Theoretical Investigation of Transition State for the Purine Alkaloids 1,3-Dimethyl Isoguanine and 6-Amino-1,3-Dimethyl-1H-Purin-2(3H)-One by Density Functional Theory (DFT)

N. Surendra Babu, Teshome Abute Lelisho, Sisay Tadesse

Department of chemistry
College of Natural and Computational science
Hawassa University, Hawassa, Ethiopia
nsbabusk@gmail.com

Abstract: Geometries of reactant (1,3-dimethylisoguanine), product (6-amino-1,3-dimethyl-1H-purin-2(3H)-one) and transition state are fully optimized at the DFT/B3LYP level of theory and using of 6-311++G(d,p) basis set. The equilibrium constant and rate of reaction were calculated. Global descriptors such as ionization energy (I), electron affinity (EA), molecular hardness (η), chemical potential (μ), electrophilicity (ω), and frontier molecular energy gaps (ΔH-L) were determined and used to identify the differences in the reactivity of reactant and product. The bond lengths of transition state were lie between the reactant and product. From the values of η, μ and ω suggested that product is more energetically stable and less reactive, that reactant is more electonegative than the product and reactant is a good electrophile and product is a good nucleophile.

Keywords: 1,3-dimethylisoguanine, 6-amino-1,3-dimethyl-1H-purin-2(3H)-one, DFT method, transition state theory and global descriptors.

1. INTRODUCTION

Marine organisms are an extremely rich source of novel bioactive secondary metabolites and several research groups have been exploring this pool of natural chemical diversity for the presence of promising antiangiogenic compounds. Many of the reports discussed antiangiogenic marine natural products are alkaloids, and their structures and biological activity profiles [1-5]. 1,3-Dimethylisoguanine(a) and its conjugate acid 1,3-dimethylisoguaniunium (b) have been found in several marine organisms [6-11]. These purine alkaloids were first identified in the marine sponge Amphimedon viridis [6,7] and later in A. paraviridis [8]. Copp and coworkers have also reported the isolation of 1,3-dimethylisoguanine from the ascidian Cnemidocarpa bicornuta [9]. Both Mitchell et al. and Chehade et al. proposed the structure of 1,3-dimethylisoguanine to be mainly on the basis of the nuclear magnetic resonance (NMR) and mass spectrometry (MS) data, although the carbon chemical shifts reported by these groups are not in agreement [6,7] and reported 1,3-dimethylisoguanine exists in a different tautomeric form (c).

Gambaradella et al. later corrected the proposed structure of 1,3-dimethylisoguanine (a) to be 6-amino-1,3-dimethyl-1H-purin-2(3H)-one(c) via X-ray crystallographic analysis of 1,3-dimethylisoguanine trihydrate [10]. Jeong et al. investigated an ethanol extract of A. paraviridis showing inhibition of the proliferation of bovine aorta endothelial cells (BAECs). Assay-guided fractionation led to the
isolation of a crystalline solid, which was determined to be the cationic form 1, 3-dimethylisoguaninium by X-ray diffraction analysis, although no charge-balancing counter ion was reported by this group [8]. Panthong et al. Have subsequently confirmed the crystal structure of 1,3-dimethylisoguanine to be 6-amino-1,3-dimethyl-1H-purin-2(3H)-one (6) and suggest that the compound isolated from Amphimedon paraviridis was erroneously identified because of the pronounced hydrogen bonding between molecules in the crystal lattice [11].

In this research work we were calculated the optimized geometrics of reactant, product and transition state by using Density functional theory (DFT) and calculated the equilibrium constant and reaction rates and global descriptors.

2. Computational Methods

Geometry optimization parameters of titled compounds were done by Becke’s three parameter hybrid density functional theory method (DFT) [12] using the Lee- Yang-Parr correlation functional (B3LYP) [13] in combination with the 6-311++G (d,p) basis set in gas phase. The reactants, transition states and products were fully optimised at the DFT level of theory using 6-311++ G (d,p) basis sets in gas phase. All calculations have been performed using the GAUSSIAN 09 package [14].

The Synchronous Transit-Guided Quasi-Newton (STQN) method [15] was used to locate the transition structures. It uses a linear synchronous transit or quadratic synchronous transit approach to get closer to the quadratic region around the transition state and then uses a quasi-Newton or eigenvector-following algorithm to complete the optimization. It performs optimizations by default using redundant internal coordinates. This method will converge efficiently to the actual transition structure using an empirical estimate of the Hessian and suitable starting structures. To characterize each stationary point as a minimum or a transition state and to estimate the zero point vibrational energies (ZPE) and vibrational frequencies for all optimized species were computed at all levels. The transition states were further confirmed by vibrational analysis and characterised by only one imaginary vibrational mode. The minimum energy path connecting these structures was obtained through an intrinsic reaction coordinate (IRC) calculation [16, 17].

3. Results and Discussion

3.1. Molecular Geometry

The optimized geometrical parameters of the reactant 1,3-Dimethylisoguanine(a), product 6-amino-1,3-dimethyl-1H-purin-2(3H)-one(c) and transition state are calculated according to labeling of atoms as shown in the Figure 1 in gas phase. The optimized bond lengths and bond angles are listed in Table 1. The reactant, product and transition state assumed as C1 point group of symmetry. Compared the bond lengths from Table 1, dimethylisoguanine(a) and 6-amino-1,3-dimethyl-1H-purin-2(3H)-one(c), most of the bond lengths were different but a few bond lengths have same values (N1-C7, N10-C11and C2-O8 same values) . The bond lengths of transition state was lie between the 1,3-dimethylisoguanine(a) and 6-amino-1,3-dimethyl-1H-purin-2(3H)-one(c). The long bond lengths are N1-C7 and N3-C9 in both molecules comparing other bonds, because of C7 and C9 are methyl carbons and the most negative charge is (8O=2C) because this electronegative atom connected to N1. The most positive charge is (17C) because of connected to two electronegative atoms (13N and 1N).

![Fig1. Optimized geometrical molecular structure of 1,3-Dimethylisoguanine(a), transition state and 6-amino-1,3-dimethyl-1H-purin-2(3H)-one(c).](image-url)
Theoretical Investigation of Transition State for the Purine Alkaloids 1,3-Dimethyl Isoguanine and 6-Amino-1,3-Dimethyl-1H-Purin-2(3H)-One by Density Functional Theory (DFT)

Table 1. Optimized geometrical parameters of 1,3-Dimethylisoguanine(a), 6-amino-1,3-dimethyl-1H-purin-2(3H)-one(c) and transition state bond length (Å).

<table>
<thead>
<tr>
<th>S.No</th>
<th>Bond</th>
<th>Reactant</th>
<th>Product</th>
<th>TS</th>
<th>S.No</th>
<th>Bond</th>
<th>Reactant</th>
<th>Product</th>
<th>TS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N1-C2</td>
<td>1.3918</td>
<td>1.4351</td>
<td>1.4072</td>
<td>14</td>
<td>C2-O8</td>
<td>1.2490</td>
<td>1.2494</td>
<td>1.2470</td>
</tr>
<tr>
<td>2</td>
<td>N1-C6</td>
<td>1.4355</td>
<td>1.3861</td>
<td>1.4214</td>
<td>15</td>
<td>C7-H14</td>
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<td>1.0838</td>
<td>1.0879</td>
</tr>
<tr>
<td>3</td>
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<td>1.4772</td>
<td>1.4722</td>
<td>1.4758</td>
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<td>C7-H15</td>
<td>1.0882</td>
<td>1.0909</td>
<td>1.0827</td>
</tr>
<tr>
<td>4</td>
<td>N3-C2</td>
<td>1.4143</td>
<td>1.3796</td>
<td>1.4027</td>
<td>17</td>
<td>C7-H16</td>
<td>1.0832</td>
<td>1.0909</td>
<td>1.0877</td>
</tr>
<tr>
<td>5</td>
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<td>1.3758</td>
<td>1.3856</td>
<td>1.3749</td>
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<td>C9-H17</td>
<td>1.0921</td>
<td>1.0849</td>
<td>1.0878</td>
</tr>
<tr>
<td>6</td>
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<td>1.4642</td>
<td>1.4728</td>
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<td>C9-H18</td>
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<td>1.0881</td>
<td>1.0901</td>
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<tr>
<td>7</td>
<td>N10-C4</td>
<td>1.3790</td>
<td>1.3400</td>
<td>1.3978</td>
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<td>C9-H19</td>
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<td>1.0839</td>
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<tr>
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<td>9</td>
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<td>1.3948</td>
<td>1.4007</td>
<td>22</td>
<td>C11-H21</td>
<td>1.0733</td>
<td>-----</td>
<td>2.0987</td>
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<tr>
<td>10</td>
<td>N12-C11</td>
<td>1.3206</td>
<td>1.3425</td>
<td>1.3753</td>
<td>23</td>
<td>N10-H20</td>
<td>1.0044</td>
<td>-----</td>
<td>1.2724</td>
</tr>
<tr>
<td>11</td>
<td>N13-C6</td>
<td>1.2877</td>
<td>1.3534</td>
<td>1.2956</td>
<td>24</td>
<td>N13-H21</td>
<td>-----</td>
<td>1.0069</td>
<td>3.1682</td>
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<tr>
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<td>C4-C5</td>
<td>1.3749</td>
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<td>N13-H22</td>
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<td>1.0015</td>
<td>1.0222</td>
</tr>
<tr>
<td>13</td>
<td>C5-C6</td>
<td>1.4414</td>
<td>1.3790</td>
<td>1.4424</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3.2. Energies

The relative energies were presented from the full geometry optimizations performed on the reactant, transition state and products in gas phase and presented in Table 2. In Table 2 results are presented for the absolute energy of reactant and relative electronic energies for product and transition state with respect to reactant. Comparison of energies the product is more stable than reactant.

Table 2. Gas phase absolute electronic energies, enthalpy and free energy in atomic units (Hartrees) and in the brackets the relative energies, enthalpy and free energy (kcal/mol) for product and transition state with respect to reactant.

<table>
<thead>
<tr>
<th>S.No</th>
<th>Energy (AE)</th>
<th>Enthalpy (ΔH)</th>
<th>Free energy (ΔG)</th>
<th>Entropy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactant(a)</td>
<td>-621.10841967</td>
<td>-620.926644</td>
<td>-620.975420</td>
<td>102.657</td>
</tr>
<tr>
<td>Product (b)</td>
<td>-621.11531701(-4.3281)</td>
<td>-620.929815(-1.9898)</td>
<td>-620.978744(-2.0858)</td>
<td>102.980</td>
</tr>
<tr>
<td>TS</td>
<td>-620.98439718(77.8253)</td>
<td>-620.806041(75.6795)</td>
<td>-620.855829(75.0445)</td>
<td>104.789</td>
</tr>
</tbody>
</table>

3.3. Thermodynamics Analysis

Results provided in Tables 2 are for the Gibbs free energy differences of the reactant, product and transition state in gas phase. Gibbs free energy is evaluated under standard condition, i.e. 298.15 K and 1 atmosphere using the aforementioned methods. Trends are similar to those found on comparing electronic energies. Reactant is lower in Gibbs free energy than the product and product is more stable than reactant. The ΔH is negative, the reaction is exothermic and the bonds formed in the products are stronger than the bonds broken in the reactants and the products are lower in energy than the reactants.

The equilibrium constant provides a measure of the degree to which reactants or products are favored during the course of a chemical reaction. As shown in Fig 1, the reactant, transition state and product structures can interconvert. Based on the Gibbs free energies of the species provided by Table 2, the equilibrium constant (K) can be readily calculated using equations

\[ K = e^{-\Delta G^\circ/RT} \]  
and

\[ pK_r = -\log K_r \]  

The equilibrium constant between for the reactant (a) and product (b) is calculated by using equation (1), K = 33.81 and \( pK_r = -1.53 \). The equilibrium constant is much greater than one (K > 1), the concentration of the products is larger than the concentration of the reactants, so the equilibrium lies to the right and favors the products.

3.4. Reaction Energies

Geometries of reactant, product and transition state are fully optimized at the DFT/B3LYP/6-311++G(d,p) level and the character of the stationary points is confirmed by frequency calculations performed at the same level. Frequency calculations were carried out for both ground and transition state geometries, with the latter having one imaginary frequency corresponding to the reaction
coordinate [18]. All the reported transition states present one, and only one imaginary frequency corresponding to the expected transition vector. The first order coefficient $K(T)$ was calculated using transition State theory (TST) assuming that the transition coefficient is unity as shown in the following equation [19]:

$$k(T) = \frac{k_B T}{h} e^{-\Delta G^*/RT}$$

(2)

Where $\Delta G^*$ is the Gibbs free energy change between the reactant and the transition state and $k_B$ and $h$ are the Boltzmann and Planck’s constants respectively. By using equation (2), the rate constant is $6.12 \times 10^{-56}$ s$^{-1}$.

3.5. Electronic and Global Reactivity Parameters

From the Koopman’s theorem [20] the ionization energy and electron affinity can be expressed through HOMO and LUMO orbital energies:

$$IP = -\varepsilon_{HOMO}$$

$$EA = -\varepsilon_{LUMO}$$

(3)

$IP$ and $EA$ are the ionization energy and electron affinity respectively.

From the Density Functional Theory, to define global reactivity parameters which give information about the general behavior of a molecule and DFT method provides definitions of important universal concepts of molecular structure. These are the electronic chemical potential ($\mu$), the electro negativity ($\eta$), hardness ($\eta$) and softness ($S$) which are defined as [21-23]:

$$\eta = \frac{1}{2}(I - A)$$

(4)

$$\mu = -\frac{1}{2}(I - A)$$

(5)

$$S = \frac{1}{\eta}$$

(6)

In addition, Parr [24] was introduce the electrophilicity index ($\omega$), it can be calculated the following equation

$$\omega = \frac{\mu^2}{2\eta}$$

(7)

The calculated values of HOMO and LUMO, and electronic and global properties ($IP$, $EA$, $\chi$, $\eta$, $S$, and $\omega$) values were presented in table 3.

As shown results in Table 3, HOMO-LUMO gap as a characteristic of reactivity shows that 6-amino-1,3-dimethyl-1H-purin-2(3H)-one(c) is expected to be more reactive than 1,3-Dimethylisoguanine(a), i.e. the product is more reactive than reactant. So for more energetically stable and less reactive is product. A higher HOMO energy and lower LUMO energy corresponds for molecular reactions with electrophiles and nucleophiles respectively [25].

**Table 3.** Electronic and Global reactivity parameters for the reactant, product and transition state at B3LYP/6-311++G(d,p) level. ($\mu^* = $ dipole moment in Dbye units)

<table>
<thead>
<tr>
<th>S.No</th>
<th>HOMO</th>
<th>LUMO</th>
<th>$\Delta$(H-L)</th>
<th>IP</th>
<th>EA</th>
<th>$\eta$</th>
<th>$\mu$</th>
<th>S</th>
<th>$\omega$</th>
<th>$\mu^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactant</td>
<td>-5.99208</td>
<td>-0.45199</td>
<td>-5.54009</td>
<td>5.99208</td>
<td>0.45199</td>
<td>2.77005</td>
<td>-2.77005</td>
<td>0.36100</td>
<td>1.38502</td>
<td>6.7541</td>
</tr>
<tr>
<td>Product</td>
<td>-5.94882</td>
<td>-1.30563</td>
<td>-4.64318</td>
<td>5.94882</td>
<td>1.30563</td>
<td>2.32160</td>
<td>-2.32160</td>
<td>0.43074</td>
<td>1.16080</td>
<td>5.5870</td>
</tr>
<tr>
<td>TS</td>
<td>-6.45305</td>
<td>-1.75409</td>
<td>-4.69897</td>
<td>6.45305</td>
<td>1.75409</td>
<td>2.34948</td>
<td>-2.34948</td>
<td>0.42563</td>
<td>1.17474</td>
<td>2.4656</td>
</tr>
</tbody>
</table>

The hardness corresponds to the gap between these two orbitals in the molecule, and it measures the resistance of a molecule to a change in their electron distribution and hardness corresponds to higher
Theoretical Investigation of Transition State for the Purine Alkaloids 1,3-Dimethyl Isoguanine and 6-Amino-1,3-Dimethyl-1H-Purin-2(3H)-One by Density Functional Theory (DFT)

stability and lower reactivity for particular aromatic systems. From the table 3, values show that the product has low hardness (η) value, so for more energetically stable and less reactive product. The chemical potential measures the escaping tendency of an electron and is minus the Mulliken electron negativity. Also, note that μ is lower value for reactant comparison to the product. This behavior indicates that reactant is more electronegative than the product. According to this definition ω measures the susceptibility of chemical species to accept electrons. Thus, low values of ω suggest a good nucleophile while higher values indicate the presence of a good electrophile. Therefore reactant is a good electrophile and product is a good nucleophile.

4. CONCLUSION

A theoretical study of the stability and reactivity was carried out at the density functional theory (DFT) calculation level for the structures of 1,3-Dimethylisoguanine(a) and 6-amino-1,3-dimethyl-1H-purin-2(3H)-one(c) The converts of two structures were studied by transition state theory (TST) by using DFT/B3LYP level and 6-311++G(d,p) basis set in gas phase. From the equilibrium constant the reaction lies to the right and favors the products and the rate constant is 6.12 x 10^{-56} s^{-1}. HOMOLUMO energy gap indicate the product is more reactive than reactant. From the values of η, μ and ω suggested that product is more energetically stable and less reactive, that reactant is more electronegative than the product and reactant is a good electrophile and product is a good nucleophile.

REFERENCES