WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 13, 259-274. Review Article ISSN 2277–7105

COMPUTATIONAL STUDY OF THE THERMODYNAMIC PROPERTIES OF NUCLEOSIDES AND NUCLEOTIDES IN RIBONUCLEIC ACID (RNA) USING THE AUSTIN MODEL-1 METHOD

[*1]Dr. Bojja Rajeshwar Rao

[*1]Senior Chemist (Retired), Chemical Division, Kakatiya Thermal Power Project (O & M), Chelpur- 506170, India.

Article Received on
07 May 2025

Revised on 27 May 2025
Accepted on 16 June 2025

DOI: 10.20959/wjpr202513-37322

***Corresponding Author**
Dr. Bojja Rajeshwar Rao
Senior Chemist (Retired),
Chemical Division,
Kakatiya Thermal Power
Project (O & M), Chelpur-
506170, India.

ABSTRACT

Thermodynamic properties associated with the Phosphorylation of nucleosides and nucleotides are crucial for the enzymatic synthesis of RNA. They participate in energy transfer processes that regulate biological activity. Changes in the base sequence of nucleotides can sometimes be beneficial and at other times harmful. The Phosphorylation of nucleosides and nucleotides has been optimized and evaluated using the semi-empirical AM1 molecular orbital method. In this context, parameters such as heats of formation (ΔH_f^o), dipole moments (μ), the energies of frontier molecular orbitals (E_{HOMO} and E_{LUMO}), and other quantum chemical descriptors have been analyzed. The stability of nucleosides in RNA has been observed in the following order based on heats of formation (ΔH_f^o): uridine > cytidine > guanosine > adenosine. The dipole moment (μ) of nucleosides in RNA follows this order: guanosine > uridine > adenosine > cytidine. Additionally, it has been found that tri-phosphates are more stable than di-phosphates and mono-phosphates of their respective nucleosides. Furthermore, the role of dipole-dipole interactions during the sequencing of RNA has been discussed, highlighting their significance in the process.

KEYWORDS: Phosphorylation, nucleosides, nucleotides, mono-phosphates, di-phosphates, tri-phosphates, RNA.

1. INTRODUCTION

Phosphorylation of nucleosides and nucleotides plays a vital role in various biological processes, including energy transfer, intracellular signalling, and the regulation of biological activity.[1] Scientists are interested in synthetic nucleotide analogs to explore complex biological systems and their potential therapeutic.[2] and diagnostic applications.[3] However, developing efficient synthetic protocols remains a challenging task due to the presence of multiple reactive centres' in nucleotide derivatives. The synthesis of nucleoside di- and tri-phosphates.[4] has been developed for the preparation of nucleoside 5'-triphosphates. However, these approaches have not been widely adopted due to significant drawbacks, such as the formation of by-products, low yields, and synthetic inconveniences.[5] Understanding the thermodynamic properties of these reactions is important for grasping the structure, folding, RNA-protein interactions, RNA engineering, and the stability of RNA molecules. In this regard, advanced genetic engineering technologies are essential for gene synthesis and the discovery of enzymes that could help cure many diseases.[6] Quantum chemistry serves as a powerful tool in gene technology, particularly in molecular modeling, drug design, enzyme design, and gene editing.[1] The Austin Model-1 (AM1) is one of the semi-empirical methods in quantum chemistry; it uses experimental parameters and applies Schrödinger's equation ($H\Psi = E\Psi$) to describe the behavior of quantum systems in material science and nanotechnology.[2]

In this context, the present research focuses on determining the thermodynamic properties of the Phosphorylation reactions of adenosine (I), guanosine (II), cytidine (III), and uridine (IV) as outlined in Scheme 1, using full optimization calculations performed with the semi-empirical molecular orbital Austin Model-1 (AM1) method.

Computational methods[8]

Semi-empirical molecular orbital calculations were performed using the AM1 method in the **MOPAC2016** (Version: 22.234w) program. Geometry calculations in the ground state were fully optimized to achieve the lowest energy conformation, using keywords such as CHARGE=0, GNORM=1, and MMOK to correct the barrier to rotation of the amide linkage. The gas-phase heat of formation (ΔH_f^o in kcal/mol) at 298^0 K for one mole of the compound was calculated from its elements in their standard states. Atom positions in the molecule are indicated in Figure - 1.

The magnitude of the induction effect[9] (μ_{ind}): Electronegative heteroatoms cause the displacement of electrons within the molecule, which in turn induces an additional dipole moment. The magnitude of this induction effect (μ_{ind}) can be estimated by comparing the corresponding reactant and product at the time of the reaction using equation (1).

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

Heat of reaction (ΔH_r in kcal/mol) refers to the amount of heat absorbed or released during a chemical reaction.

Heat of reaction (ΔH_r) = $\sum n\Delta H_f^o$ Products - $\sum n\Delta H_f^o$ Reactants ----(2)

Quantum Chemical Descriptors[10]**:** Various descriptors are being developed to identify drugs or toxins and are particularly useful in assessing chemical reactivity. They play a significant role in predicting toxicity, biological activities, chemical reactive sites, group identification, molecular reactivities, and cost-effective processes. The fields of chemistry, agro-chemistry, pharmaceuticals, and biotechnology require substantial contributions from both bioinformatics and chemo-informatics. These disciplines are employed in the development of Quantitative Structure-Activity Relationships (QSAR) and Quantitative Structure-Property Relationships (QSPR) for a variety of applications.

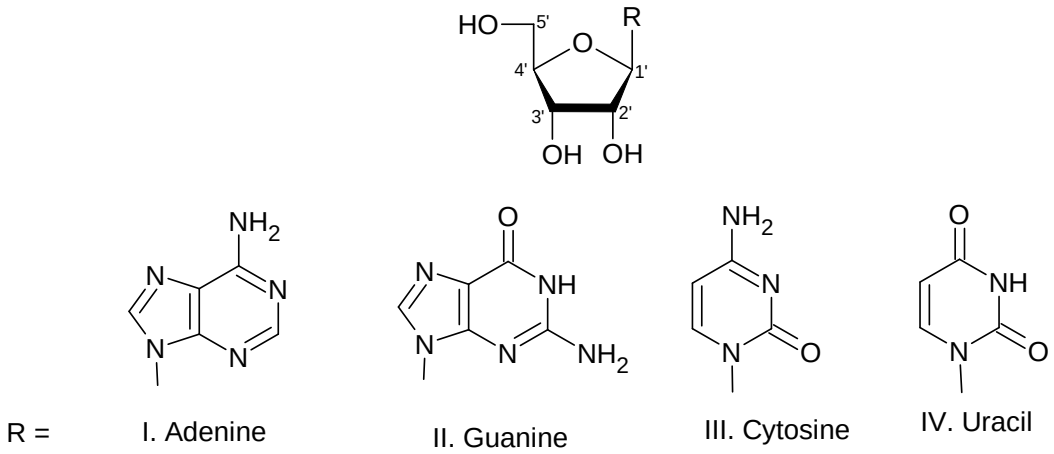
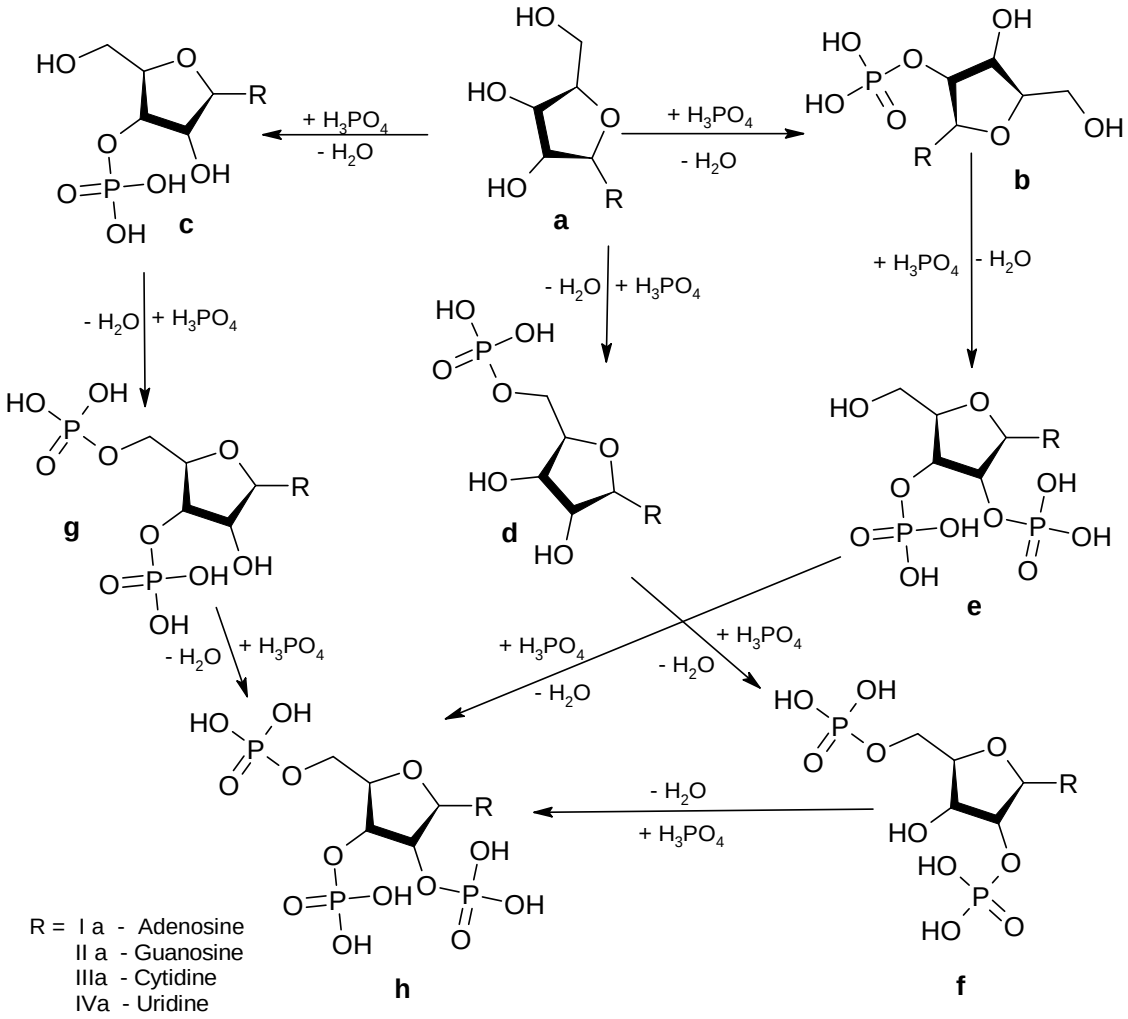


Figure - 1

RESULTS AND DISCUSSIONS

The optimized electronic structure of the Phosphorylation of nucleosides and nucleotides of ribonucleic acid (RNA) is illustrated in **Scheme -** 1 (**a** to **h**). The calculated values include the heat of formation (ΔH_f° in kcal/mol), dipole moment (μ in Debye), and frontier molecular orbital energies (HOMO and LUMO) as shown in Table I. Additionally, quantum chemical descriptors are provided in Table II, while the heat of reaction (ΔH_r) can be found in **Tables**

III, V, VII, and IX. Other parameters such as the induction effect (μ_{ind}), COSMO area (Sq. Ang), and COSMO volume (Cu. Ang) are presented in **Tables IV, VI, VIII,** and X. According to the heat of formation (ΔHf°) data, the stability of the nucleosides is ranked in the following order: uridine > cytidine > guanosine > adenosine. The dipole moment (μ) of the nucleosides in RNA follows this order: guanosine > uridine > adenosine > cytidine.



Scheme - 1: - Phosporylation of Ribonucleoside (a) and Ribonucleotides (b to h) in Ribonucleic acid (RNA)

Table- I		Heat of formation (ΔH_f^o in kcal/mol), dipole moment (μ in Debye), frontier orbital energy (HOMO & LUMO), Cosmo area and Cosmo volume for nucleosides (I to IV)a and nucleotides (I to IV) b to h of RNA from AM1 calculation.						
Comp No.	**RNA Nucleotides**	**ΔHf (Kcal/mol)**	**Dipole moment (Debye)**	**HOMO ev**	**LUMO ev**	**Cosmo Area (sq ang)**	**Cosmo Volume (cu ang)**	**Molecular weight**
	Water	-59.2499	1.8602	-12.463	+4.412	42.61	26.03	18.0152
	H_3PO_4	-238.1239	5.8959	-11.716	+0.598	100.39	82.58	97.9951
Ia	Adenosine	+68.2895	5.2706	-8.412	-0.413	296.42	314.01	267.2438
b	2'-AMP	-261.6443	6.4645	-8.637	-0.987	327.25	365.27	347.2237
c	3'-AMP	-192.3474	4.9319	-8.495	-0.468	359.59	377.24	347.2237
d	5'-AMP	-241.3522	8.0607	-8.870	-1.230	341.23	367.88	347.2237
e	2',3'-ADP	-443.9854	4.6489	-8.754	-0.671	414.00	445.83	427.2035
f	2',5'-ADP	-487.8084	5.6033	-8.641	-0.333	401.66	440.09	427.2035
g	3',5'-ADP	-440.8976	13.2988	-6.364	-1.494	391.67	422.42	427.2035
h	2',3',5'-ATP	-635.2768	12.1586	-8.269	-2.531	427.30	495.80	507.1834
IIa	Guanosine	+29.3602	10.1821	-8.618	-0.693	317.51	323.46	283.2432
b	2'-GMP	-297.5326	11.8149	-8.541	-1.063	354.69	387.13	363.2231
c	3'-GMP	-120.1933	9.4714	-8.293	-0.417	351.46	390.00	363.2231
d	5'-GMP	-243.5627	3.5216	-8.966	-1.632	356.47	384.97	363.2231
e	2',3'-GDP	-517.8493	4.0646	-8.747	-1.020	394.39	433.14	443.2029
f	2',5'-GDP	-527.3458	9.3953	-8.590	-0.734	406.27	456.61	443.2029
g	3',5'-GDP	-462.1553	12.5971	-6.978	-1.806	381.61	432.83	443.2029
h	2',3',5'-GTP	-723.4928	3.0399	-8.974	-1.843	441.30	491.30	523.1828
IIIa	Cytidine	-12.4845	3.7679	-8.201	-0.432	271.78	287.30	243.2188
b	2'-CMP	-304.6469	7.5975	-8.846	-0.856	337.42	351.62	323.1987
c	3'-CMP	-317.6752	8.3071	-9.263	-1.422	322.98	345.48	323.1987
d	5'-CMP	-290.2979	7.2282	-8.291	-0.874	356.11	359.78	323.1987
e	2',3'-CDP	-513.2955	14.1740	-7.992	-1.684	361.49	408.92	403.1785
f	2',5'-CDP	-518.7125	9.2400	-9.351	-1.778	375.99	417.57	403.1785
g	3',5'-CDP	-538.8453	7.8426	-9.104	-1.052	393.58	413.44	403.1785
h	2',3',5'-CTP	-768.7118	3.7603	-9.236	-1.117	414.95	484.24	483.1584
IVa	Uridine	-165.2896	8.1295	-8.178	-0.556	264.54	275.83	244.2036
b	2'-UMP	-288.2137	3.0158	-7.362	-0.883	322.14	341.45	324.1835
c	3'-UMP	-312.1617	4.0657	-8.459	-0.723	331.91	341.05	324.1835
d	5'-UMP	-351.5270	2.8586	-7.079	-1.422	317.40	340.87	324.1835
e	2',3'-UDP	-521.9583	4.5884	-8.687	-0.965	375.53	412.85	404.1633
f	2',5'-UDP	-460.2901	14.4776	-8.946	-3.270	388.17	407.86	404.1633
g	3',5'-UDP	-594.4748	4.4784	-9.922	-2.386	374.41	401.94	404.1633
h	2',3',5'-UTP	-807.0312	13.3211	-8.010	-1.572	412.25	467.34	484.1432

Quantum chemical descriptors have provided valuable insights into the properties of RNA nucleosides and nucleotides in Table - II. The energy gap reflects reactivity in the order of adenosine > guanosine > cytidine > uridine.

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 (Ia to IVa) and nucleotides (Ib to IVh) of RNA are calculated from frontier orbital energy (HOMO & LUMO).									
Comp No.	**RNA Nucleotides**	**HOMO (eV)**	**LUMO (eV)**	**Energy gap (ΔE) eV**	**IP (eV)**	**EA (eV)**	**EN (eV)**	**Global Hardness**	**Softness**	**Chemical Potential**	**Eletro philicity Index**
	Water	-12.463	+4.412	16.875	12.463	-4.412	4.026	8.438	1.477	-4.026	0.960
	H_3PO_4	-11.716	+0.598	12.314	11.716	-0.598	5.559	6.157	1.903	-5.559	2.510
Ia	Adenosine	-8.412	-0.413	7.999	8.412	0.413	4.413	4.000	2.103	-4.413	2.434
b	2’-AMP	-8.637	-0.987	7.650	8.637	0.987	4.812	3.825	2.258	-4.812	3.027
c	3’-AMP	-8.495	-0.468	8.027	8.495	0.468	4.482	4.014	2.117	-4.482	2.502
d	5’-AMP	-8.870	-1.230	7.640	8.870	1.230	5.050	3.820	2.322	-5.050	3.338
e	2’,3’-ADP	-8.754	-0.671	8.083	8.754	0.671	4.713	4.042	2.166	-4.713	2.747
f	2’,5’-ADP	-8.641	-0.333	8.308	8.641	0.333	4.487	4.154	2.080	-4.487	2.423
g	3’,5’-ADP	-6.364	-1.494	4.870	6.364	1.494	3.929	2.435	2.614	-3.929	3.170
h	2’,3’,5’-ATP	-8.269	-2.531	5.738	8.269	2.531	5.400	2.869	2.882	-5.400	5.082
IIa	Guanosine	-8.618	-0.693	7.925	8.618	0.693	4.656	3.963	2.175	-4.656	2.735
b	2’-GMP	-8.541	-1.063	7.478	8.541	1.063	4.802	3.739	2.284	-4.802	3.084
c	3’-GMP	-8.293	-0.417	7.876	8.293	0.417	4.355	3.938	2.106	-4.355	2.408
d	5’-GMP	-8.966	-1.632	7.334	8.966	1.632	5.299	3.667	2.445	-5.299	3.829
e	2’,3'-GDP	-8.747	-1.020	7.727	8.747	1.020	4.884	3.864	2.264	-4.884	3.086
f	2’,5’-GDP	-8.590	-0.734	7.856	8.590	0.734	4.662	3.928	2.187	-4.662	2.767
g	3’,5’-GDP	-6.978	-1.806	5.172	6.978	1.806	4.392	2.586	2.698	-4.392	3.730
h	2’,3’,5’-GTP	-8.974	-1.843	7.131	8.974	1.843	5.409	3.566	2.517	-5.409	4.102
IIIa	Cytidine	-8.201	-0.432	7.769	8.201	0.432	4.317	3.885	2.111	-4.317	2.398
b	2’-CMP	-8.846	-0.856	7.990	8.846	0.856	4.851	3.995	2.214	-4.851	2.945
c	3’-CMP	-9.263	-1.422	7.841	9.263	1.422	5.343	3.921	2.363	-5.343	3.640
d	5’-CMP	-8.291	-0.874	7.417	8.291	0.874	4.583	3.709	2.236	-4.583	2.831
e	2’,3’-CDP	-7.992	-1.684	6.308	7.992	1.684	4.838	3.154	2.534	-4.838	3.711
f	2’,5’-CDP	-9.351	-1.778	7.573	9.351	1.778	5.565	3.787	2.470	-5.565	4.089
g	3’,5’-CDP	-9.104	-1.052	8.052	9.104	1.052	5.078	4.026	2.261	-5.078	3.202
h	2’,3’,5’-CTP	-9.236	-1.117	8.119	9.236	1.117	5.177	4.060	2.275	-5.177	3.300
IVa	Uridine	-8.178	-0.556	7.622	8.178	0.556	4.367	3.811	2.146	-4.367	2.502
b	2’-UMP	-7.362	-0.883	6.479	7.362	0.883	4.123	3.240	2.273	-4.123	2.623
c	3’-UMP	-8.459	-0.723	7.736	8.459	0.723	4.591	3.868	2.187	-4.591	2.725
d	5’-UMP	-7.079	-1.422	5.657	7.079	1.422	4.251	2.829	2.503	-4.251	3.194
e	2’,3’-UDP	-8.687	-0.965	7.722	8.687	0.965	4.826	3.861	2.250	-4.826	3.016
f	2’,5’-UDP	-8.946	-3.270	5.676	8.946	3.270	6.108	2.838	3.152	-6.108	6.573
g	3’,5’-UDP	-9.922	-2.386	7.536	9.922	2.386	6.154	3.768	2.633	-6.154	5.025
h	2’,3’,5’-UTP	-8.010	-1.572	6.438	8.010	1.572	4.791	3.219	2.488	-4.791	3.565

Ionization Potential (IP) is ranked in the following order: guanosine > adenosine > cytidine > uridine. The order of Electron Affinity (**EA)** is guanosine > uridine > cytidine > adenosine. Global hardness is arranged as follows: uridine > cytidine > guanosine > adenosine. Softness is ranked in the order of guanosine > uridine > cytidine > adenosine. The chemical potential is noted in the order of guanosine > adenosine > uridine > cytidine. Finally, the Electrophilicity Index follows the order: guanosine > uridine > adenosine > cytidine.

The Phosphorylation of adenosine (from Ia to Ih), as illustrated in Scheme - 1, along with the calculated values, is presented in Table - I. The stability of the compounds follows this order based on the heat of formation data: 2'3'5'-ATP > 2'5'-ADP > 2'3'-ADP > 3'5'-ADP > 2'-AMP > 5'-AMP > 3'-AMP > adenosine. Additionally, the dipole moment, which depends on the composition of atoms and bonds within the molecules as well as their arrangement, shows

an increasing trend in the following order: 2'3'-ADP < 3’-AMP < adenosine < 2’5’-ADP < 2’-AMP < 5’-AMP < 2’3’5’-ATP < 3’5’-ADP.

Quantum chemical descriptors, as detailed in Table - II, provide significant insights into the properties of adenosine and its nucleotides. The energy gap indicates reactivity in the following order: 2’5’-ADP < 2'3'-ADP < 3'-AMP < adenosine < 2’-AMP < 5'-AMP < 2'3'5'-ATP < 3'5'-ADP. The ionization potential (IP) follows this sequence: 5’-AMP > 2’3’-ADP > 2’5’-ADP > 2’-AMP > 3’-AMP > adenosine > 2’3’5’-ATP > 3’5’-ADP. For electron affinity (**EA)**, the order is: 2’3’5’-ATP > 3’5’-ADP > 5’-AMP > 2’-AMP > 2’3’-ADP > 3’-AMP > adenosine > 2'5'-ADP. Lastly, electro-negativity (EN) is observed in the following order: 2’3’5’-ATP > 5'-AMP > 2'-AMP > 2'3'-ADP > 2'5'-ADP > 3’-AMP > adenosine > 3'5'-ADP. Global hardness is ranked in the following order: 2'5'-ADP > 2'3'-ADP > 3'-AMP > adenosine > 2'-AMP > 5'-AMP > 2’3’5’-ATP > 3’5’-ADP. Softness is ranked from highest to lowest as: 2'3'5'-ATP > 3'5'-ADP > 5'-AMP > 2'-AMP > 2'3'-ADP > 3'-AMP > adenosine > 2'5'-ADP. Chemical potential follows this order: 2’3’5’-ATP > 5'-AMP > 2'-AMP > 2'3'-ADP > 2'5'-ADP > 3'-AMP > adenosine > 3'5'-ADP. The Electrophilicity index is ranked as: 2'3'5'-ATP > 5'-AMP > 3'5'-ADP > 2'-AMP > 2'3'-ADP > 3'-AMP > adenosine > 2'5'-ADP.

The heats of reaction are calculated and the values are presented in Table III. The process in which heat is released from the system to the surroundings is known as **an exothermic process**, and the Heat of Reaction (ΔH_r) is negative (-). Conversely, when heat is absorbed by the system from the surroundings, it is called an **endothermic process**, and the Heat of Reaction (ΔH_r) is positive (+). All reactions are exothermic, and their Heat of Reactions (ΔH_r) is negative (-), except for the formation of 2’,3’,5’-ATP from 2’,5’-ADP, which is positive (+).

Table - III	**Calculation of Heat of Reaction (ΔH_r) in case of Adenosine as per as per Schemes-1(Ia to If) from AM1 Method.**
Reactions as per **Scheme - 1**	Heat of Reaction (ΔH_r) k.cal/mol.
Adenosine + H_3PO_4 → 2’-AMP + H_2O	-151.0598
Adenosine + H_3PO_4 → 3’-AMP + H_2O	-81.7629
Adenosine + H_3PO_4 → 5’-AMP + H_2O	-130.7677
2’-AMP + H_3PO_4 → 2’,3’-ADP + H_2O	-3.4670
2’-AMP + H_3PO_4 → 2’,5’-ADP + H_2O	-47.2900
3’-AMP + H_3PO_4 → 2’,3’-ADP + H_2O	-72.7639
3’-AMP + H_3PO_4 → 3’,5’-ADP + H_2O	-69.6761
5’-AMP + H_3PO_4 → 2’,5’-ADP + H_2O	-67.5821
5’-AMP + H_3PO_4 → 3’,5’-ADP + H_2O	-20.6713
2’,3’-ADP + H_3PO_4 → 2’,3’,5’-ATP + H_2O	-12.4173
2’,5’-ADP + H_3PO_4 → 2’,3’,5’-ATP + H_2O	+31.4057
3’,5’-ADP + H_3PO_4 → 2’,3’,5’-ATP + H_2O	-15.5051

Dipole-dipole attractions play a significant role in determining the nature of hydrogen bonding in nucleic acids.[4] This bonding is affected during the conversion of adenosine to its respective nucleotides due to the induction effect. The magnitude of this induction effect.[9] (μ_{ind}) can be estimated using Equation (1). The electronegative nitrogen atoms induce a displacement of electrons in the π-framework, creating an additional dipole moment during the conversion process. The order of the induction effects has been calculated and the values are presented in Table **IV**. It is noted that all conversions exhibit a positive induction effect, except for 3'-AMP and 2',3'-ADP. Additionally, the Cosmo area and Cosmo volume are crucial for studying the solvation properties of molecules, which include their solubility, partition coefficients, and reactivity in solution. These properties are particularly significant in the formation of 2',3',5'-ATP.

Table-IV	**Change of Induction effect, Cosmo area (Sq.Ang), and Cosmo volume (Cu.Ang) in the formation of adenosine nucleotides (RNA).**		
Conversions	**Induction effect (μ_{ind})**	**Cosmo area (Sq.Ang)**	**Cosmo Volume (Cu.Ang)**
Adenosine → 2'-AMP	+1.1939	30.83	51.26
Adenosine → 3'-AMP	-0.3389	63.17	63.23
Adenosine → 5'-AMP	+2.7901	44.81	53.87
Adenosine → 2',3'-ADP	-0.6217	117.58	131.82
Adenosine → 2',5'-ADP	+0.3327	105.24	126.08
Adenosine → 3',5'-ADP	+8.0282	95.25	108.41
Adenosine → 2',3',5'-ATP	+6.8880	130.88	181.79

Phosphorylation of guanosine (from IIa to IIh) is outlined in **Scheme - 1**, and the calculated values are presented in **Table** I. The stability of the compounds is observed to follow this order based on the heat of formation data: 2',3',5'-GTP > 2'5'-GDP > 2'3'-GDP > 3'5'-GDP > 2'-GMP > 5'-GMP > 3'-GMP > guanosine. Additionally, the dipole moment, which depends on the types of atoms and bonds within the molecules as well as their arrangement, shows an increasing trend in the following order: 2',3',5'-GTP < 5'-GMP < 2'3'-GDP < 2'5'-GDP < 3'-GMP < guanosine < 2'-GMP < 3'5'-GDP.

Quantum chemical descriptors have provided valuable insights into the properties of guanosine (**IIa**) and its nucleotides (**IIb to IIh**). The energy gap indicates reactivity in the following order: 3'5'-GDP < 2'3'5'- GTP < 5'-GMP < 2'-GMP < 2'3'-GDP < 2'5'-GDP < 3'-GMP < Guanosine. The ionization potential (IP) is ranked as follows: 2'3'5'-GTP > 5'-GMP > 2'3'-GDP > Guanosine > 2'5'-GDP > 2'-GMP > 3'5'-GDP. Electron affinity (**EA)** is

observed in this order: 2’3’5’-GTP > 3’5’-GDP > 5’-GMP > 2’-GMP > 2’3’-GDP > 2’5’-GDP > Guanosine > 3’-GMP. Finally, Electronegativity (EN) is ranked as: 2’3’5’-GTP > 5’-GMP > 2'3'-GDP > 2’-GMP > 2’5’-GDP > Guanosine > 3’5’-GDP > 3’-GMP.Global hardness ranks as follows: Guanosine > 3’-GMP > 2’5’-GDP > 2’3’-GDP > 2’-GMP > 5’-GMP > 2’3’5’-GTP > 3’5’-GDP. In terms of softness, the order is: 3'5'-GDP > 2’3’5’-GTP > 5’-GMP > 2’-GMP > 2’3’-GDP > 2’5’-GDP > Guanosine > 3’-GMP. The chemical potential is ranked in the following order: 2’3’5’-GTP > 5’-GMP > 2’3’-GDP > 2’-GMP > 2’5’-GDP > Guanosine > 3’5’-GDP > 3’-GMP. Lastly, the Electrophilicity index is presented in this order: 2’3’5’-GTP > 5’-GMP > 3’5’-GDP > 2’3’-GDP > 2’-GMP > 2'5'-GDP > Guanosine > 3’-GMP.

The heats of reaction have been calculated and the values are presented in Table V. It was found that all reactions are exothermic, resulting in negative heats of reaction (ΔH_r) except for the formation of 3’-GMP from Guanosine, which has a positive heat of reaction. This is illustrated in Scheme - 1.

Table - V	**Calculation of Heat of Reaction (ΔH_r) in case of Guanosine (IIa) as per Schemes-1(IIb to IIf) from AM1 Method.**
Reactions as per **Scheme - 1(IIa** to **IIf**)	Heat of Reaction (ΔH_r) k.cal/mol.
Guanosine + H_3PO_4 → 2’-GMP + H_2O	-148.0188
Guanosine + H_3PO_4 → 3’-GMP + H_2O	+29.3205
Guanosine + H_3PO_4 → 5’-GMP + H_2O	-94.0489
2’-GMP + H_3PO_4 → 2’,3’-GDP + H_2O	-41.4427
2’-GMP + H_3PO_4 → 2’,5’-GDP + H_2O	-50.9392
3’-GMP + H_3PO_4 → 2’,3’-GDP + H_2O	-218.7820
3’-GMP + H_3PO_4 → 3’,5’-GDP + H_2O	-163.0880
5’-GMP + H_3PO_4 → 2’,5’-GDP + H_2O	-104.9091
5’-GMP + H_3PO_4 → 3’,5’-GDP + H_2O	-39.7186
2’,3’-GDP + H_3PO_4 → 2’,3’,5’-GTP + H_2O	-26.7695
2’,5’-GDP + H_3PO_4 → 2’,3’,5’-GTP + H_2O	-17.2730
3’,5’-GDP + H_3PO_4 → 2’,3’,5’-GTP + H_2O	-82.4635

The study of heat transfer between a system and its surroundings involves two types of processes: exothermic and endothermic. An **exothermic process** occurs when the system releases heat to the surroundings, resulting in a negative heat of reaction (ΔHr). Conversely, an endothermic process takes place when the system absorbs heat from the surroundings, leading to a positive heat of reaction (ΔH_r). It is worth noting that while many reactions are exothermic with negative heat of reactions (ΔH_r), there are exceptions, as shown in **Table V**.

The dipole moment in the conversion of guanosine **II (**from **a** to h) has increased due to the induction effect. The magnitude of this induction effect.[9] (μ_{ind}) can be estimated using Equation (1). The order of the induction effect has been determined and the values have been incorporated into Table - **VI**. It is observed that all effects are negative, except in the formations of 2'-GMP and 3',5'-GDP. Additionally, it has been found that COSMO area and COSMO volume are important for studying the solvation properties of molecules, including their solubility, partition coefficients, and reactivity in solution. This is especially significant in the formation of 2',3',5'-GTP.

Table-VI	**Change of Induction effect, Cosmo area (Sq.Ang), and Cosmo volume (Cu.Ang) in the formation of guanosine nucleotides (IIa to IIf) in RNA.**		
Conversions	**Induction effect (μ_{ind})**	**Cosmo area (Sq.Ang)**	**Cosmo Volume (Cu.Ang)**
Guanosine → 2'-GMP	+1.6328	37.18	63.67
Guanosine → 3'-GMP	-0.7107	33.95	66.54
Guanosine → 5'-GMP	-6.6605	38.96	61.51
Guanosine → 2',3'-GDP	-6.1175	76.88	109.68
Guanosine → 2',5'-GDP	-0.7868	88.76	133.15
Guanosine → 3',5'-GDP	+2.4150	64.10	109.37
Guanosine → 2',3',5'-GTP	-7.1422	123.79	167.84

The Phosphorylation of cytidine (from **IIIa to IIIh)**, as outlined in **Scheme -** 1, is detailed in Table I with the calculated values. The stability of the compounds follows this order based on the heat of formation data: 2',3',5'-CTP > 3',5'-CDP > 2',5'-CDP > 2',3'-CDP > 3'-CMP > 2'-CMP > 5'-CMP > cytidine. Additionally, the dipole moment is influenced by the specific atoms and bonds within the molecules, as well as their structural arrangement. The observed dipole moment values are ranked in the following order: 2',3',5'-CTP < cytidine < 5'-CMP < 2'-CMP < 3',5'-CDP < 3'-CMP < 2',5'-CDP > 2',3'-CDP.

Quantum chemical descriptors (as shown in Table - II) provide valuable insights into the properties of cytidine (**IIIa**) and its nucleotides (**IIIb to IIIh**). The energy gap indicates reactivity in the following order: 2'3'5'-CTP < 3'5'-CDP < 3'-CMP < cytidine < 2'5'-CDP < 5'-CMP < 2'3'-CDP. The ionization potential (IP) follows this sequence: 5'-CMP > cytidine > 2'-CMP > 3'5'-CDP > 2'3'5'-CTP > 3'-CMP > 2'5'-CDP. For electron affinity (**EA)**, the order is: 2'5'-CDP > 2'3'-CDP > 3'-CMP > 2'3'5'-CTP > 3'5'-CDP > 5'-CMP > 2'-CMP > cytidine. Electronegativity (EN) is revealed in the following order: 2'5'-CDP > 3'-CMP > 2'3'5'-CTP > 3'5'-CDP > 2'-CMP > 5'-CMP > cytidine. Lastly, global hardness is indicated

in this order: 2’3’5’-CTP > 3’5’-CDP > 2’-CMP > 3’-CMP > cytidine > 2’5’-CDP > 5’-CMP > 2’3’-CDP.Softness is ranked in the following order: 2'3’-CDP > 2’5’-CDP > 3’-CMP > 2’-CMP > 2’3’5’-CTP > 3'5’-CDP > 2’-CMP > cytidine. Chemical potential is indicated in this order:

2'5'-CDP > 3’-CMP > 2’3’5’-CTP > 3'5’-CDP > 2’-CMP > 2’3’-CDP > 5’-CMP > cytidine. The Electrophilicity index is presented in the following order: 2'5’-CDP > 2’3’-CDP > 3’-CMP > 2’3’5’-CTP > 3’5’-CDP > 2’-CMP > 5’-CMP > cytidine.

The heats of reactions have been calculated, and the values are presented in **Table VII**. The investigation focuses on the heat of reaction (ΔH_r) according to Scheme - 1. All the reactions are exothermic, resulting in negative values for their heat of reactions (ΔH_r).

Table – VII:- Calculation of Heat of Reaction (ΔH_r) in cytidine (IIIa to IIIf) as per Schemes-1 from AM1 Method.

Reactions as per Scheme - 1 cytidine (Ia to IIIf)	Heat of Reaction (ΔH_r) k.cal/mol.
Cytidine + H_3PO_4 → 2’-CMP + H_2O	-113.2884
Cytidine + H_3PO_4 → 3’-CMP + H_2O	-126.3167
Cytidine + H_3PO_4 → 5’-CMP + H_2O	-98.9394
2’-CMP + H_3PO_4 → 2’,3’-CDP + H_2O	-29.7746
2’-CMP + H_3PO_4 → 2’,5’-CDP + H_2O	-35.1916
3’-CMP + H_3PO_4 → 2’,3’-CDP + H_2O	-16.7463
3’-CMP + H_3PO_4 → 3’,5’-CDP + H_2O	-42.2961
5’-CMP + H_3PO_4 → 2’,5’-CDP + H_2O	-49.5406
5’-CMP + H_3PO_4 → 3’,5’-CDP + H_2O	-69.6734
2’,3’-CDP + H_3PO_4 → 2’,3’,5’-CTP + H_2O	-76.5423
2’,5’-CDP + H_3PO_4 → 2’,3’,5’-CTP + H_2O	-71.1254
3’,5’-CDP + H_3PO_4 → 2’,3’,5’-CTP + H_2O	-50.9925

The dipole moment increases during the conversion of cytidine from **IIIa** to **IIIf** due to the induction effect. The magnitude of this induction effect (μ_{ind}) can be estimated using Equation (1). The order of the induction effect has been determined, and the values are summarized in Table - **VIII**. It is observed that all effects are positive, except for the formation of 2’3’5’-CTP. Additionally, the Cosmo area and Cosmo volume are important factors for studying the solvation properties of molecules, including their solubility, partition coefficients, and reactivity in solution. This is especially significant for the formation of 2’3'5'-CTP.

Table-VIII	Change of Induction effect, Cosmo area (Sq.Ang), and Cosmo volume (Cu.Ang) in the formation of Cytidine nucleotides (IIIa to IIIf) in RNA.		
Conversions	**Induction effect (μ_{ind})**	**Cosmo area (Sq.Ang)**	**Cosmo Volume (Cu.Ang)**
Cytidine → 2'-CMP	+3.8296	65.64	64.32
Cytidine → 3'-CMP	+4.5392	51.20	58.18
Cytidine → 5'-CMP	+3.4603	84.33	72.48
Cytidine → 2',3'-CDP	+10.4061	89.71	121.62
Cytidine → 2',5'-CDP	+5.4721	104.21	130.27
Cytidine → 3',5'-CDP	+4.0747	121.80	126.14
Cytidine → 2',3',5'-CTP	-0.0076	143.17	196.94

Phosphorylation of Uridine (IVa to IVh) is outlined in Scheme - 1, with the calculated values presented in **Table -** I. Based on the heat of formation (ΔH_f^o) data, the stability of the compounds is ranked in the following order: 2'3'5'-UTP > 3'5'-UDP > 2'3'-UDP > 2'5'-UDP > 5'-UMP > 3'-UMP > 2'-UMP > Uridine. The dipole moment is influenced by the types of atoms and bonds within the molecules, as well as their arrangement. The order of dipole moments is observed to increase as follows: 5'-UMP < 2'-UMP < 3'-UMP < 3',5'-UDP < 2',3'-UDP < Uridine < 2',3',5'-UTP < 2',5'-TDP.

Quantum chemical descriptors, as outlined in Table - II, provide significant insights into the properties of uridine (**IVa**) and its nucleotides (**IVb to IVIh**). The energy gap indicates reactivity in the following order: 3'-UMP < 2'3'-UDP < uridine < 3'5'-UDP < 2'-UMP < 2'3'5'-UTP < 2'5'-UDP < 5'-UMP. The ionization potential (IP) is ranked as follows: 3'5'-UDP > 2'5'-UDP > 2'3'-UDP > 3'-UMP > uridine > 2'3'5'-UTP > 2'-UMP > 5'-UMP. For electron affinity (**EA**), the order is: uridine > 3'-UMP > 2'-UMP > 2'3'-UDP > 5'-UMP > 2'3'5'-UTP > 3'5'-UDP > 2'5'-UDP. Electronegativity (EN) is presented in this order: 3'5'-UDP > 2'5'-UDP > 2'3'-UDP > 2'3'5'-UTP > 3'-UMP > uridine > 5'-UMP > 2'-UMP. Lastly, global hardness is ranked as follows: 2'3'-UDP > 5'-UMP > 2'3'5'-UTP > 2'3'-UDP > 2'5'-UDP > uridine > 3'5'-UDP > 5'-UMP. Softness is ranked in the following order: 2'5'-UDP > 3'5'-UDP > 5'-UMP > 2'3'5'-UTP > 2'-UMP > 2'3'-UDP > 3'-UMP > uridine. Chemical potential is ordered as follows: 3'5'-UDP > 2'5'-UDP > 2'3'-UDP > 2'3'5'-UTP > 3'-UMP > uridine > 5'-UMP > 2'-UMP. The Electrophilicity index is outlined in this sequence: 2'5'-UDP > 3'5'-UDP > 2'3'5'-UTP > 3'-UMP > 2'3'-UDP > 3'-UMP > 2'-UMP > uridine.

The heats of the reactions (ΔH_r) have been calculated and the values are presented in **Table - IX**. According to **Scheme** - 1, it has been observed that some reactions are exothermic, indicated by a negative heat of reaction (ΔH_r). In an exothermic process, heat is released from the system to the surroundings, resulting in a negative value for ΔHr. Conversely, when heat is absorbed by the system from the surroundings, the process is termed **endothermic**, and the heat of reaction (ΔH_r) is positive. As shown in Table - IX, several reactions are exothermic, with their heat of reactions being negative.

Table - IX	**Calculation of Heat of Reaction (ΔH_r) as per Schemes-1 Uridine (IVa) and its nucleotides (IVb to IVh) in RNA from AM1 Method.**
Reactions as per **Scheme - 1** Uridine **(IVa to IVh)**	Heat of Reaction (ΔH_r) k.cal/mol.
Uridine + H_3PO_4 → 2'-UMP + H_2O	+55.9499
Uridine + H_3PO_4 → 3'-UMP + H_2O	+32.0019
Uridine + H_3PO_4 → 5'-UMP + H_2O	-7.3634
2'-UMP + H_3PO_4 → 2',3'-UDP + H_2O	-54.8706
2'-UMP + H_3PO_4 → 2',5'-UDP + H_2O	+6.7976
3'-UMP + H_3PO_4 → 2',3'-UDP + H_2O	-30.9226
3'-UMP + H_3PO_4 → 3',5'-UDP + H_2O	-103.4391
5'-UMP + H_3PO_4 → 2',5'-UDP + H_2O	+70.1109
5'-UMP + H_3PO_4 → 3',5'-UDP + H_2O	-64.0738
2',3'-UDP + H_3PO_4 → 2',3',5'-UTP + H_2O	-106.1989
2',5'-UDP + H_3PO_4 → 2',3',5'-UTP + H_2O	-167.8671
3',5'-UDP + H_3PO_4 → 2',3',5'-UTP + H_2O	-33.6824

The dipole moment increases during the conversion of uridine (from IV**a** to IVh) due to the induction effect. The magnitude of the induction effect (μ_{ind}) can be estimated using Equation (1). It has been observed that the induction effect negatively impacts the formation of 5'-UMP and 3',5'-UDP, while the effects on the other compounds are positive (see Table – **X)**.

Table- X	**Change of Induction effect, Cosmo area (Sq.Ang), and Cosmo volume (Cu.Ang) in the formation of Uridine (IVa to IVh) nucleotides in RNA.**		
Conversions	Induction effect (μ_{ind})	Cosmo area (Sq.Ang)	Cosmo Volume (Cu.Ang)
Uridine → 2'-UMP	-5.1137	57.60	65.62
Uridine → 3'-UMP	-4.0638	67.37	65.22
Uridine → 5'-UMP	-5.2709	52.86	65.04
Uridine → 2',3'-UDP	+3.5411	110.99	137.02
Uridine → 2',5'-UDP	+6.3481	123.63	132.03
Uridine → 3',5'-UDP	-3.6511	109.87	126.11
Uridine → 2',3',5'-UTP	+5.1916	147.71	191.51

It has been found that the Cosmo area and Cosmo volume are important for studying the solvation properties of molecules, including their solubility, partition coefficients, and reactivity in solution. This is particularly relevant in the formation of 2'3'5'-UTP.

CONCLUSIONS

Naturally occurring nucleosides and nucleotides are essential for RNA synthesis. The presence of reactive centers in nucleotide derivatives, advanced genetic engineering techniques, and remarkable enzymes is vital for treating diseases. Austin Model-1 (AM1) is a semi-empirical quantum chemistry method that uses Schrödinger's equation ($H\Psi = E\Psi$) to optimize molecules and calculate thermodynamic properties such as heats of formation (ΔH_f^o), dipole moment (μ), and frontier molecular orbital energies (E_{HOMO} and E_{LUMO}). Additionally, it has been found that tri-phosphates are more stable than di-phosphates and mono-phosphates of their respective nucleosides. Furthermore, the role of dipole-dipole interactions during the sequencing of RNA has been discussed, highlighting their significance in the process, for analyzing base sequences linked to mutations and genetic diseases.

Disclosure statement

The author did not report any potential conflicts of interest.

Funding

The author has not received any financial support for this research or the publication of the article.

Author's contribution

The author has been involved in the conception, design, analysis, interpretation of data, drafting the article, and approving the final version.

REFERENCES

1. Rachwalak, M.; Romanowska, J.; Sobkowski, M.; Stawinski, J. Nucleoside Di- and Triphosphates as a New Generation of Anti-HIV Pronucleotides. Chemical and Biological Aspects. Appl. Sci., 2021; 11: 2248. https:// doi.org/10.3390/app11052248.
2. (a). Depaix, A.; Peyrottes, S.; Roy, B. One-pot synthesis of nucleotides in water medium. Phosphorus Sulfur Silicon Relat. Elem. 2018; 194: 335–336. (b). Burgess, K.; Cook, D. Syntheses of Nucleoside Triphosphates. Chem. Rev. 2000; 100: 2047–2059.

3. (a). Hollenstein, M. Nucleoside Triphosphates—Building Blocks for the Modification of Nucleic Acids. Molecules, 2012; 17: 13569–13591. (b). Hou, S.; Qu, Z.; Tang, L.; Shuhua, Q.Z.H. Advances in the Synthesis of Organic Pyrophosphate. Chin. J. Org. Chem. 2014; 34: 54. (c). Sherstyuk, Y.V.; Abramova, T.V. How to Form a Phosphate Anhydride Linkage in Nucleotide Derivatives. Chembiochem Eur. J. Chem. Biol., 2015; 16: 2562–2570. (d). Tanaka, H. Recent Approaches to the Chemical Synthesis of Sugar Nucleoside Diphosphates. Trends Glycosci. Glycotechnol, 2015; 27: 99–110. (e). Ahmadipour, S.; Miller, G.J. Recent advances in the chemical synthesis of sugar-nucleotides. Carbohydr. Res., 2017; 451: 95–109. (f). Kaczynski, T.P.; Chmielewski, M.K. Mini-Review of the Phosphate Center Activation Strategy in Nucleoside Triphosphate Preparation. Mini Rev. Org. Chem., 2017; 14: 448–452. (g). Rajeshwar Rao B,2023 Computational study on the Phosphorylation of nucleosides and nucleotides in deoxyribonucleic acid (DNA) by Austin Model-1 Method, World J Pharmaceutical Research, 2023; 12(3): 867-878. www.wjpr.net
4. (a). Baddiley, J.; Michelson, A.M.; Todd, A.R. Nucleotides. Part II. A Synthesis of Adenosine Triphosphate. J. Chem. Soc. 1949; 582–586. (b). Baddiley, J.; Michcelson, A.M.; Todd, A.R. Synthesis of Adenosine Triphosphate. Nat. Cell Biol., 1948; 161: 761–762.
5. (a). Khorana, G.; Todd, A.R. Studies on Phosphorylation. XI. The Reaction Between Carbodi-imides and Acid Esters of Phosphoric Acid—A New Method for the Preparation of Pyrophosphates. J. Chem. Soc., 1953; 2257–2260. (b). Baddiley, J.; Hughes, N.A. The Synthesis of Nucleotide Coenzymes. In Advances in Enzymology and Related Areas of Molecular Biology; Wiley: Hoboken, NJ, USA, 2006; 22: 157–203. (c). Smith, M.; Khorana, H.G. Nucleoside Polyphosphates. VI. An Improved and General Method for the Synthesis of Ribo- and Deoxyribonucleoside 5’-Triphosphates. J. Am. Chem. Soc., 1958; 80: 1141–1145. (d). Chambers, R.W.; Khorana, H.G. Nucleoside Polyphosphates. VII. The Use of Phosphoramidic Acids in the Synthesis of Nucleoside-5’-Pyrophosphates. J. Am. Chem. Soc. 1958; 80: 3749–3752. (e). Moffatt, J.G.; Khorana, H.G. Nucleoside Polyphosphates. VIII. New and Improved Syntheses of Uridine Diphosphate Glucose and Flavin Adenine Dinucleotide Using Nucleoside-5’-Phosphoramidates. J. Am. Chem. Soc., 1958; 80: 3756–3761. (f). Clark, V.M.; Kirby, G.W.; Todd, A.R. Studies on Phosphorylation. Part XV. The Use of Phosphoramidic Esters in Acylation. A New Preparation of Adenosine-5’-Pyrophsphate and Adenosine-5’-Triphosphate. J. Chem.

Soc., 1957; 79: 1497–1501. (g). Moffatt, J.G. A General Synthesis of Nucleoside 5'-Triphosphates. Can. J. Chem., 1964; 599–604.

6. (a). Watson JD, Molecular biology of the Genes, 3rd Edn (WA Benjamin, New York) 1976. (b). Levin BL, Genes (John Wiley & Sons Inc, New York) 1983.
7. (a). Rajeshwar Rao B, Study of [1,3]Sigmatropic hydrogen migration in cytosine and cytidine by AM1 method, Indian J. Chem., 2003; 42B(12): 3081-3088. (b). Rajeshwar Rao B, Study of [1,3] Sigmatropic hydrogen migration in uracil, uridine and uridylic acid by AM1 method, Indian J. Chem., 2006; 45B(9): 2083-2090. (c). Rajeshwar Rao B, Study of [1,3]sigmatropic hydrogen migration in thymine, thymidine and thymidylic acid by AM1 method., Indian J. Chem, 2009; 48B (10): 1411- 1415. (d). Rajeshwar Rao B, Study of [1,3]sigmatropic hydrogen migration in adenine and guanine by AM1 method, Int J Res Pharmaceutical and Biomed Sci., 2012; 3(1): 275-281. www.ijrpbsonline.com. (e). Rajeshwar Rao B, Critical Review on computational study of [1,3]sigmatropic hydrogen migration in pyrimidines and purines of nucleic acids by Austin Model-1 Method. World J Pharmacy and Pharmaceutical Sciences., 2022; 11(4): 904-926. www.wjpps.com. (f) Rajeshwar Rao B, Computational study on Phosphorylation of nucleosides and nucleotides in deoxyribonucleic acid (DNA) by Austin Model-1 Method, World J Pharmaceutical Research, 2023; 12(3): 867-878. www.wjpr.net. (g). Rajeshwar Rao B, Computational study on nucleosides of ribonucleic acid (RNA) by Austin Model-1 Method, World J Pharmaceutical Research, 2025; 14(10): 1289-1297. www.wjpr.net
8. (a). Dewar MJS, Zeobisch EG, Healy EF, Stewart JJP, AM1: a new general purpose quantum mechanical molecular model, J am chem soc., 1985; 107: 3902-9. (b). Stewart J J P, MOPAC, A general molecular orbital package, QCPE 455, 5th edn, 1988. (c). MOPAC2016 (Version: 22.234w).
9. Paperno TYA, Pozdnyakov VP, Smirnova AA, Elagin LM, Physico-Chemical Laboratory Techniques in Organic and Biological Chemistry (Translated from Russian by Oleg Glebov), (MIR Publishers, Moscow) 1979.
10. (a). Tomasz Puzyn, Jerzy Leszczynski, Mark T.D. Cronin, edited, Recent Advances in QSAR Studies-Methods and Applications, DOI 10.1007/978-1-4020-9783-6, Springer Dordrecht Heidelberg London New York, 2009. (b). Hansch C, Hockman D, Leo A, Wininger D, Selassic C, Chem Rev., 2002; 102: 783.