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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)

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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 electronegative than the product and reactant is a good electrophile and product is a good nucleophile.*
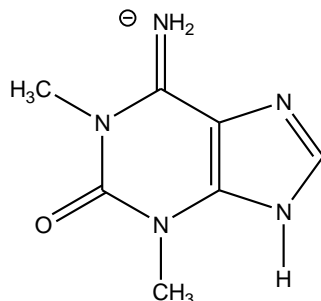
Keywords: *1,3-dimethylisoguanine,6-amino-1,3-dimethyl-1H-purin-2(3H)-one, DFT method, transition state theory and global descriptors.*
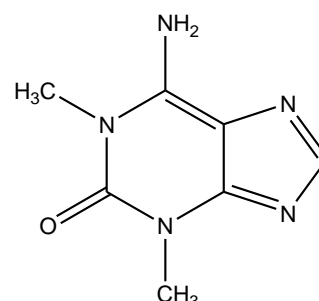
1. INTRODUCTION

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-dimethylisoguaninium (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).
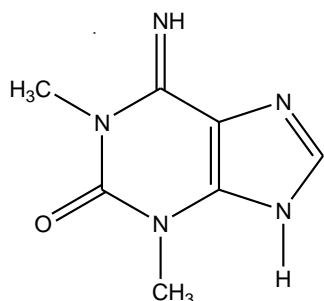
1,3-Dimethylisoguanine (a)   1,3-dimethylisoguaninium(b)   6-amino-1,3-dimethyl-1H-purin-2(3H)-one(c)

Gambardella 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.
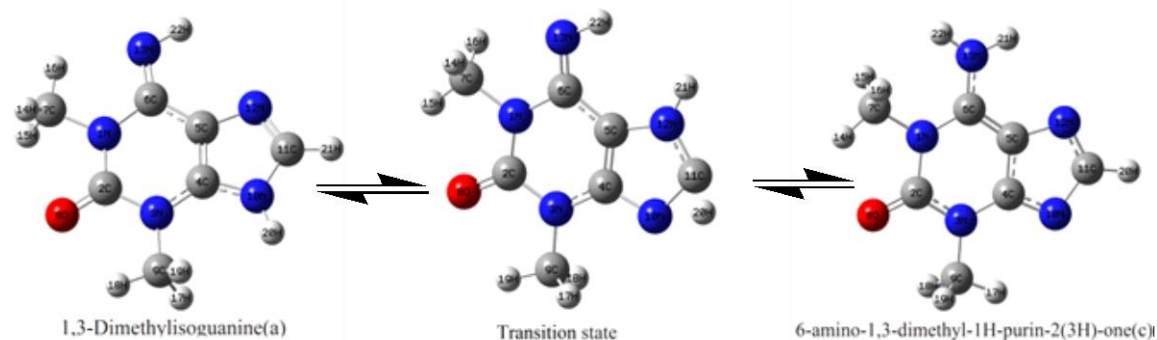
2. COMPUTATIONAL METHODS

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 longest 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).*

Table1. *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).*

S.No	Bond	Reactant	Product	TS	S.No	Bond	Reactant	Product	TS
1	N1-C2	1.3918	1.4351	1.4072	14	C2-O8	1.2490	1.2494	1.2470
2	N1-C6	1.4355	1.3861	1.4214	15	C7-H14	1.0882	1.0838	1.0879
3	N1-C7	1.4772	1.4722	1.4758	16	C7-H15	1.0882	1.0909	1.0827
4	N3-C2	1.4143	1.3796	1.4027	17	C7-H16	1.0832	1.0909	1.0877
5	N3-C4	1.3758	1.3856	1.3749	18	C9-H17	1.0921	1.0849	1.0878
6	N3-C9	1.4642	1.4728	1.4705	19	C9-H18	1.0849	1.0881	1.0901
7	N10-C4	1.3790	1.3400	1.3978	20	C9-H19	1.0921	1.0881	1.0839
8	N10-C11	1.4012	1.4010	1.4286	21	C11-H20	-----	1.0744	1.3488
9	N12-C5	1.3956	1.3948	1.4007	22	C11-H21	1.0733	-----	2.0987
10	N12-C11	1.3206	1.3425	1.3753	23	N10-H20	1.0044	-----	1.2724
11	N13-C6	1.2877	1.3534	1.2956	24	N13-H21	-----	1.0069	3.1682
12	C4-C5	1.3749	1.4109	1.3693	25	N13-H22	1.0224	1.0015	1.0222
13	C5-C6	1.4414	1.3790	1.4424					

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.

Table2. *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.*

S.No	Energy (ΔE)	Enthalpy (ΔH)	Free energy(ΔG)	entropy
Reactant(a)	-621.10841967	-620.926644	-620.975420	102.657
Product (b)	-621.11531701 (-4.3281)	-620.929815(-1.9898)	-620.978744 (-2.0858)	102.980
TS	-620.98439718 (77.8253)	-620.806041(75.6795)	-620.855829 (75.0445)	104.789

3.3. Thermodynamics Analysis

Results provided in Tables 2 are for the Gibbs free energy differences of the reactant, product and transition state in ga 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

$$K = e^{-\Delta G^0/RT} \text{ and } pK_T = -\log K_T \tag{1}$$

The equilibrium constant between for the reactant (a) and product (b) is calculated by using equation (1), K = 33.81 and pK_T = -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]:

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

(2)

Where $\Delta G^{\neq}$ 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 6.12×10^{-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 (μ), the electro negativity (χ), hardness (η) 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 (ω), 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, χ, η, S, and ω 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].

Table3. *Electronic and Global reactivity parameters for the reactant, product and transition state at B3LYP/6-311++G(d,p) level.(μ* = dipole moment in Dbye units)*

S.No	HOMO	LUMO	Δ(H-L)	IP	EA	η	μ	S	ω	μ*
Reactant	-5.99208	-0.45199	-5.54009	5.99208	0.45199	2.77005	-2.77005	0.36100	1.38502	6.7541
Product	-5.94882	-1.30563	-4.64318	5.94882	1.30563	2.32160	-2.32160	0.43074	1.16080	5.5870
TS	-6.45305	-1.75409	-4.69897	6.45305	1.75409	2.34948	-2.34948	0.42563	1.17474	2.4656

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

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 electro 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}. HOMO-LUMO 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

[1] Abdollahi A. Hlatky L. and Huber P. E. 2005. *Drug Resistance Update.,* **8**, 59.

[2] Folkman, J. (1971) *the New England Journal of Medicine*., **285**, 1182.

[3] Carmeliet P. and Jain R. K. 2000. *Nature*, **407**, 249.

[4] Boehm T. Folkman J. Browder T. and O'Reilly M. S. 1997. *Nature*., **390**, 404.

[5] Hurwitz H. Fehrenbacher L. Novotny, W. Cartwright T. Hainsworth J. Heim W. Berlin J. Baron A. Griffing S. Holmgren E. Ferrara N. Fyfe G. Rogers B. Ross R. and Kabbinavar F. 2004. *The New England Journal of Medicine.*, **350**, 2335.

[6] Mitchell S.S. Whitehill A.B. Trapido-Rosenthal H.G. and Ireland C.M. 1997. *Journal of Natural Products,* **60**, 727.

[7] Chehade C.C. Dias R.L.A. Berlinck R.G.S. Ferreira A.G. Costa L.V. Rangel M. Malpezzi E.L.A. de Freitas J.C. and Hajdu E.1997. *Journal of Natural Products.*, **60**, 729.

[8] Jeong S.J. Inagaki M. Higuchi R. Miyamoto T. Ono M. Kuwano M. and Van Soest R.W.M. 2003.*Chemical and Pharmaceutical Bulletin*., **51**, 731.

[9] Lindsay BS. Battershill C.N. and Copp B.R.1998. *Journal of Natural Products.*, **61**, 857.

[10] Gambardella M.T.D.P. Dias R.L.A. Chehade C.C. Berlinck R.G.D.S.1999. *Acta Crystallographica Section C*., **55**, 1585.

[11] Panthong K. Garson M.J. and Bernhardt P.V. 2006. *Acta Crystallographica Section C.*, **62**, 193.

[12] Becke A.D.1993. *J. Chem. Phys*., **98,** 5648.

[13] Lee C. Yang W. and Parr R.G. 1988.*Phys. Rev., B 37,* 785.

[14] Frisch M.J. Trucks G.W. and Schlegel, H.B. et al., 2009. Gaussian 09, Rev. A.1 Gaussian,Inc.,Wallingford CT.

[15] Foresman J.B. and Frisch A.1996. Exploring Chemistry with Electronic Structure Methods, 2nd Edition, Gaussian, Inc.

[16] Gonzales C. and Schlegel H.B.1989. *J. Chem. Phys., 90,* 2154.

[17] Gonzales C. and Schlegel H.B. 1990.*J. Phys. Chem., 94,* 5523.

[18] Gonza´lez C. and Schlegel H.B. 1990. *J. Phys. Chem., 94*, 5523.

[19] Keith J. Laidler.1978.Physical chemistry with biological applications, the Benjamin/cummings publishing company, Inc.California,.p.396.

[20] Koopmans T. 1933. *Physica*., 1, 104.

[21] Parr R.G. Yang W.1989.*Density Functional Theory of Atoms and Molecules*, Oxford University Press, New York.

[22] Gázquez J.L.2008. *J. Mex. Chem. Soc*., **52(1),** 3.

[23] Geerlings P. De Proft F. Langenaeker W. 2003.*Chem. Rev*., **103**, 1793.

[24] Parr R.G. Szentpaly L. Liu S.199. *J. Am. Chem. Soc*., **121,** 1922.

[25] Rank A.2001.*Orbital Interaction Theory of Organic Chemistry* 2nd Edition, John Wiley and Sons, New York.