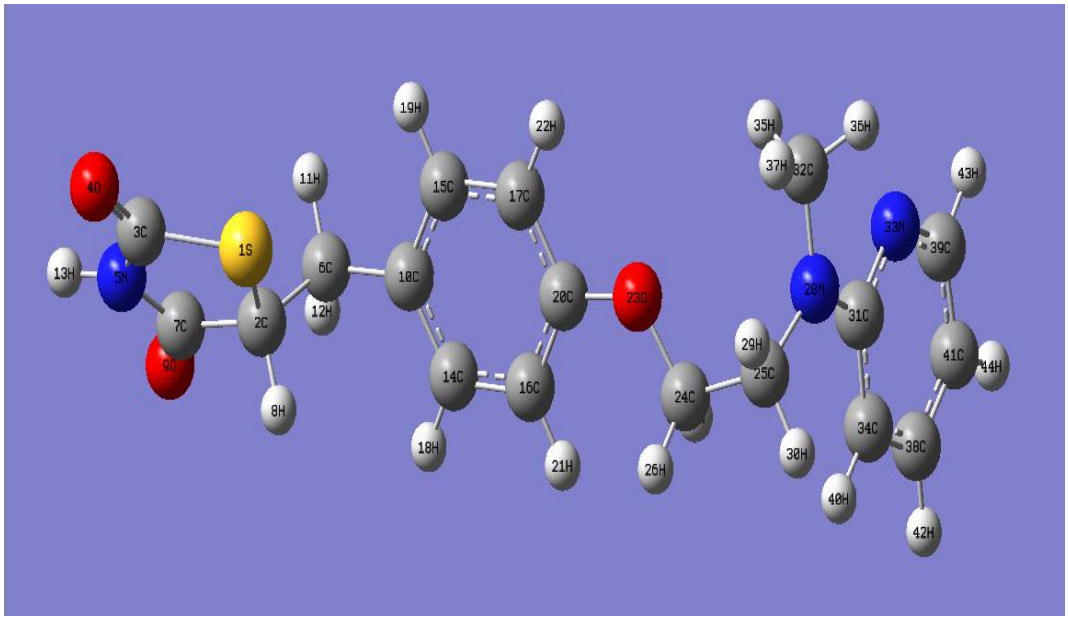

Fig. 1. Optimized molecular structure of Rosiglitazone

Table 2. Bond lengths of Rosiglitazone for 6-31+G(d,p)

Bond lengths (Å)	Gas phase	Solvents			
		Water	Ethanol	DMSO	Acetonitrile
R(1,2)	1.8494	1.8494	1.8494	1.8494	1.8494
R(1,3)	1.7932	1.7849	1.7853	1.785	1.7851
R(2,6)	1.5457	1.5452	1.5453	1.5452	1.5452
R(24,25)	1.5299	1.5277	1.5278	1.5278	1.5278
R(2,7)	1.5313	1.5288	1.5289	1.5288	1.5288
R(5,13)	1.0142	1.0155	1.0155	1.0155	1.0155
R(34,40)	1.0827	1.0821	1.0821	1.0821	1.0821
R(16,21)	1.0832	1.0831	1.0831	1.0831	1.0831
R(41,44)	1.0844	1.0844	1.0844	1.0844	1.0844
R(17,22)	1.0851	1.0855	1.0855	1.0855	1.0855

Table 3. Bond lengths of Rosiglitazone for 6-31G++(d,p)

Bond lengths (Å)	Gas phase	Solvents			
		Water	Ethanol	DMSO	Acetonitrile
R(1,2)	1.8495	1.8493	1.8494	1.8494	1.8494
R(1,3)	1.7932	1.7849	1.7853	1.785	1.7851
R(2,6)	1.5458	1.5453	1.5453	1.5453	1.5453
R(24,25)	1.5299	1.5277	1.5278	1.5277	1.5278
R(2,7)	1.5313	1.5288	1.5289	1.5288	1.5288
R(5,13)	1.0142	1.0155	1.0155	1.0155	1.0155
R(34,40)	1.0826	1.0821	1.0821	1.0821	1.0821
R(16,21)	1.0832	1.0831	1.0831	1.0831	1.0831
R(41,44)	1.0844	1.0844	1.0844	1.0844	1.0844
R(17,22)	1.0851	1.0855	1.0854	1.0855	1.0855

3.2 Optimized Bond Angle (in Degrees) in Gas Phase and in Solvents

Bond angle is the average angle between the orbitals of the central atoms containing the bonding electron pairs in the molecule [19]. The optimized bond angles of Rosiglitazone in the gas phase and in solvents are shown in Tables 4, 5 and 6.

In Table 4, the solvents, in particular water has the least value of 92.6758˚ and the highest value is 125.2157˚ while in the gas phase lowest value is 92.7235˚ and the highest value is 125.0557˚. This implies that the bond angles in the gas phase are expected to be greater than in water and others solvents. The bond angles with the least values is A(2,1,3): C2-S1-C3 and the highest values is A(4,3,5): O4-C3-N5 in both the gas phase and solvents.

3.3 Frontier Molecular Orbitals (FMOs) Energy and Chemical Indices of Rosiglitazone in Gas Phase and Solvents

The calculated values of HOMO- LUMO energy and chemical indices in the gas phase and solvents are presented in Tables 7, 8 and 9.

The results shown in Table 7 of the energy gap in the gas phase is 4.4451eV which is close to a value of 4.4628eV reported by Maltarollo et al. [4] compared to the results in Tables 8 and 9. The highest HOMO value of -5.43288eV was found in the gas phase followed by -5.45954eV in ethanol both in 6-31G(d,p). This indicates that the molecule will be best electron donor in the gas phase followed by in ethanol compared to other solvents. The value of the HOMO was observed to increase with the decrease in dielectric constants of the solvents across all the basis sets used. The lowest LUMO energy of -1.44795eV was found to be in ethanol which shows that the molecule will be the best electron acceptor in ethanol compared to the gas phase and other solvents. The largest HOMO-LUMO gap of 4.28507eV was found in water which implies a higher kinetic stability and less chemical reactivity [20] followed by 4.28344eV found in the gas phase both in the 6-31+G(d,p) basis set and a gradual increase in the frontier molecular orbital energy gap as the dielectric constants of the solvents increased was observed, this can be observed across all the basis sets used [21-22].

Also in Tables 7- 9 the chemical softness of the molecule was found to decrease as the dielectric constants of the solvents increased from ethanol to water and was observed across all the basis sets. Further, it was observed that as the dielectric constant of the solvents was increased from ethanol to water, the chemical hardness was found to slightly increased and this was observed across all the basis sets. The chemical potential was found to decrease as the dielectric constant of the solvents increased namely from ethanol to water.

3.4 Dipole Moment (μ) of Rosiglitazone Molecule in Gas Phase and Solvents

The electric dipole moment is defined as the product of the magnitude of charge at either end of the dipole and the distance between the centers of positive and negative charge. The dipole moment is expressed in Debye (D). The trend that the higher the value of dipole Moment the stronger the intermolecular interactions would be expected. Also, higher dipole moment means higher polarity of the molecule. For calculating the total dipole moment, the mathematical expression is defined as $< \mu >= (\mu_x^2 + \mu_y^2 + \mu_z^2)^{1/2}$ [12] and the obtained dipole moments of the Rosiglitazone in the gas phase and in solvents are shown in Tables 10, 11 and 12.

In Table 10, the dipole moment in the gas phase was found to be 3.1948D which is closer to a value of 3.24931D reported by Kumar [3] compared to the results in Tables 11 and 12. From Tables 10, 11 and 12, it can be seen that the dipole moment increased as the dielectric constants of the solvent increased from ethanol to water. The highest value of the dipole moment of 4.6874D was found in water as shown in Table 11 indicating that the molecule will have strongest intermolecular interactions in water compared to other solvents and the gas phase [3].

3.5 Thermodynamic Properties of Rosiglitazone Molecule

The total energy of a molecule is the sum of translational, rotational, vibrational and electronic energies. i.e., $E = E_t + E_r + E_v + E_e$. Thus, the molecular partition function is the product of the translational, rotational, vibrational and electronic

Table 4. Bond angle of rosiglitazone for 6-31G(d,p)

Bond angle (Degree)	Gas phase	Solvents			
		Water	Ethanol	DMSO	Acetonitrile
A(1,3,4)	125.6565	125.1499	125.175	125.1577	125.1638
A(4,3,5)	125.0557	125.2157	125.2023	125.2115	125.2083
A(16,20,23)	124.6675	124.6095	124.6118	124.61	124.6107
A(5,7,9)	124.6071	124.413	124.4212	124.4157	124.4176
A(33,39,41)	124.3824	124.4448	124.4453	124.4451	124.4452
A(2,1,3)	92.7235	92.6758	92.6764	92.6759	92.6761
A(2,6,12)	106.0085	106.014	106.0183	106.0152	106.0163
A(29,25,30)	106.4154	106.357	106.3609	106.3584	106.3594
A(1,2,7)	106.9436	106.6192	106.6359	106.6245	106.6286
A(7,2,8)	107.18	107.2646	107.2597	107.2632	107.262

Table 5. Bond angle of rosiglitazone for 6-31+G(d,p)

Bond angle (Degree)	Gas phase	Solvents			
		Water	Ethanol	DMSO	Acetonitrile
A(1,3,4)	125.5962	125.1555	125.1782	125.1627	125.1682
A(4,3,5)	124.786	124.7454	124.7418	124.7442	124.7433
A(16,20,23)	124.5853	124.4906	124.4945	124.4917	124.4927
A(5,7,9)	124.3737	124.1137	124.1258	124.1176	124.1205
A(33,39,41)	124.2988	124.3408	124.3429	124.3415	124.3421
A(2,1,3)	92.7103	92.6326	92.6347	92.6332	92.6338
A(2,6,12)	106.273	106.2484	106.2591	106.252	106.2544
A(29,25,30)	106.4053	106.322	106.3282	106.324	106.3256
A(1,2,7)	106.7453	106.4052	106.422	106.4104	106.4146
A(7,2,8)	107.1984	107.2997	107.3004	107.3001	107.3003

Table 6. Bond angle of rosiglitazone for 6-31++G(d,p)

Bond angle (Degree)	Gas phase	Solvents			
		Water	Ethanol	DMSO	Acetonitrile
A(1,3,4)	125.5924	125.1536	125.1756	125.1602	125.1657
A(4,3,5)	124.7902	124.7488	124.7448	124.7473	124.7459
A(16,20,23)	124.5889	124.4943	124.4964	124.4939	124.4952
A(5,7,9)	124.3742	124.1171	124.1295	124.1212	124.1239
A(33,39,41)	124.2994	124.3409	124.343	124.3418	124.342
A(2,1,3)	92.713	92.6359	92.6374	92.6361	92.6363
A(2,6,12)	106.2666	106.2418	106.2525	106.2452	106.2492
A(29,25,30)	106.4028	106.3212	106.3275	106.3235	106.3243
A(1,2,7)	106.7375	106.4021	106.4179	106.4065	106.4104
A(7,2,8)	107.2316	107.3286	107.3305	107.3299	107.3299

Table 7. HOMO-LUMO energy and chemical indices of rosiglitazone for 6-31G(d,p)

Parameters (eV)	Gas phase	Solvents			
		Water	Ethanol	DMSO	Acetonitrile
HOMO	-5.43288	-5.46607	-5.45954	-5.46389	-5.46226
LUMO	-0.98779	-1.01119	-1.01201	-1.01147	-1.01174
HOMO-LUMO Gap	4.4451 a(4.4628)	4.4549	4.4475	4.4524	4.4505

Parameters (eV)	Gas phase	Solvents			
		Water	Ethanol	DMSO	Acetonitrile
I= $-E_{HOMO}$	5.43288	5.46607	5.45954	5.46389	5.46226
A= $-E_{LUMO}$	0.98779	1.01119	1.01201	1.01147	1.01174
Chemical Hardness	2.22255	2.22757	2.22376	2.22621	2.22526
Chemical Softness	0.44993	0.44892	0.44969	0.44919	0.44939
Electronegativity	3.21047	3.23877	3.23578	3.23768	3.23714
Chemical Potential	-3.21047	-3.23877	-3.23578	-3.23768	-3.23714
Electrophilicity Index	2.3185	2.3538	2.3538	2.3538	2.3538

a [4]

Table 8. HOMO-LUMO energy and chemical indices of rosiglitazone for 6-31+G(d,p)

Parameters (eV)	Gas phase	Solvents			
		Water	Ethanol	DMSO	Acetonitrile
HOMO	-5.70962	-5.71125	-5.70499	-5.70908	-5.70772
LUMO	-1.42618	-1.42618	-1.44605	-1.44550	-1.44577
HOMO-LUMO Gap	4.28344 a(4.4628)	4.28507	4.25894	4.26358	4.26195
I= $-E_{HOMO}$	5.70962	5.71125	5.70499	5.70908	5.70772
A= $-E_{LUMO}$	1.42618	1.42618	1.44605	1.44550	1.44577
Chemical Hardness	2.14172	2.14254	2.12947	2.13179	2.13098
Chemical Softness	0.46691	0.46674	0.46960	0.46909	0.46927
Electronegativity	3.56790	3.56872	3.57552	3.57729	3.57675
Chemical Potential	-3.56790	-3.56872	-3.57552	-3.57729	-3.57675
Electrophilicity Index	2.97189	2.97212	3.00177	3.00147	3.00169

a [4]

Table 9. HOMO-LUMO energy and chemical indices of rosiglitazone 6-31++G(d,p)

Parameters (eV)	Gas phase	Solvents			
		Water	Ethanol	DMSO	Acetonitrile
HOMO	-5.71071	-5.71262	-5.70636	-5.71044	-5.70908
LUMO	-1.42863	-1.44741	-1.44795	-1.44768	-1.44768
HOMO-LUMO Gap	4.28208 a(4.4628)	4.26521	4.25841	4.26276	4.26140
I= $-E_{HOMO}$	5.71071	5.71262	5.70636	5.71044	5.70908
A= $-E_{LUMO}$	1.42863	1.44741	1.44795	1.44768	1.44768
Chemical Hardness	2.14104	2.13261	2.12921	2.13138	2.13070
Chemical Softness	0.46706	0.46891	0.46966	0.46918	0.46933
Electronegativity	3.56967	3.58002	3.57716	3.57906	3.57838
Chemical Potential	-3.56967	-3.58002	-3.57716	-3.57906	-3.57838
Electrophilicity Index	2.97578	3.00489	3.00489	3.00502	3.00483

a [4]

Table 10. Dipole moment of rosiglitazone for 6-31G(d,p)

	μ_x(D)	μ_y(D)	μ_z(D)	μ(D)	
Gas phase	-1.8015	1.4681	2.1923	3.1948	b(3.2493)
Water	-1.6396	2.1049	3.4253	4.3418	b(4.4240)
Ethanol	-1.6560	2.0789	3.3434	4.2711	
DMSO	-1.6447	2.0965	3.3987	4.3187	
Acetonitrile	-1.6487	2.0903	3.3787	4.3015	

b [3]

Table 11. Dipole moment of rosiglitazone for 6-31+G(d,p)

	μ_x (D)	μ_y (D)	μ_z (D)	μ (D)	
Gas phase	-2.1369	1.3458	2.2985	3.4148	b(3.2493)
Water	2.0321	1.9435	-3.7503	4.6874	b(4.4240)
Ethanol	-2.0469	1.9097	3.6477	4.5981	
DMSO	2.0367	1.9324	-3.7167	4.6579	
Acetonitrile	2.0404	1.9242	-3.6918	4.6363	

b [3]

Table 12. Dipole moment of rosiglitazone for 6-31++G(d,p)

	μ_x (D)	μ_y (D)	μ_z (D)	μ (D)	
Gas phase	-2.1455	1.3318	2.2906	3.4094	b(3.2493)
Water	2.0457	1.9193	-3.7381	4.6736	b(4.4240)
Ethanol	2.0607	1.8832	-3.6343	4.5827	
DMSO	2.0505	1.9073	-3.7040	4.6435	
Acetonitrile	2.0545	1.8973	-3.6783	4.6207	

b [3]

partition functions of the molecule [23]. The relations between partition functions and various thermodynamic functions were used to evaluate the latter due to translation, vibration and rotation degrees of freedom of molecular motions. The calculated thermodynamic parameters of rosiglitazone both in the gas phase and solvents are presented in Tables 13-15. From Tables 13-15, the values of the thermodynamic properties obtained appeared to be much closer to one another across all the solvents and gas phase. This shows that the solvents have no effect on the thermodynamic properties of rosiglitazone. Also, from the observed results, the values of the Heat capacity, Entropy, Rotational constants and Zero Point Vibrational Energy (ZPVE) in both the gas phase and solvents are approximately the same when considering only one decimal place.

3.6 Total Energy of Rosiglitazone Molecule in the Gas Phase and in Solvents

The calculated total energy of the Rosiglitazone in gas phase and in solvents is shown in Tables 16, 17 and 18. The results obtained in the gas phase Tables 16-18 were in good agreement with those reported by Maltarollo [4]. In Tables 16, 17 and 18, the values of the total energy increased as the dielectric constant of the solvents decreased from water to ethanol. The minimum energy was found to be -1485.58768572a.u in water as shown in Table 18.

3.7 Vibrational Frequencies and IR Intensities of Rosiglitazone in the Gas Phase and Solvents

The vibrational frequencies and intensities of Rosiglitazone in the gas phase and solvents are shown in Tables 19-21.

The most intense frequency was found to be about 1724.3 cm^{-1} which occurred at an intensity of 1726.4 Km/mole in water in Table 21. The second most intense frequency was found to be about 1724.3103cm^{-1} which occurred at an intensity of 1725.8 Km/mole in water in Table 20. Also the third most intense frequency was found to be about 1777.3 cm^{-1} which occurred at an intensity of 1295.6 Km/mole in water in Table 19. At these frequencies, there is strong C=O stretch asymmetry mode of vibrations. From Tables 19, 20 and 21, it can be seen that the intensities increased as the dielectric constants of the solvents increased namely from ethanol to water. For, the correction of theoretical errors in this work, the theoretical harmonic frequencies above *1700* cm^{-1} were scaled by a scaling factor of 0.958, and frequencies less than *1700* cm^{-1} were scaled by 0.983 [24].

3.8 Some Selected Values of Vibrational Frequencies and Intensities

Tables 19-21 show the vibrational frequencies and intensities of rosiglitazone in both the gas phase and in different solvents for the three basis sets.

Table 13. Thermodynamic properties of rosiglitazone for 6-31G(d,p)

	Gas phase		Water		Ethanol	
Position	**Heat capacity (Cal/mol-Kelvin)**	**Entropy (Cal/mol-Kelvin)**	**Heat capacity (Cal/mol-Kelvin)**	**Entropy (Cal/mol-Kelvin)**	**Heat capacity (Cal/mol-Kelvin)**	**Entropy (Cal/mol-Kelvin)**
Electronic	0.000	0.000	0.000	0.000	0.000	0.000
Translational	2.981	43.512	2.981	43.512	2.981	43.512
Rotational	2.981	36.330	2.981	36.324	2.981	36.324
Vibrational	80.146	90.542	80.172	89.932	80.167	89.943
Total	86.108	170.384	86.134	169.768	86.129	169.779
Rotational Constants (GHZ)	0.62393		0.62288		0.62341	
	0.05775		0.05795		0.05793	
	0.05544		0.05567		0.05564	
Zero Point Vibrational Energy (ZPVE) (Kcal/mol)	220.08825		219.99057		220.00287	

	DMSO		Acetonitrile	
Position	**Heat capacity (Cal/mol-Kelvin)**	**Entropy (Cal/mol-Kelvin)**	**Heat capacity (Cal/mol-Kelvin)**	**Entropy (Cal/mol-Kelvin)**
Electronic	0.000	0.000	0.000	0.000
Translational	2.981	43.512	2.981	43.512
Rotational	2.981	36.324	2.981	36.324
Vibrational	80.171	89.955	80.169	89.968
Total	86.132	169.791	86.131	169.804
Rotational Constants (GHZ)	0.62306		0.62320	
	0.05794		0.05794	
	0.05566		0.05565	
Zero Point Vibrational Energy (ZPVE) (Kcal/mol)	219.99439		219.99733	

Table 14. Thermodynamic properties of Rosiglitazone for 6-31+G(d,p)

	Gas phase		Water		Ethanol	
Position	**Heat capacity (Cal/mol-Kelvin)**	**Entropy (Cal/mol-Kelvin)**	**Heat capacity (Cal/mol-Kelvin)**	**Entropy (Cal/mol-Kelvin)**	**Heat capacity (Cal/mol-Kelvin)**	**Entropy (Cal/mol-Kelvin)**
Electronic	0.000	0.000	0.000	0.000	0.000	0.000
Translational	2.981	43.512	2.981	43.512	2.981	43.512
Rotational	2.981	36.345	2.981	36.341	2.981	36.341
Vibrational	80.374	90.807	80.399	90.179	80.402	90.496
Total	86.335	170.664	86.361	170.032	86.364	170.349
Rotational Constants (GHZ)	0.62789		0.62402		0.62447	
	0.05713		0.05742		0.05740	
	0.05483		0.05513		0.05511	
Zero Point Vibrational Energy (ZPVE) (Kcal/mol)	219.53272		219.41399		219.41260	

	DMSO		Acetonitrile	
Position	**Heat capacity (Cal/mol-Kelvin)**	**Entropy (Cal/mol-Kelvin)**	**Heat capacity (Cal/mol-Kelvin)**	**Entropy (Cal/mol-Kelvin)**
Electronic	0.000	0.000	0.000	0.000
Translational	2.981	43.512	2.981	43.512
Rotational	2.981	36.341	2.981	36.341
Vibrational	80.400	90.259	80.401	90.336
Total	86.362	170.112	86.362	170.189
Rotational Constants (GHZ)	0.62417		0.62428	
	0.05741		0.05741	
	0.05513		0.05512	
Zero Point Vibrational Energy (ZPVE) (Kcal/mol)	219.41430		219.41402	

Table 15. Thermodynamic properties of Rosiglitazone for 6-31++G(d,p)

	Gas phase		Water		Ethanol	
Position	**Heat capacity (Cal/mol-Kelvin)**	**Entropy (Cal/mol-Kelvin)**	**Heat capacity (Cal/mol-Kelvin)**	**Entropy (Cal/mol-Kelvin)**	**Heat capacity (Cal/mol-Kelvin)**	**Entropy (Cal/mol-Kelvin)**
Electronic	0.000	0.000	0.000	0.000	0.000	0.000
Translational	2.981	43.512	2.981	43.512	2.981	43.512
Rotational	2.981	36.345	2.981	36.341	2.981	36.342
Vibrational	80.377	90.806	80.396	90.196	80.401	90.595
Total	86.338	170.664	86.358	170.050	86.362	170.448
Rotational Constants	0.62698		0.62294		0.62333	
(GHZ)	0.05716		0.05745		0.05743	
	0.05486		0.05516		0.05514	
Zero Point Vibrational Energy (ZPVE) (Kcal/mol)	219.52615		219.41032		219.40613	

	DMSO		Acetonitrile	
Position	**Heat Capacity (Cal/mol-Kelvin)**	**Entropy (Cal/mol-Kelvin)**	**Heat Capacity (Cal/mol-Kelvin)**	**Entropy (Cal/mol-Kelvin)**
Electronic	0.000	0.000	0.000	0.000
Translational	2.981	43.512	2.981	43.512
Rotational	2.981	36.342	2.981	36.342
Vibrational	80.398	90.325	80.399	90.406
Total	86.360	170.179	86.360	170.259
Rotational Constants	0.62307		0.62313	
(GHZ)	0.05744		0.05744	
	0.05515		0.05515	
Zero Point Vibrational Energy (ZPVE) (Kcal/mol)	219.40830		219.40787	

Table 16. Total energy of rosiglitazone for 6-31G(d,p)

	Total energy		
	(a.u)	(eV)	
Gas phase	-1485.52565826	-40424.12421	**In Gas phase**
Water	-1485.54290398	-40424.59348	a (-1485.5854 a.u)
Ethanol	-1485.54204931	-40424.57024	a (-40425.7499 eV)
DMSO	-1485.54263192	-40424.58607	
Acetonitrile	-1485.54242393	-40424.58041	

a[4]

Table 17. Total energy of rosiglitazone for 6-31+G(d,p)

	Total energy		
	(a.u)	(eV)	
Gas phase	-1485.56679200	-40425.24354	**In Gas phase**
Water	-1485.58716633	-40425.79796	a (-1485.5854 a.u)
Ethanol	-1485.58613979	-40425.77001	a (-40425.7499 eV)
DMSO	-1485.58683932	-40425.78906	
Acetonitrile	-1485.58658948	-40425.78226	

a [4]

Table 18. Total energy of rosiglitazone for 6-31++G(d,p)

	Total energy		
	(a.u)	(eV)	
Gas phase	-1485.56735914	-40425.25897	**In Gas phase**
Water	-1485.58768572	-40425.81208	a (-1485.5854 a.u)
Ethanol	-1485.58666137	-40425.78422	a(-40425.7499 eV)
DMSO	-1485.58735937	-40425.80321	
Acetonitrile	-1485.58710998	-40425.79641	

a[4]

Table 19. Vibrational frequencies and intensities of rosiglitazone for 6-31G(d,p)

Gas phase		Water		Ethanol	
Frequency	Intensity	Frequency	Intensity	Frequency	Intensity
1823.4605	659.5572	1777.3042	1295.63	1779.4797	1262.1074
1288.9854	486.431	1280.4535	600.5999	1280.8465	599.0695
1546.693	259.9662	1539.9364	395.3251	1540.385	385.977
1656.535	269.0981	1650.0193	376.9528	1650.314	371.4033
1323.0752	217.8641	1321.0194	367.2942	1321.1988	360.2493
25.6816	0.0075	26.5313	0.0334	26.5062	0.0338
62.7469	0.0359	61.7593	0.0828	62.0969	0.0825
33.075	0.0433	35.464	0.1203	35.5273	0.1152
46.6348	0.0924	15.2418	0.2006	44.9437	0.1839
13.9723	0.1773	15.2418	0.2006	15.0385	0.1896

DMSO		Acetonitrile	
Frequency	**Intensity**	**Frequency**	**Intensity**
1777.9997	1284.9509	1778.5286	1276.786
1280.5839	600.0653	1280.6801	599.6399
1540.0862	392.2909	1540.204	389.9213
1650.1165	375.1845	1650.1878	373.8289
1321.0709	365.1194	1321.1129	363.4361
26.5091	0.0341	26.5004	0.0344
61.8698	0.0834	61.9672	0.0837
35.4821	0.1177	35.4976	0.1163
45.0077	0.1937	44.9005	0.1895
15.1763	0.1968	15.1229	0.1941

Table 20. Vibrational frequencies and intensities of rosiglitazone for 6-31+G(d,p)

Gas phase		Water		Ethanol	
Frequency	**Intensity**	**Frequency**	**Intensity**	**Frequency**	**Intensity**
1789.1283	849.7389	1724.3103	1725.7785	1727.467	1677.5066
1279.3981	503.6094	1268.6036	435.9116	1269.0596	468.9467
1539.7682	266.2268	1532.2012	415.7792	1532.7203	405.9961
1646.1383	305.688	1639.4958	437.6898	1639.7649	431.3961
1322.0872	224.9443	1322.4794	392.6738	1322.6153	383.1451
25.0717	0.0201	25.7266	0.0276	25.3949	0.0283
60.9003	0.0151	59.5114	0.1745	58.5184	0.1384
32.7727	0.0977	34.6629	0.312	34.413	0.2849
44.7636	0.0535	46.8142	0.2641	46.3231	0.2904
14.783	0.2208	16.5159	0.3153	16.2997	0.2873
DMSO		**Acetonitrile**			
Frequency	**Intensity**	**Frequency**	**Intensity**		
1725.3105	1710.3367	1726.0814	1698.6039		
1268.7451	447.0253	1268.8554	455.144		
1532.3789	412.5115	1532.5156	410.0266		
1639.5804	435.7071	1639.6454	434.1826		
1322.5235	389.6349	1322.5562	387.3057		
25.6204	0.0273	25.5371	0.0275		
59.1901	0.1645	58.9418	0.1555		
34.5919	0.3029	34.5308	0.2962		
46.7199	0.2729	46.6041	0.2796		
16.4756	0.3059	16.419	0.299		

Table 21. Vibrational frequencies and intensities of rosiglitazone for 6-31++G(d,p)

Gas phase		Water		Ethanol	
Frequency	**Intensity**	**Frequency**	**Intensity**	**Frequency**	**Intensity**
1789.0468	849.0196	1724.2718	1726.4059	1727.4128	1677.8912
1279.2518	504.5875	1268.3718	443.951	1268.8294	479.7689
1539.4409	265.0407	1531.8544	416.4613	1532.3543	406.7253
1645.9775	304.8604	1639.3157	437.289	1639.5815	430.9777
1322.117	224.2846	1322.465	392.3501	1322.6115	382.6015
25.0928	0.02	25.5922	0.0253	25.1776	0.0234
60.7918	0.0148	59.4854	0.1828	58.32	0.1601
32.6603	0.0998	34.1396	0.3114	33.6902	0.2829
44.8145	0.0543	46.737	0.2622	46.3603	0.2841
14.7831	0.2192	16.5287	0.3204	16.3163	0.2938
DMSO		**Acetonitrile**			
Frequency	**Intensity**	**Frequency**	**Intensity**		
1725.2706	1710.8528	1726.0147	1699.0202		
1268.5159	456.3994	1268.62	465.314		
1532.0083	413.3726	1532.1171	411.1129		
1639.4019	435.2329	1639.4639	433.7244		
1322.5103	389.2687	1322.5578	386.8128		
25.4695	0.0244	25.3779	0.0235		
59.1095	0.1786	58.8376	0.1754		
33.9608	0.3016	33.8242	0.2944		
46.6652	0.2672	46.5966	0.2713		
16.4973	0.3115	16.461	0.3059		

4. CONCLUSION

The geometry of Rosiglitazone was optimized using DFT methods using 6-31G (d,p), 6-31+G(d,p) and 6-31++G(d,p) basis sets. Solvent effects on molecular structural parameters, electronic and thermodynamic properties of the optimized geometry of the molecule were investigated and reported. From the results obtained, the solvents have little influence on the optimized parameters (bond lengths and bond angles) of the molecule. The bond R(5,13):N5-H13 between Nitrogen and Hydrogen atoms at the indicated position has the lowest value of *1.013Å* showing it is the strongest bond and large amount of energy is needed to break it. The bond R(1,2):S1-C2 between sulphur and carbon atoms at the specified position has the highest value of *1.8472Â* showing it is the weakest bond of the molecule. The vibrational frequencies of the fundamental modes of the compounds have been precisely assigned and analyzed. The values of the vibrational frequencies obtained in the gas phase and in solvents are observed to be positive which shows that the studied molecule was very stable that is no imaginary frequencies exist. Also, the vibrational band assignments of the frequencies in solvents were the same. The dipole moment of Rosiglitazone was found to be higher in different solvents than in gas phase. We found that the frontier molecular orbitals energy gap decreases rapidly in the low dielectric solvents and gradually comes to saturation in high dielectric solvents. In a nutshell, it was found that the variation of the environment (solvent effects) influences the structural, electronic and molecular properties of the Rosiglitazone and will be useful in the design and development of rosiglitazone as an anti-diabetes drug.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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