

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-diabetes drug.

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

32 **Introduction**

33 Diabetes mellitus is a group of complex metabolic disorders characterized by deficient insulin secretion,
34 impaired insulin action, or a combination of both resulting in hyperglycemia. People with diabetes have an
35 increased risk of developing a number of serious life-threatening health problems resulting in highly medical
36 care costs, reduced quality of life and increased mortality. Persistently high blood glucose levels cause
37 generalized vascular damage affecting the heart, eyes, kidney and nerve and resulting in various
38 complications [1]. Diabetes is now one of the most common diseases that cause sudden death in most of the
39 African countries and cause most of the severe heart disease and stroke, kidney damage, nerve damage,
40 amputation and vision loss. Rosiglitazone is ant- hyperglycemic agent that reduces insulin resistance in
41 patients with type 2 diabetes. Type 2 diabetes is a disability of the pancreas related to the secretion of insulin
42 and peripheral insulin resistance. Rosiglitazone belongs to the thiazolidinedione class of oral antidiabetic
43 agents [2]. Molecular modeling study of Rosiglitazone and its metabolites by using PM6 method have been
44 reported by [3]. Similarly, Geometry optimization and the calculation of electronic properties of
45 Rosiglitazone and Pioglitazone using DFT method were reported by [4]. Such as HOMO, LUMO, HOMO-
46 LUMO energy gap, dipole moment, total energy of Rosiglitazone and Pioglitazone in gas phase and solvents.
47 Physical and chemical property of a molecule depends on the structure and the various kinds of energies of
48 the molecule. Chemical reaction of a molecule in solution is affected by the nature of the solvent; solvent
49 affects not only the energies of HOMO and LUMO of the molecule, but also other properties of the molecule
50 [5]].

51 The purpose of this work is to investigate the influence of solvation media upon the structural,
52 electronic and thermodynamic properties of rosiglitazone based on DFT employing three basis sets
53 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
54 Water, Ethanol, Dimethyl sulfoxide (DMSO) and Acetonitrile and the dielectric constants of the solvents at
55 25°C are Water ($\epsilon = 79$), Ethanol ($\epsilon = 25$), Dimethyl sulfoxide (DMSO) ($\epsilon = 47$) and Acetonitrile
56 ($\epsilon = 38$).

57 **Theoretical Background**

58 **Density Functional Theory (DFT)**

59 Density functional theory (DFT) is a computational quantum mechanical method used in physics, chemistry
60 and materials science to investigate the electronic structure (principally the ground state) of many body
61 systems, in particular atoms, molecules, and the condensed phases. Using this theory, the properties of many
62 electron systems can be determined by using functional, that is functions of another function, in which case

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

$$67 \quad \rho(r) = \sum_{i=1}^n |\psi_i(r)|^2 \quad (1)$$

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

70 **Local Density Approximation (LDA)**

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

$$75 \quad E_{XC}^{LDA}[\rho] = \int \rho(\vec{r}) E_{XC}(\rho(\vec{r})) d\vec{r} \quad (2)$$

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

$$79 \quad E_{XC}(\rho(\vec{r})) = E_X(\rho(\vec{r})) + E_C(\rho(\vec{r})) \quad (3)$$

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

$$82 \quad E_X = -\frac{3}{4} \left(\frac{3\rho(\vec{r})}{\pi} \right)^{1/3} \quad (4)$$

83 **Generalized Gradient Approximation (GGA)**

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

$$90 \quad E_{XC}^{GGA}[\rho(\vec{r})] = \int f^{GGA}[\rho(\vec{r}), \nabla\rho(\vec{r})] d\vec{r} \quad (5)$$

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

$$93 \quad E_{XC}^{GGA} = E_X^{GGA} + E_C^{GGA} \quad (6)$$

94 **Frontier Molecular Orbitals (FMOs) Energy and Chemical Indices**

95 To explain several types of reaction and for predicting the most reactive position in conjugated systems,
96 molecular orbitals and their properties such as energy are used [9]. The energies of the Highest Occupied
97 Molecular Orbital (HOMO) and the Lowest Unoccupied Molecular Orbital (LUMO) are the most important
98 orbitals in a molecule. HOMO can be through the outermost orbital containing electrons tends to give these
99 electrons such as an electron donor. On the other hand, LUMO can be through the innermost orbital
100 containing free places to accept electron [10]. The Energy of the HOMO is directly related to the ionization
101 potential and LUMO Energy is directly related to the electron affinity [11]. Energy difference between
102 HOMO and LUMO orbital is called as energy gap which is an important parameter that determines the
103 stability of the structures. The energy gap is used in determining molecular electrical transport properties
104 [12].

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

$$112 \quad I = -E_{HOMO} \quad (7)$$

$$113 \quad A = -E_{LUMO} \quad (8)$$

$$114 \quad (\mu) = -\frac{I+A}{2} \quad (9)$$

$$115 \quad (\eta) = \frac{I-A}{2} \quad (10)$$

$$116 \quad (S) = \frac{1}{\eta} \quad (11)$$

$$117 \quad (\chi) = \frac{I+A}{2} \quad (12)$$

$$118 \quad (\omega) = \frac{\mu^2}{2\eta} \quad (13)$$

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

$$121 \quad E_{gap} = (E_{LUMO} - E_{HOMO}) \approx IP - EA \quad (14)$$

122 **Computational Methods**

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

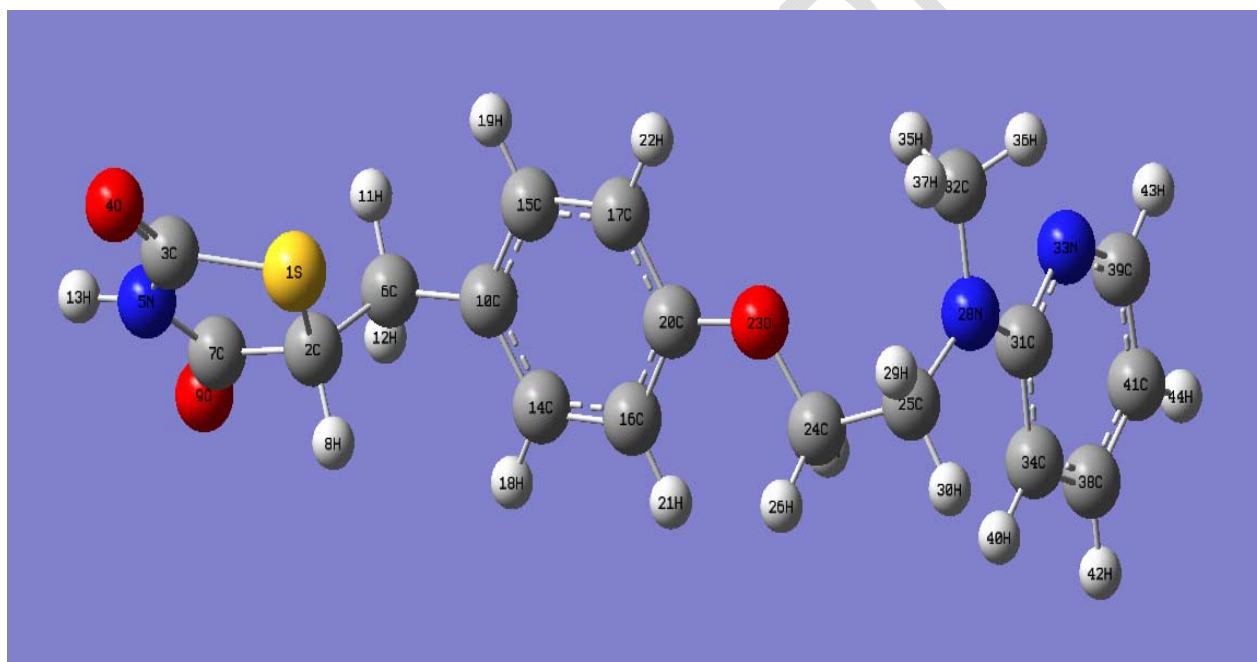
142 **Results and Discussion**

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

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

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

153 Also, from the results of bond length obtained that the highest value 1.8472Å for B3LYP/6-31G(d,p),
 154 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
 155 and solvents. The bonds R(1,2):S1-C2 between sulphur and carbon atoms at the specified positions have the
 156 highest values of bond lengths. From the results obtained increasing or decreasing the dielectric of the
 157 solvents has little influence on the bond lengths particularly the shorter bond lengths.



158
 159 Figure 1: Optimized molecular structure of Rosiglitazone

160 **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

161

162 **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

163

164 **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

165

166 **Optimized bond angle (in degrees) in gas phase and in solvents**

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

170 In Table 4, the solvents, specifically water has the least value of 92.6758° and the highest value is 125.2157°
 171 while in gas phase lowest value is 92.7235° and the highest value is 125.0557°. This implies that the bond
 172 angles in gas phase is expected to be stronger than in water and others solvents. The bond angles with least
 173 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.

174 **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

175

176 **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

177

178

179 **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

180

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

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

186 The results shown in Table 7 of energy gap in gas phase is 4.4451eV which close is to a value of
 187 4.4628eV reported by [4] compare to the results in Tables 8 and 9. The highest HOMO value of -
 188 5.43288eV was found in gas phase followed by -5.45954eV in ethanol both in 6-31G(d,p). This
 189 indicates that the molecules will be best electron donor in gas phase and follow by ethanol compare to
 190 other solvents. Therefore, the value of the HOMO was observed to increase with decrease in dielectric
 191 constants of the solvents across all the basis sets used. The lowest LUMO energy of -1.44795eV was
 192 found to be in ethanol which shows that the molecule will best accept electron in ethanol compare to
 193 gas phase and other solvents. The largest HOMO-LUMO gap of 4.28507eV was found in water solvent
 194 which implies higher kinetic stability and less chemical reactivity [20] followed by 4.28344eV found in
 195 gas phase both in the 6-31+G(d,p) basis set and a gradual increase in the frontier molecular orbital
 196 energy gap as the dielectric constants of the solvents increased was observed, this can be observed
 197 across all the basis sets used.

198 Also in Tables 7, 8 and 9 the chemical softness of the molecule was found to be decreased as the
 199 dielectric constants of the solvents increased from ethanol to water and was observed across all the
 200 basis sets. Further, it was observed that as the dielectric constant of the solvents was increased from
 201 ethanol to water, the chemical hardness was found to be slightly increased and this was observed across
 202 all the basis sets. The chemical potential was confirmed to decrease as the dielectric constant of the
 203 solvents increased from ethanol to water.

204

205

206 **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= $-E_{\text{HOMO}}$	5.43288	5.46607	5.45954	5.46389	5.46226
A= $-E_{\text{LUMO}}$	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

207 a [4]

208 **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= $-E_{\text{HOMO}}$	5.70962	5.71125	5.70499	5.70908	5.70772
A= $-E_{\text{LUMO}}$	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

209 a [4]

210 **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= $-E_{\text{HOMO}}$	5.71071	5.71262	5.70636	5.71044	5.70908
A= $-E_{\text{LUMO}}$	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

211 a [4]

212 **Dipole moment (μ) of Rosiglitazone molecule in gas phase and solvents**

213 The electric dipole moment is defined as the product of the magnitude of charge at either end of the
 214 dipole and the distance between the centers of positive and negative charge. Dipole moment is
 215 expressed in Debye (D). The higher the value of dipole Moment the stronger the intermolecular
 216 interactions would be expected. Also higher dipole moment means that the polarity of the molecule is
 217 higher. For calculating the total dipole moment the mathematical expression is defined as $\langle \mu \rangle = (\mu_x^2$
 218 $+ \mu_y^2 + \mu_z^2)^{1/2}$ [12]. The calculated dipole moments of the Rosiglitazone in gas phase and in
 219 solvents are shown in Tables 10, 11 and 12.

220 In Table 10, the dipole moment in gas phase was found to be 3.1948D which is closer to a value of
 221 3.24931D reported by Kumar [3] compare to the results in Tables 11 and 12. From Tables 10, 11 and
 222 12, it can be seen that the dipole moment increased as the dielectric constants of the solvent increased
 223 from ethanol to water. The highest value of the dipole moment was found to be in water with a value
 224 of 4.6874D as shown in Table 11, indicating that the molecule will have strongest intermolecular
 225 interactions in water compare to other solvents and gas phase [3].

226 **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	

227 b [3]

228 **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
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b [3]

Table 12: Dipole Moment of Rosiglitazone for 6-31++G(d,p)

	$\mu_x(\text{D})$	$\mu_y(\text{D})$	$\mu_z(\text{D})$	$\mu(\text{D})$
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.

Table 13: Thermodynamic properties of Rosiglitazone for 6-31G(d,p)

Position	Gas phase		Water		Ethanol	
	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			

245

246 **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	

247

248 **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	

249

250 **Total Energy of Rosiglitazone molecule in gas phase and in solvents**

251 The calculated total energy of the Rosiglitazone in gas phase and in solvents is shown in Tables 16, 17 and
252 18. The results obtained in gas phase Tables 16, 17 and 18 were agreed with reported by Maltarollo
253 [4]. In Tables 16, 17 and 18, the values of the total energy increased as the dielectric constant of the
254 solvents decreased from water to ethanol. The minimum energy was found to be -1485.58768572a.u
255 in water as shown in Table 18.

256 **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 -40425.7499eV
Ethanol	-1485.54204931	-40424.57024	
DMSO	-1485.54263192	-40424.58607	
Acetonitrile	-1485.54242393	-40424.58041	

257

258 **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 -40425.7499eV
Ethanol	-1485.58613979	-40425.77001	
DMSO	-1485.58683932	-40425.78906	
Acetonitrile	-1485.58658948	-40425.78226	

259

260 **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 -40425.7499eV
Ethanol	-1485.58666137	-40425.78422	
DMSO	-1485.58735937	-40425.80321	
Acetonitrile	-1485.58710998	-40425.79641	

261

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

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

265 The most intense frequency was found to be about 1724.2718cm^{-1} which occurred at an intensity of
266 1726.4059Km/mole in water in Table 21. The second most intense frequency was found to be about
267 1724.3103cm^{-1} which occurred at an intensity of 1725.7785Km/mole in water in Table 20. Also the third
268 most intense frequency was found to be about 1777.3042cm^{-1} which occurred at an intensity of
269 1295.63Km/mole in water in Table 19. At these frequencies, there is strong C=O stretch asymmetry
270 mode of vibrations. From Tables 19, 20 and 21, it can be seen that the intensities increased as the
271 dielectric constants of the solvents increased from ethanol to water.

272 **Some selected values of vibrational frequencies and intensities**273 **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

274

275

276 **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		

277

278 **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		

279

280 **Conclusion**

281 The geometry of Rosiglitazone was optimized through DFT methods using 6-31G (d,p), 6-
282 31+G(d,p) and 6-31++G(d,p) basis sets. Solvent effects on molecular structural parameters,
283 electronic and thermodynamic properties of the optimized geometry of the molecule were
284 investigated and reported. The vibrational frequencies of the fundamental modes of the
285 compounds have been precisely assigned and analyzed. The values of the vibrational frequencies
286 obtained in gas phase and in solvents are observed to be positive which shows that the studied
287 molecule was very stable that is no imaginary frequencies exist. Also, the vibrational band
288 assignments of the frequencies in solvents were the same. The dipole moment of Rosiglitazone

289 was found to be higher in different solvents than in gas phase. Therefore, the dipole moment
290 increases with the increasing polarity of the solvent. We found that the frontier molecular orbitals
291 energy gap decreases rapidly in the low dielectric solvents and gradually comes to saturation in
292 high dielectric solvents. In a nutshell, it was found that the variation of environment (solvent
293 effects) influences the structural, electronic and molecular properties of the Rosiglitazone and will
294 be useful in the design and development of rosiglitazone as an anti-diabetes drug.

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