Original Research Article

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

Abstract

Rosiglitazone ($C_{18}H_{19}N_3O_3S$) is an anti-diabetic drug that reduces insulin resistance in patient with type 2 diabetes. The ~~optimized~~ 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 -5.43288eV was found in gas phase showing that the molecule will best donate electron in gas phase and follow by ethanol compare to other solvents. The values of the HOMO were observed to increase with 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 best accept electron in ethanol compare to gas phase and other solvents. The largest HOMO-LUMO gap of 4.28507eV was found in water which implies higher kinetic stability and less chemical reactivity. The chemical softness of the molecule was found to decrease as the dielectric constants of the solvents increased from ethanol to water. The chemical hardness was found to slightly increased with increase in dielectric constants of the solvents . The highest value of the dipole moment was found to be in water with a value of 4.6874D indicating that the molecule will have strongest intermolecular interactions in water compare to other solvents and 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-diabates drug.

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Keywords: DFT, Diabetes, Gaussian 09, Rosiglitazone and Solvents

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. Persistently high blood glucose levels cause generalized vascular damage affecting the heart, eyes, kidney and nerve and 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 ant- hyperglycemic agent that reduces insulin resistance in patients with type 2 diabetes. Type 2 diabetes is 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]. Molecular modeling study of Rosiglitazone and its metabolites by using PM6 method have been reported by [3]. Similarly, Geometry optimization and the calculation of electronic properties of Rosiglitazone and Pioglitazone using DFT method were reported by [4]. Such as HOMO, LUMO, HOMO-LUMO energy gap, dipole moment, total energy of Rosiglitazone and Pioglitazone in gas phase and solvents. Physical and chemical property of a molecule depends on the structure and the various kinds of energies of the molecule. Chemical reaction of a molecule in solution is affected by the nature of the solvent; solvent affects not only the energies of HOMO and LUMO of the molecule, but also other properties of the molecule [5]].

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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 are Water, Ethanol, Dimethyl sulfoxide (DMSO) and Acetonitrile and the dielectric constants of the solvents at 25°C are Water $(\varepsilon = 79)$, Ethanol $(\varepsilon = 25)$, Dimethyl sulfoxide (DMSO) $(\varepsilon = 47)$ and Acetonitrile $(\varepsilon = 38)$.

Theoretical Background

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 by using functional, that is functions of another function, in which case is the spatially dependent electron density. Hence the name density functional theory comes from the functional of electron density. DFT is among the most popular and versatile methods available in condensed-matter physics, computational physics, and computational chemistry [6]. Within DFT the ground state energy can be determined by the relationship given as [7]:

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

Where $\rho(r)$ is electron density and $\psi_{i\,(r)}$ is the wave function of the electrons, we employ this relation to determine the ground state energy of the molecules.

Local Density Approximation (LDA)

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:

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

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]:

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

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 1920's

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

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 not only the information about the density $\rho(\vec{r})$ at a particular point $\vec{r}$, but also information about 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 real system. Thus, we may write the exchange-correlation energy in a form known as Generalized Gradient Approximation (GGA)

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

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

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

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]. Energy difference between HOMO and LUMO orbital is called as energy gap which is an important parameter that determines the stability of the structures. The energy gap is 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) 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].

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

Computational Methods

All computations were carried out using windows version of Gaussian 09 software. 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 salvation 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 Guassian 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. The chemical hardness, chemical softness, chemical potential, electronegativity and electronphilicity index were also calculated using HOMO and LUMO energies. The total energy, thermodynamic properties and dipole moment of the molecule were calculated. All computation were carry out in gas phase and in solvents and IR pal 2.0 was used for interpretation of the vibrational frequencies.

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Results and Discussion

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

The bond length is a measurable distance between two covalently bonded together. It is worth noting that shorter the bond length higher is the value of bond energy and stronger the bond [18]. The optimized bond lengths of rosiglitazone in 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 gas phase. In water, ethanol, DMSO and acetonitrile it was observed that the lowest value was 1.0143Å for B3LYP/6-31G(d,p) in Table 1. This indicates that the value are a bit higher in solvents than in gas phase which implies that the bonds will be slightly stronger in gas phase than in solvents. The bond R(5,13):N5-H13 between Nitrogen and Hydrogen atoms at the indicated positions have lowest values of bond lengths. These are the strongest bonds and large amount of energy is needed to break them.

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Also, from the results of bond length obtained that 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 of the solvents has little influence on the bond lengths particularly the shorter bond lengths.

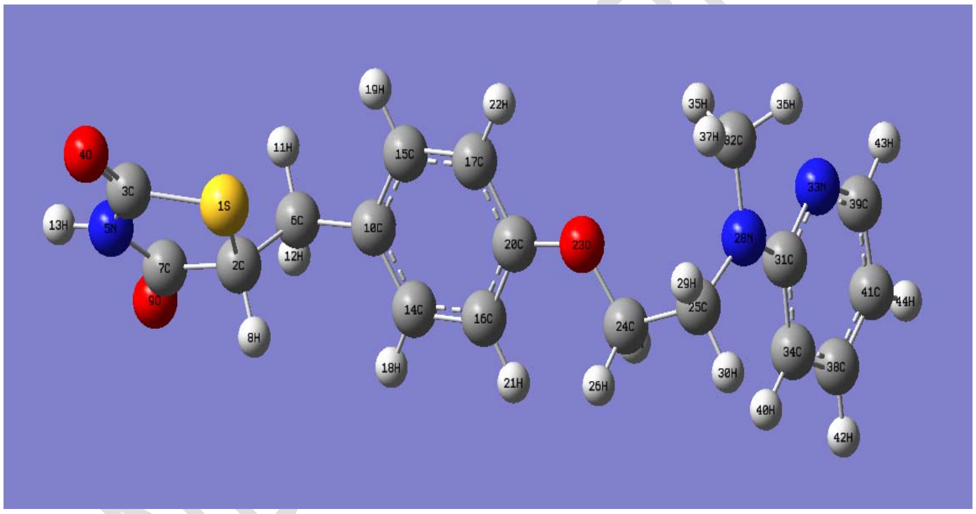

Figure 1: Optimized molecular structure of Rosiglitazone

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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**

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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**

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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**

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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 gas phase and in solvents are shown in Tables 4, 5 and 6.

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

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

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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**

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

The acronym HOMO; means Highest Occupied Molecular Orbital while LUMO stands for Lowest Unoccupied Molecular Orbital. The calculated values of HOMO- LUMO energy and chemical indices in gas phase and solvents are presented in Tables 7, 8 and 9.

The results shown in Table 7 of energy gap in gas phase is 4.4451eV which close is to a value of 4.4628eV reported by [4] compare to the results in Tables 8 and 9. The highest HOMO value of -5.43288eV was found in gas phase followed by -5.45954eV in ethanol both in 6-31G(d,p). This indicates that the molecules will be best electron donor in gas phase and follow by ethanol compare to other solvents. Therefore, the value of the HOMO was observed to increase with 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 best accept electron in ethanol compare to gas phase and other solvents. The largest HOMO-LUMO gap of 4.28507eV was found in water solvent which implies higher kinetic stability and less chemical reactivity [20] followed by 4.28344eV found in 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.

Comment [I24]: Authors should make effort to discuss this appropriately. Its is not flowing and the discussion is disjointed.

Comment [I25]: Add more references as follows

Adesoji A. Olanrewaju, Collins U. Ibeji**2**, Festus S. Fabiyi**1** Synthesis, Characterization, and Computational Studies of Metal(II) Complexes Derived from β-diketone and Para-aminobenzoic Acid. Indian Journal of Heterocyclic Chemistry Vol. 28 - Number 03 (Jul-Sep 2018) 351-361

Ibeji, C.U., Adejoro, I.A., Adeleke, B.B. A benchmark study on the properties of unsubstituted and some substituted polypyrroles, *J. Phys. Chem. Biophys.*, **2015**, *5*, 1–11.

Also in Tables 7, 8 and 9 the chemical softness of the molecule was found to be decreased 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 be slightly increased and this was observed across all the basis sets. The chemical potential was confirmed to decrease as the dielectric constant of the solvents increased from ethanol to water.

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
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]

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. Dipole moment is expressed in Debye (D). The higher the value of dipole Moment the stronger the intermolecular interactions would be expected. Also higher dipole moment means that the polarity of the molecule is higher. 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]. The calculated dipole moments of the Rosiglitazone in gas phase and in solvents are shown in Tables 10, 11 and 12.

In Table 10, the dipole moment in gas phase was found to be 3.1948D which is closer to a value of 3.24931D reported by Kumar [3] compare 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 was found to be in water with a value of 4.6874D as shown in Table 11, indicating that the molecule will have strongest intermolecular interactions in water compare to other solvents and gas phase [3].

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]

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 partition functions of the molecule [21]. 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 gas phase and solvents are presented in Tables 13, 14 and 15.

From Tables 13, 14 and 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 value of Heat capacity, Entropy, Rotational constants and Zero Point Vibrational Energy (ZPVE) in both gas phase and solvents there are approximately the same by considering only one decimal place.

Comment [I26]: This should be Table 13-15

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 Constant (GHZ)	**0.62393** **0.05775** **0.05544**		**0.62288** **0.05795** **0.05567**		**0.62341** **0.05793** **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 Constant (GHZ)	**0.62306** **0.05794** **0.05566**		**0.62320** **0.05794** **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 Constant (GHZ)	**0.62789** **0.05713** **0.05483**	**0.62402** **0.05742** **0.05513**	**0.62447** **0.05740** **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 Constant (GHZ)	**0.62417** **0.05741** **0.05513**		**0.62428** **0.05741** **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 Constant (GHZ)	**0.62698** **0.05716** **0.05486**	**0.62294** **0.05745** **0.05516**	**0.62333** **0.05743** **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 Constant (GHZ)	**0.62307** **0.05744** **0.05515**		**0.62313** **0.05744** **0.05515**	
Zero Point Vibrational Energy (ZPVE) (Kcal/mol)	**219.40830** **219.99439**		**219.40787** **219.99733**	

Total Energy of Rosiglitazane molecule in 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 gas phase Tables 16, 17 and 18 were agreed with 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.

Table 16: Total Energy of Rosiglitazone for 6-31G(d,p)

	Total Energy	

	(a.u)	(eV)	[4]
Gas phase	-1485.52565826	-40424.12421	In Gas phase
Water	-1485.54290398	-40424.59348	-1485.5854a.u
Ethanol	-1485.54204931	-40424.57024	-40425.7499eV
DMSO	-1485.54263192	-40424.58607	
Acetonitrile	-1485.54242393	-40424.58041	

Comment [I27]: Remove reference from this Table. Indicate it at the bottom o f the Table.

Table 17: Total Energy of Rosiglitazone for 6-31+G(d,p)

	Total Energy		[4]
	(a.u)	(eV)	
Gas phase	-1485.56679200	-40425.24354	In Gas phase
Water	-1485.58716633	-40425.79796	-1485.5854a.u
Ethanol	-1485.58613979	-40425.77001	-40425.7499eV
DMSO	-1485.58683932	-40425.78906	
Acetonitrile	-1485.58658948	-40425.78226	

Table 18: Total Energy of Rosiglitazone for 6-31++G(d,p)

	Total Energy		[4]
	(a.u)	(eV)	
Gas phase	-1485.56735914	-40425.25897	In Gas phase
Water	-1485.58768572	-40425.81208	-1485.5854a.u
Ethanol	-1485.58666137	-40425.78422	-40425.7499eV
DMSO	-1485.58735937	-40425.80321	
Acetonitrile	-1485.58710998	-40425.79641	

Vibrational frequencies and IR Intensities of Rosiglitazone in Gas phase and Solvents

The vibrational frequencies and intensities of Rosiglitazone in gas phase and solvents are shown in Tables 19, 20 and 21.

The most intense frequency was found to be about 1724.2718cm^{-1} which occurred at an intensity of 1726.4059Km/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 1725.7785Km/mole in water in Table 20. Also the third most intense frequency was found to be about 1777.3042cm^{-1} which occurred at an intensity of 1295.63Km/mole in water in Table 19. At these frequencies, there is strong C=O stretch asymmery 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 from ethanol to water.

Comment [I28]: Authors should mention the scaling factors used for the IR vibrational frequencies.

See references on an example of scaling factor

Adesoji A. Olanrewaju**1**, Collins U. Ibeji, Festus S. Fabiyi**1** Synthesis, Characterization, and Computational Studies of Metal(II) Complexes Derived from β-diketone and Para-aminobenzoic Acid. Indian Journal of Heterocyclic Chemistry Vol. 28 - Number 03 (Jul-Sep 2018) 351-361

Comment [I29]: One decimal and space between numbers and units

Some selected values of vibrational frequencies and intensities

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

Conclusion

The geometry of Rosiglitazone was optimized through 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. The vibrational frequencies of the fundamental modes of the compounds have been precisely assigned and analyzed. The values of the vibrational frequencies obtained in 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

Comment [I30]: “using”

was found to be higher in different solvents than in gas phase. Therefore, the dipole moment increases with the increasing polarity of the solvent. 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 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-diabates drug.

Comment [I31]: Spelling error

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