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Quantum Chemical Analysis, Biological Activity and *In-Silico* ADME Properties of N,N´ - Diphenylguanidinium Hydrogen (+) –L-Tartrate Monohydrate

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Abstract : Good quality single crystal of N,N´ -Diphenylguanidinium Hydrogen (+) – L-Tartrate Monohydrate (DPGTM) was grown by low temperature solution growth. The lattice parameters and crystal system were elucidated by single crystal X-ray diffraction analysis. The molecular structure of DPGTM was optimized by DFT/B3LYP level. The UV-vis spectral activity was computed from optimized molecular structure in order to understand the electronic properties.The HOMO-LUMO analysis was carried out in order to assess the charge transfer and various chemical factors.The thermodynamic properties were computed and examined. The biological activities of DPGTM were expounded. The pre-ADME and pharmacokinetics activities of DPGTM were evaluated through, absorption, distribution, metabolism, excretion (ADME) properties.
Key Words : Crystal growth, DFT, UV-vis spectral analysis, Biological activity, ADME.

1. Introduction

N,N´ -diphenylguanidine also called as melaniline are broadly utilized in the mechanical divisions as quickening agent for vulcanization of rubber [1]. N,N´ -diphenylguanidine is a di-substituted relative of guanidine. While, guanidine being a solid natural base and a compound with hydrophilic nature has been distinguished as an appropriate contender for improvement of potential medications acting at central nervous system, anti-inflammatory agents, anti-diabetic, chemotherapeutic operators and also as beautifying agents [2]. Some N,N´ -diarylguanidines are powerful ligands for the N-methyl-D-aspartate/PCP (Phencyclidine) receptor and have neuroprotective against glutamate incited neuronal cell demise [3]. As, such di-substituted guanidine compounds are of extensive enthusiasm for pharmaceutical applications, as neuroleptic and antipsychotic drugs

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[4]. In proceeding with reads on a quest for organically dynamic substances among guanidine subordinates, various aroyldiphenylguanidines were synthesized and their pharmacological properties were contemplated and detailed [5]. Inferable from the promising organic and remedial properties of guanidine and subordinates of guanidine, the authors are provoked an enthusiasm for investigating the pharmacological exercises of the titular material. Computational analysis of a material provide various insightful information and reliable data that helps the researchers to carry out further research at laboratory level. Density Functional Theory (DFT) approaches, particularly those utilizinghybrid functional, have advanced to be a ground-breaking and truly dependable instrument, being routinely utilized for the assurance of different atomic properties. Becke's three-parameterhybrid functional combined with the Lee-Yang-Parr connection (B3LYP) has been recently appeared to give a magnificent trade off among precision and computational effectiveness [6]. Thus we report on the synthesis, single crystal X-ray diffraction analysis, Density Functional Theory (DFT) investigation with an extraordinary accentuation on molecular structure, computed UV-visactivity, HOMO-LUMO investigation, thermodynamic parameters, forecast of biological actions, pre-ADME and pharmacokinetics of N,N′ -Diphenylguanidinium Hydrogen (+) – L-Tartrate Monohydrate (DPGTM).

2. Experimental Methods

Equimolarproportions of the precursors N,N′ -diphenylguanidine and L (+) – Tartaric acid were taken and dissolved in a mixed solvent of water + ethanol (1:1). The entire synthesis and growth process of the titular material are reported by us earlier [1]. The photo of as grown single crystal of DPGTM is presented in Figure 1.

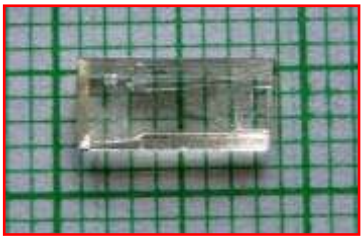

Figure 1: Photograph of as grown DPGTM crystal

3. Computational Details

All calculations were carried out with the Gaussian 03 W [7]. The molecular structure of DPGTM was optimized using B3LYP,hybrid function consisting of Becke's three-parameter non-localexchange function with the correlation function of Lee, Yang and Parr [8].In order to arrive at a precise molecular geometry and to calculate several more quantum chemical properties, the basis set level of B3LYP/6-31G (d) was used.

4. Results and Discussions

4.1 Single crystal X-ray diffraction analysis

The DPGTM single crystal was subjected to single crystal X-ray diffraction analysis. It was observed from the analysis that the titular material has the following lattice parameters, a = 7.05 (9) Å, b = 14.72 (19) Å, c = 18.20 (2) Å, volume V = 1889 (6) Å^3 and $\alpha = \beta = \gamma = 90^o$. The DPGTM was found to have crystallized in orthorhombic crystal system. These values of lattice parameters and crystal system are found to be in line with the reported data [1, 9].

4.2 Molecular structure

Improving the molecular geometry is viewed as the essential advance in the whole DFT examination. Considering this, the Crystallographic Information File (CIF) (CCDC information base identifier: HOFDAH, Deposition number: 135492) [9] was utilized as the input to streamline the molecular geometry of titular material for additional examinations in molecular structure investigation, computed UV-vis spectral activity and HOMO-LUMO examination at B3LYP/6-31G (d) level in gas phase. The streamlined molecular geometry was found to have no negative vibrational frequencies thereby building up the optimized structure to be valid and stable one. The optimized molecular structure of DPGTM is shown in Figure 2.

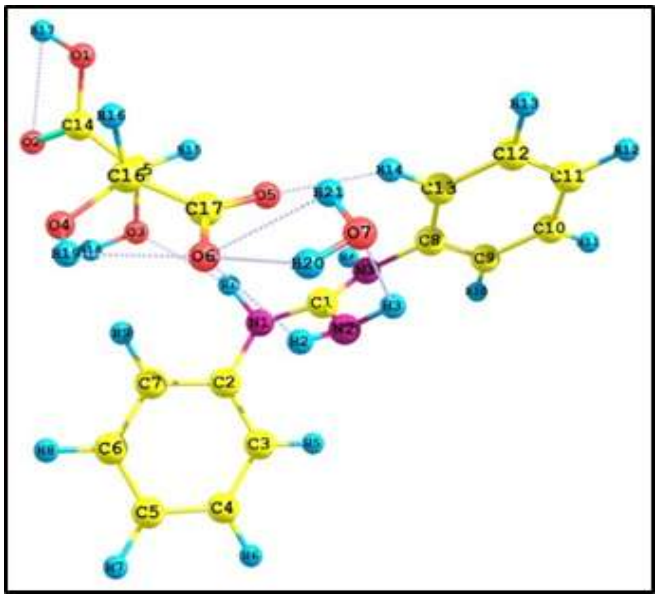

Figure 2: Optimized molecular structure of DPGTM

Geometrical boundaries, for example, bond length, bond angle, and torsion angle determined by DFT are taken to be effective, if the deviation of bond length among determined and trial esteems are just about 0.01 – 0.02 Å and the deviation of bond angle and torsion angles are around 1-2^{o} [10, 11]. The experimental and some selected most stable optimized geometrical parameters obtained by DFT of DPGTMare within the acceptable range and are listed in Table 1.

Table 1 Selected optimized molecular geometrical parameters for DPGTM molecule

Parameters	**B3LYP/6-31G (d)**	**Experimental [9]**
Bond length (Å)		
N1 – C1	1.348	1.330
N2 – C1	1.335	1.314
N3 – C1	1.356	1.332
O1 – C14	1.347	1.289
O5 – C17	1.278	1.276
Bond Angle (^{o})		
N2–C1–N1	121.3	120.6
N2–C1–N3	121.2	121.8
C17–C16–O4	110.6	111.0
C15–C14–O3	107.9	109.6
O1–C14–O2	123.5	125.5

This optimized molecular geometry provides a basic insight towards the structural stability, nature of bonding and other basic chemical data.

4.3 UV-vis spectral analysis

Optimized molecular structure was utilized to register the electronic retention range of DPGTM molecule utilizing TD-DFT at B3LYP/6-31G (d) level in gas stage. The processed UV-vis range of DPGTM is shown in Figure 3. It is seen from the processed UV-vis range, the maximum absorption happens at 288.23 nm with an oscillator strength of 0.1003. The maximum absorption peak at 288.23 nm might be credited to electron

excitation from an oxygen lone pair (non – bonding) to π-anti-bonding orbitals. So as to contrast the processed UV-vis range and the experimental one, the previous report [1] was considered. It is seen from [1] that the experimental UV-vis transmission range of DPGTM has the cut-off frequency at 298 nm. Over the cut-off frequency of 298 nm there are no noteworthy absorption in the UV-vis transmission range. Hence, the different electronic properties and basic data can be perused from the processed UV-vis range of DPGTM molecule.

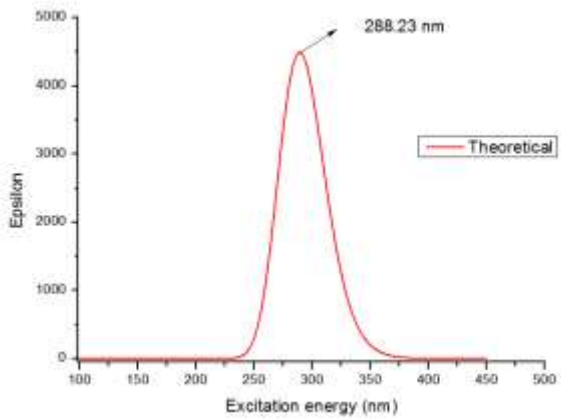

Figure 3: Computed UV-vis spectrum of DPGTM

4.4 HOMO-LUMO analysis

The frontier molecular orbitals (FMO's) so called Highest Occupied Molecular Orbital (HOMO), Lowest Unoccupied Molecular Orbital (LUMO) and their properties are valuable in investigating the few sorts of response in a conjugated framework and furthermore for anticipating the most receptive situation in π-electron frameworks [12]. HOMO represents the capacity to give an electron and related with ionization potential (IP). LUMO represents the capacity to get an electron and related with electron affinity (EA). However, the variation in the energy difference between HOMO and LUMO is related to molecular chemical stability. The FMO's of the DPGTM molecule was computed from the optimized molecular structure utilizing B3LYP/6-31G (d) level in gas phase. The HOMO-LUMO plot for DPGTM molecule is presented in Figure 4.

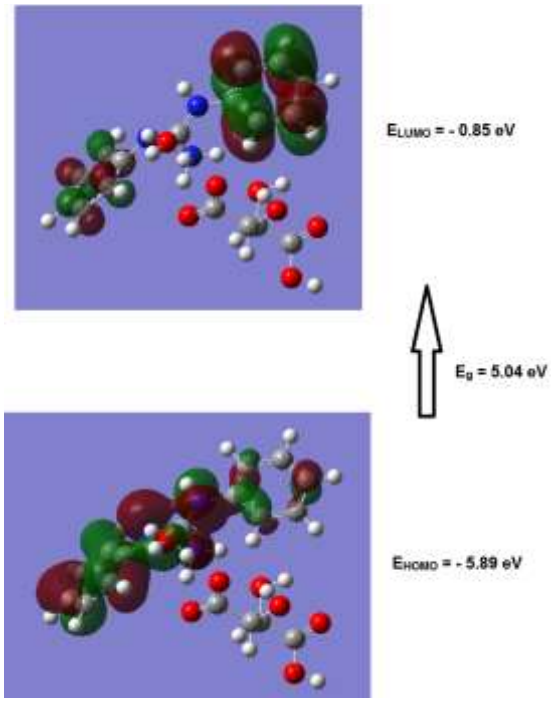

Figure 4: HOMO-LUMO plot of DPGTM

The processed estimation of E_{HOMO} and E_{LUMO} for the DPGTM particle were seen as – 5.89 eV and – 0.85 eV separately. It is additionally seen from the HOMO-LUMO plots that there are some outstanding charge move occurring inside the DPGTM. The red and green shade of the plot are to be deciphered as positive and negative stage separately. The electron conveyance is primarily dispersed in HOMO over the phenyl ring, guanidinium section and oxygen atom of water molecule, while the LUMO is mostly spread over the other phenyl ring. This charge move gives some essential thoughts regarding broadening the titular material towards pharmacological applications. Past reports [13, 14] talks that the molecule with negative extents of E_{HOMO} and E_{LUMO} sets up the strength of organic compounds. The watched negative values of E_{HOMO} and E_{LUMO} of DPGTM molecule, claims it to be a steady one. The HOMO-LUMO energy gap was resolved with the help of E_{HOMO} and E_{LUMO} values. The worth was seen as, $\Delta Egap = E_{LUMO} - E_{HOMO} = (-0.85) – (-5.89) = 5.04$ eV. An enormous HOMO-LUMO energy gap suggests high atomic solidness and aromaticity [15]. The HOMO and LUMO energy esteems were utilized to figure global chemical reactivity descriptors. These global descriptors gives different educational information of a material while centering its application in pharmaceutical fields.In order to evaluate the global descriptors, Koopmans's Theorem [16] was employed.

The IP and EA are considered as follows, $IP = - E_{HOMO} = - (-5.89 \text{ eV}) = 5.89$ eV and $EA = - E_{LUMO} = - (-0.85 \text{ eV}) = 0.85$ eV. The calculated value of global reactivity descriptors for DPGTM molecule are listed in Table 2.

Table 2 List of global reactivity descriptors for DPGTM molecule

Parameters	**DPGTM (B3LYP/6-31G(d))**
E_{HOMO} (eV)	-5.89
E_{LUMO} (eV)	-0.85
ΔE_{gap}(eV)	5.04
Ionization potential (IP) (eV)	5.89
Electron affinity (EA) (eV)	0.85
Chemical potential (μ) (eV)	-3.37
Hardness (η) (eV)	2.52
Softness (s) (eV^{-1})	0.19
Electronegativity (χ) (eV)	3.37
Electrophilicity index (ω) (eV)	2.25

Electrophilicityindex is one of the most significant global descriptors which determine the poisonousness of moleculein terms of their reactivity and site selectivity thereby providing ideal information regarding biological activity of drug receptor interaction [16]. The Eigen estimations of HOMO, LUMO and their energy gap offers further help that a charge move exists inside DPGTM molecule which could advance its bioactivity and capacity to frame organic connections. Furthermore, the low total energy and large energy gap of HOMO-LUMO suggest that the molecule has good stability.

4.5 Thermodynamic properties

The thermodynamic parameters gives data about the strength and reactivity of molecules as these parameters are significant in foreseeing the reactivity of compound responses and reaction routes. Thermodynamics has long been a key theory in biology, utilized in issues running from the understanding of authoritative in both in vitro and in vivo investigations [17]. Thermodynamic parameters, for example, entropy and enthalpy are significant necessities for contemplating the bioengineering thermodynamic of natural cells [18]. So as to illuminate the thermodynamic parameters of DPGTM molecule, the computation was finished utilizing B3LYP/6-31G (d) level in gas stage. The figured thermodynamic parameters of DPGTM molecule are presented in Table 3.

Table 3 List of calculated thermodynamic parameters at 298.15 K for DPGTM molecule

Parameters	**DPGTM (B3LYP/6-31G(d))**
Point group	C1
Zero-point vibrational energy (J mol^{-1})	1000412.8
Rotational constant (GHz)	0.22377
0.14068	
0.10625	
Thermal energy (k.cal mol^{-1})	
Total	256.261
Translational	0.889
Rotational	0.889
Vibrational	254.484
Molar heat capacity at constant volume (cal /mol-K)	
Total	101.759
Translational	2.981
Rotational	2.981
Vibrational	95.798
Entropy (cal /mol-K)	
Total	187.228
Translational	43.691
Rotational	35.817
Vibrational	107.720
Dipole moment (Debye)	
μ_x	- 1.6967
μ_y	3.4135
μ_z	- 1.4366
μ_{total}	4.0736

The positive entropy shows the unconstrained and irreversible responses displayed by DPGTM which assigns it as a possible up-and-comer in the organic and pharmacological applications as cells are open complex thermodynamic frameworks [18].

4.6 Biological activity

Whenever a drug is to be marketed it requires several clinical trials and several experiments at laboratory level. However, this requires a lot of efforts, enormous work and a very time consuming process. In order to minimise the above said factors as well as to have some basic information and data regarding the material under study, computational chemistry and biology play crucial roles. In this point of view, the biological activity of DPGTM was predicted using PASS (Prediction of Activity Spectra) [19]. PASS analysis of DPGTM predicted various biological activities. However based on the values of probability to be active (P_a) and probability to be inactive (P_i) the top five activities were listed in Table 4.

Table 4 Prediction of biological activity for DPGTM

P_a	P_i	Biological activity
0.939	0.002	Bisphosphoglycerate phosphatase inhibitor
0.927	0.004	Ubiquinol-cytochrome-c reductase inhibitor
0.918	0.003	Monodehydroascorbatereductase (NADH) inhibitor
0.915	0.003	Superoxide dismutase inhibitor
0.899	0.003	Fusarinine-C ornithinesterase inhibitor

The top five activities were listed with P_a>0.700, indicates the molecule has potential to react on the predicted biological activity. Out of the listed top five predicted biological activity, the DPGTM acts as very good Bisphosphoglycerate phosphatase inhibitor. This predication of biological activities lays the foundation for further research that may be carried out for DPGTM.

4.7 Pre-ADME and pharmacokinetics analysis

The absorption, distribution, metabolism, excretion (ADME) properties were calculated with the help of online server pre-ADMET (http://preadmet.bmdrc.org/). A chemical compound when introduced into a living being should show faultless ADMET properties to be accepted as a drug in clinical tests. The solubility of DPGTM in pure water was predicted to be 897.788 mg/L. The important pre-ADME and pharmacokinetics properties such as, Blood Brain Barrier (BBB) penetration, Human Intestinal Absorption (HIA), Mandin Darby Canine Kidney (MDCK) cell permeability, Plasma Protein Binding (PPB) and skin permeability for DPGTM are presented in Table 5.

Table 5 Pre-ADME and pharmacokinetics for DPGTM

Activity	Value
Blood Brain Barrier (BBB)	0.0679308
Human Intestinal Absorption (HIA)	11.81391 %
Mandin Darby Canine Kidney (MDCK) cell permeability	13.146 10^{-6} cm/sec
Plasma Protein Binding (PPB)	72.020407%
Skin permeability (Transdermal delivery)	-2.7984 cm/hour

4.8 Drug-Likeness and ADME predictions

So as to investigate more data about the physicochemical descriptors, drug likeness, ADME expectations and pharmacokinetics properties of DPGTM, it was exposed to SwissADME [20]. ADME depends on Lipinski's standard (Rule of Five) and establishes the framework for chemical compound to be assigned as an effective medication. Rule of Five relies upon physicochemical boundary, for example, sub-atomic weight which ought to be under 500 g/mol, (DPGTM – (379.36 g/mol)), lipophilicity (Log P) under 5 (DPGTM – (-1.37)), and number of hydrogen bond benefactors and acceptors under 5 and 10 (DPGTM – (7 and 7)) individually. Molar refractivity ought to have a worth 40–130 (DPGTM – (97.15)). Be that as it may, DPGTM abuses one boundary out of five. In this manner the drug likeness of DPGTM might be expected to greatest degree with the thought of infringement in the quantity of hydrogen bond benefactors with a bioavailability score of 0.55. These physicochemical boundaries are associated with intestinal porousness and watery dissolvability and decide the initial step of bioavailability [21]. The water dissolvability of DPGTM was

screened as "Modestly Soluble" and this concurs well with the solvency anticipated from pre-ADMET online server. The pharmacokinetics and medicinal chemistry information are listed in Table 6.

Table 6Pharmacokinetics and medicinal chemistry information for DPGTM

Parameters	Insightful data
Pharmacokinetics	
GI absorption	Low
BBB permeant	No
P-glycoprotein substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p(Skin permeation)	-8.46 cm/s
Medicinal Chemistry	
PAINS	0 Alert
Brenk	2 Alerts
Leadlikeness	No
Synthetic accessibility	3.49

It is seen that the Gastrointestinal Absorption (GI) and BBB permeant are "Low" and "No" individually. Though those anticipated from pre-ADMET are 11.81% for GI and 0.0679308 for BBB individually. In this way, the anticipated aftereffects of SWISS ADME concurs well the outcomes acquired from pre-ADMET.This provides some basic insights into the biological and pharmacological activity of titular material.

5. Conclusion

DPGTM single crystal of good quality was synthesized and subjected to various experimental and theoretical studies. Single crystal XRD data revealed the crystal system of the titular compound to be orthorhombic along with the lattice parameters. DFT analysis with suitable basis sets were carried out to arrive at the optimized molecular geometry of the titular compound the output of which is further used in other studies.The computed UV-vis spectrum's maximum absorption peak (at 288.23 nm) is attributed to electron excitation from an oxygen lone pair to π-anti-bonding orbitals. The low total energy and large energy gap of the molecule's HOMO-LUMO analysis suggest good stability for the compound. Various global descriptors calculated for the titular compound, using HOMO-LUMO energies, facilitates the understanding of different biological activity of the molecule. Thermodynamic calculations on DPGTM nominates it as a potential candidate in biological and pharmacological applications. Biological activity of the compound predicted using PASS analysis. The ADME and Pharmacokinetics studies carried out on the compound further strengths the claim of DPGTM as a potential candidate in the field of biological and pharmacological production subjected to further research.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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