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COMPUTATIONAL STUDY ON NUCLEOSIDES OF RIBONUCLEIC ACID (RNA) BY THE AUSTIN MODEL-1 METHOD

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ABSTRACT

Quantum chemistry is used to study the mechanism of gene editing techniques to design new proteins with improved binding affinity and specificity. It helps in understanding the role of RNA in various biological processes for gene regulation and protein synthesis. Nucleosides have been optimized and evaluated by the semi-empirical molecular orbital AM1 method. In this connection, the heats of formation (ΔH_f^o), dipole moment (μ), energies of frontier molecular orbitals (E_{HOMO} and E_{LUMO}), and quantum chemical descriptors have been performed. It is observed that the stability of nucleosides in RNA (uridine > cytidine > guanosine > adenosine) as per heat of formation (ΔH_f^o) data. The dipole moment (μ) of nucleosides is investigated in RNA (guanosine > uridine > adenosine > cytidine). Furthermore, the dipole-dipole interactions play a critical role during the sequencing of RNA, as has been discussed.

KEYWORDS: Nucleoside, AM1 method, dipole moment, heats of formation, quantum chemical descriptors, E_{HOMO} and E_{LUMO}.

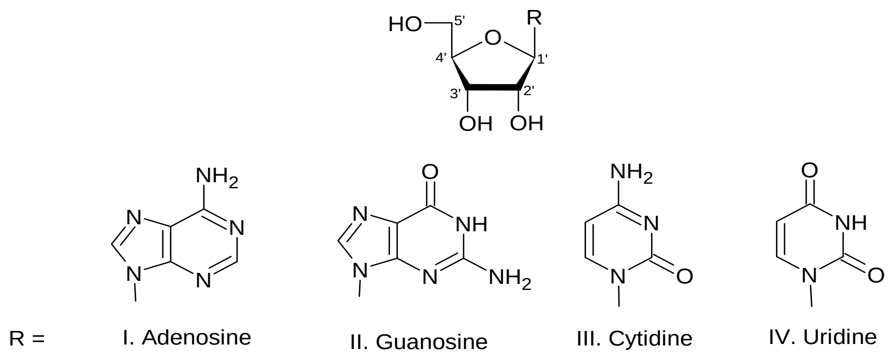
1. INTRODUCTION

Quantum chemistry involves the use of mathematical models and computer simulations to predict the behaviour of chemical systems and analyse the properties of nucleosides of RNA in the design of new drugs, enzyme design, molecular modelling, and gene technology.[1] Nucleosides and Nucleotides play vital roles in various biological processes, including energy transfer processes, intracellular signalling, the regulation of biological activity, and the design of enzymes with novel properties. These enzymes can be used for various applications, including biosensors, bioremediation, and industrial biotechnology.[2] However, due to the presence of multiple reactive centres in nucleosides, the significant formation of side products, low yields, and synthetic inconveniences, these approaches have not found wider application. Thermodynamic properties play an important role in understanding the RNA-protein interactions for the development of materials with specific properties.[3] In this connection, the advanced technology of genetic engineering for the synthesis of genes and the discovery of miracle enzymes is required to cure many diseases.[4] In continuation of research work[5], Austin Model-1 (AM1) is one of the semi-empirical methods of quantum chemistry that uses experimental parameters and the extensive simplification of Schrödinger's equation ($H\Psi = E\Psi$) to describe the behaviour of quantum systems in material science and nanotechnology.[6]

In this context, the present research focuses on the thermodynamic properties and Quantum Chemical Descriptors of Adenosine **I**, Guanosine **II**, Cytidine **III,** and Thymidine **IV** (Figure-1) have been determined by full optimization calculations (**MOPAC 2016** (Version: 22.234w)) by using the semi-empirical molecular orbital Austin Model-1 (AM1) method.

Computational methods[7]

Semi-empirical molecular orbital calculations were performed using the AM1 (Austin Model 1) method included in the **MOPAC2016** (Version: 22.234w) programme. Geometry calculations in the ground state (keywords: CHARGE=0, GNORM=1, AIGOUT, DEBUG, PRECISE, GEO-OK, and MMOK to correct the increase in the barrier to rotation of the amide linkage) were completely optimised until the lowest energy conformation was found. The gas-phase the Heat of formation (ΔH_f^o in kcal/mol) at 298^0K of one mole of a compound was calculated from its elements in their standard state. The position of the atom in the molecule is mentioned, as shown in **Figure - 1**.



I. Adenosine II. Guanosine III. Cytidine IV. Uridine

Figure - 1

Magnitude of the induction effect[8] (μ_{ind}):- A dipole moment is a measure of the separation of charge in nucleosides (**I** to **IV**) of RNA, resulting in a net dipole, as it can influence their physical and chemical properties. Nucleosides of RNA with high dipole moments tend to have higher boiling points, greater solubility in polar solvents, and may exhibit dipole-dipole interactions. The dipole moment of nucleosides of RNA can also be used to predict its molecular geometry as well as to determine its polarity. The electronegative heteroatoms cause the displacement of electrons in the nucleosides of RNA, which induces an additional dipole moment. The magnitude of the induction effect (μ_{ind}) can be estimated with the corresponding reactant and product at the time of reaction by using equation (1).

Induction effect (μ_{ind}) = μ(Product) - μ(Reactant) ----- (1)

Quantum Chemical Descriptors[9]: These parameters are used to describe the electronic structure and properties of nucleosides (**I** to **IV**) of RNA, based on quantum mechanical calculations as well as to design new nucleosides of RNA with desired properties, especially in the prediction of toxicity, biological activities, chemical reactive sites, group identification, molecular reactivity, and cost-effective processes. These were used for the development of QSAR and QSPR for different applications.

RESULTS AND DISCUSSIONS

The optimized electronic structure of Nucleosides in ribonucleic acid (RNA) is shown in **Figure 1.** The calculated values of Heat of formation (ΔH_f^O in kcal/mol), dipole moment (μ in Debye), frontier molecular orbital energy (E_{HOMO} & E_{LUMO}) are included in Table-**I** and quantum chemical descriptors such as Induction effect (μ_{ind}), Cosmo area (Sq.Ang), and Cosmo volume (Cu.Ang) are incorporated in Table-**II**. The stability of nucleosides is observed in the order of uridine > cytidine > guanosine > adenosine as per Heat of formation (ΔH_f^O) data.

The dipole moment (μ) of nucleosides is investigated in RNA in the order of guanosine > uridine > adenosine > cytidine. The dipole moment of nucleosides (**I** to **IV**) of RNA is the sum of the dipole moments of its individual bonds and it can influence their physical and chemical properties. Nucleosides of RNA with high dipole moments tend to have higher boiling points, greater solubility in polar solvents, and may exhibit dipole-dipole interactions. The dipole moment of nucleosides of RNA can also be used to predict the shape and geometry.

Table- I	**Heat of formation (ΔH_f^o in kcal/mol), dipole moment (μ in Debye), frontier orbital energy (E_{HOMO} & E_{LUMO}), Cosmo area and Cosmo volume for nucleosides (I to IV) of RNA from AM1 calculation**			
	Adenosine I	**Guanosine II**	**Cytidine III**	**Uridine IV**
ΔH_f (Kcal/mol)	+68.2895	+29.3602	-12.4845	-165.2896
Dipole moment (Debye)	5.2706	10.1821	3.7679	8.1295
E_{HOMO} ev	-8.412	-8.618	-8.201	-8.178
E_{LUMO} ev	-0.413	-0.693	-0.432	-0.556
Cosmo Area (Sq ang)	296.42	317.51	271.78	264.54
Cosmo Volume (Cu ang)	314.01	323.46	287.30	275.83

The COSMO (COnductor like Screening MOdel) method has been widely used in the field of computational chemistry to study the solvation properties of nucleosides (**I** to **IV**) of RNA, including their solubility, partition coefficients, and reactivity in solution. The COSMO area is typically calculated using a software programme, such as COSMOtherm, which uses a numerical algorithm to discretize the nucleosides of RNA surface into small triangles and calculate their areas. The resulting surface area is then used in the COSMO solvation calculation. The method has been validated against experimental data and has been shown to provide accurate predictions for a wide range of solvent-solute interactions. The COSMO area is observed in the order of guanosine > adenosine > cytidine > uridine in RNA to determine the surface charges on the nucleosides of RNA that interact with the solvent continuum.[10]

The COSMO volume[11] is typically calculated using a software program, such as COSMOtherm, which uses a numerical algorithm to discretize the molecular volume into small tetrahedrons and calculate their volumes. The resulting volume is then used in the field of computational chemistry to study the solvation properties of nucleosides (I to IV) of RNA, including their solubility, partition coefficients, and reactivity in solution. The COSMO volume is observed in the order of guanosine > adenosine > cytidine > uridine in RNA. In general, the COSMO volume is considered to be a more accurate descriptor of the solvation behaviour of a nucleosides of RNA than the COSMO area, as it takes into account the three-dimensional shape of the nucleosides of RNA and its interactions with the solvent. However, both parameters can be useful in predicting the solvation behaviour of nucleosides of RNA in different solvents and under different conditions.

Table- II	**Quantum Chemical descriptors like Energy gap (ΔE, in eV), Ionization Potential (IP), Electron Affinity (EA), Electro Negativity(EN), Global hardness, Softness, Chemical potential and Electrophilicity Index for nucleosides (I to IV) of RNA are calculated from frontier orbital energy (E_{HOMO} & E_{LUMO}).**			
	Adenosine I	**Guanosine II**	**Cytidine III**	**Uridine IV**
Energy gap (ΔE) (eV)	**7.999**	**7.925**	**7.769**	**7.622**
Ionization Potential (eV)	**8.412**	**8.618**	**8.201**	**8.178**
Electron Affinity (eV)	**0.413**	**0.693**	**0.432**	**0.556**
Electro Negativity (eV)	**4.413**	**4.656**	**4.317**	**4.367**
Global Hardness	**4.000**	**3.963**	**3.885**	**3.811**
Softness	**2.103**	**2.175**	**2.111**	**2.146**
Chemical Potential	**-4.413**	**-4.656**	**-4.317**	**-4.367**
Eletrophilicity Index	**2.434**	**2.735**	**2.398**	**2.502**

Quantum chemical descriptors[9] provide insights into the electronic structure and reactivity of nucleosides (**I** to **IV**) of RNA, and can be used to predict various properties of molecular energy, dipole moment, polarizability, and frontier molecular orbitals. These are used to understand the chemical and physical behaviour of nucleosides of RNA, as well as to design new molecules with desired properties (as per Table-II).

E_{HOMO} and E_{LUMO} refer to the highest occupied molecular orbital and the lowest unoccupied molecular orbital, respectively. Frontier orbital energies (E_{HOMO} and E_{LUMO}) play an important role in determining the chemical and physical properties of nucleosides (**I** to **IV**) of RNA. Energy gap indicates the reactivity in the order of adenosine > guanosine > cytidine > uridine. The energy difference between the E_{HOMO} and E_{LUMO} is known as energy gap (ΔE) and it is an important parameter for determining the optical and electronic properties of nucleosides (**I** to **IV**) of RNA. Nucleosides of RNA with a small energy gap (ΔE) tend to absorb light in the visible region of the electromagnetic spectrum and may exhibit strong coloration or fluorescence. E_{HOMO} of a ligand interacts with the electron-rich region of the protein, while the E_{LUMO} of the protein interacts with the electron-poor region of the ligand. The size of the energy gap (ΔE) can be used to predict the binding affinity of the ligand to the protein.[12]

Ionization Potential (IP)[13] is in the order of guanosine > adenosine > cytidine > uridine. The ionization potential can be used to predict the reactivity of nucleosides (I to IV) of RNA. Generally, nucleosides of RNA with lower ionization potentials are more reactive because they are more likely to lose an electron and form a cation. This energy corresponds to the difference in energy between the ground state of the nucleosides of RNA and their ionized state. The ionization potential can also be used to predict the chemical properties of a molecule. Nucleosides of RNA with low ionization potentials tend to form cations and are more reactive, and with high ionization potentials tend to form anions and are less reactive.

Electron affinity (EA)[14] is defined as the energy released when an electron is added to a neutral nucleosides (I to IV) of RNA in the gas phase and observed in the order of guanosine > uridine > cytidine > adenosine. A positive electron affinity means that energy is released when an electron is added, while a negative electron affinity means that energy is required to add an electron. The electron affinity is important in understanding electron transfer processes in redox reactions, the electron affinity of nucleosides of RNA determines whether it is an oxidizing agent (accepts electrons) or a reducing agent (donates electrons). Electron affinity is an important factor in determining their ability to form anions, participate in chemical reactions and can also affect the physical properties of materials, such as their electrical conductivity and optical properties.

Global hardness[15] is a fundamental concept in the study of chemical reactivity and refers to the resistance of nucleosides (**I** to **IV**) of RNA to donate or accept electrons. It is a measure of the energy required to add or remove an electron from nucleosides of RNA. Global hardness is closely related to other molecular properties such as electronegativity, ionization potential, and electron affinity. Nucleosides of RNA with high hardness are more stable and less likely to undergo chemical reactions, while those with low hardness are more reactive and can undergo a wide range of chemical reactions. Global hardness is shown in the order of uridine > cytidine > guanosine > adenosine.

Softness[16] is the inverse of global hardness and a measure of the ability of nucleosides (**I** to **IV**) of RNA to undergo polarizability. It is a measure of the ability of nucleosides of RNA to donate or accept electrons. Softness is closely related to other nucleosides of RNA properties such as electronegativity, ionization potential, and electron affinity and found in the order of guanosine > uridine > cytidine > adenosine. Nucleosides of RNA with high softness are more reactive and can undergo a wide range of chemical reactions, while those with low softness are more stable and less likely to undergo chemical reactions.

Chemical potential[17] is a fundamental concept in thermodynamics that describes the tendency of nucleosides (**I** to **IV**) of RNA to move from one region to another. It is defined as the change in Gibbs free energy of a system when nucleosides of RNA are added to the system while holding the temperature, pressure, and other conditions constant. It is observed in the order of guanosine > adenosine > uridine > cytidine. Chemical potential is used to understand the equilibrium between phases of a substance in a particular phase determines the tendency of the substance to move between phases to reach equilibrium. In the phase diagram of a substance, the chemical potential of nucleosides of RNA in each phase determines the boundaries between phases and the conditions at which equilibrium is reached. The difference in chemical potential between the reactants and products determines the potential difference between the electrodes in an electrochemical cell.

Electrophilicity index[18] describes the ability of nucleosides (**I** to **IV**) of RNA to donate electrons and form a new bond and exposed in the order of guanosine > uridine > adenosine > cytidine. The electrophilicity index is its ability to predict the relative reactivity of different nucleosides of RNA in a reaction. Nucleosides of RNA with a higher electrophilicity index are more likely to react with a lower index. The electrophilicity index has also been used in the study of biological systems, including the interaction of drugs with receptors and enzymes.

CONCLUSIONS

Naturally occurring nucleosides and nucleotides are basic building blocks for the synthesis of DNA and RNA. The presence of multiple reactive centres in nucleosides derivatives, the advanced technology of genetic engineering for the synthesis of genes and discovery of miracle enzymes are required to cure many diseases. Austin Model-1 (AM1) is one of the semi-empirical methods of quantum chemistry which uses experimental parameters and extensive simplification of Schrödinger's equation ($H\Psi = E\Psi$) to optimize molecules for calculation of various thermodynamic properties like heats of formation (ΔH_f^o), dipole moment (μ), the energies of frontier molecular orbitals (E_{HOMO} and E_{LUMO}) and quantum chemical descriptors. Further, the utility of theoretical predictions are discussed to determine mutation and genetic diseases.

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Author's contribution

The author has participated in conception, design, analysis, interpretation of the data, drafting the article, and approval of the final version.

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