RASĀYAN *J. Chem.*
Vol. 16 | No. 1 |447-455| January - March | 2023
ISSN: 0974-1496 | e-ISSN: 0976-0083 | CODEN: RJCABP
http://www.rasayanjournal.com
http://www.rasayanjournal.co.in

COMPUTATIONAL STUDY OF NICOTINAMIDE WITH PARENT URACIL AND ANTICANCER URACIL DERIVATIVES

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ABSTRACT

The density functional theory calculations have been applied to investigate hydrogen-bonded complexes of nicotinamide with parent uracil and its anticancer derivatives namely 5 fluorouracil and 2 thiouracil. The optimized complexes are analyzed in terms of structural, electronic, and energetic changes, binding free energy and enthalpy changes, dipole moments, atomic charge variation, electron delocalizations, topological parameters, chemical reactivity descriptors, etc. The study suggests that the most stable complexes are formed by nicotinamide with fluorouracil and the least stable with thiouracil. The uracil and its derivatives act as far better hydrogen bond donors than nicotinamide in the optimized complexes. Significant charge transfer between nicotinamide and parent uracil and its derivatives is suggested by Frontier Molecular Orbital (FMO) analysis and $E^{(2)}$ from Natural Bond Orbital analysis. The present computational study shows that uracil drugs form stable intercalation sites with nicotinamide. The results may prove useful in the molecular designing of new anticancer agents.

Keywords: Nicotinamide, Uracil, NBO, Hydrogen Bonding, Charge Transfer.

RASĀYAN*J. Chem.*, Vol. 16, No.1, 2023

INTRODUCTION

Intermolecular interactions are important in all aspects of chemistry, biochemistry, and biophysics including nanotechnology, sensors, protein folding, drug design, and the origin of life.[1,2] Hydrogen bonding (H-bonding) is the most important intermolecular interaction conferring structural stability to proteins, DNA, and other macromolecules.[3,4] Elfi Kraka *et al.* in a recent work studied H-bonding in a diverse set of natural and unnatural base pairs adenine-thymine, adenine-uracil, and guanine-cytosine using local vibrational mode study, QTAIM study, and NBO analysis.[5] Uracil (U), an important biological organic heterocyclic is a pyrimidine derivative and nucleobase in ribonucleic acid. The presence of several consecutive H-bond donor and acceptor groups in uracil makes it ideal for studying H-bond interactions.[6] A number of uracil derivatives were reported to be an antiviral as well as an antitumor agent.[7] 5 fluorouracil (5FU) is an antimetabolite drug that interferes with DNA synthesis and is widely used as a chemotherapeutic drug for colorectal, pancreatic and breast cancer.[8] 2 thiouracil (2TU) is sulphur analog of 5FU whose structure closely resembles 5FU. Propyl thiouracil is used for the treatment of hyperthyroidism.[9] Thiouracils have been used as an antithyroid, coronary vasodilator, and in congestive heart failure.[10] Niacinamide or nicotinamide is a chemical form of vitamin B3 used in medicines and as a diet supplement.[11] It is a water-soluble vitamin with formula $C_6H_6N_2O$. 3 pyridine carboxamide, niacinamide, nicotinic acid amide, vitamin PP, and nicotinic amide are some of their other names.[12] It has antipruritic, antimicrobial, vasoactive, photo-protective, sebostatic, and lightening effects.[13] Nicotinamide deficiency symptoms include pellagra, dementia, fatigue, diarrhea, light-sensitive dermatitis, etc.[14] Vitamins and drugs interact to have positive or negative impacts on health. Long-term use of nicotinamide might increase blood sugar and decrease the effectiveness of diabetes medicines.[15] Fluorouracil, levodopa, cycloserine, etc. may lower levels of vitamin B in the body. Nicotinamide consumption slows the progression of type 1 diabetes, suppresses hyperphosphatemia, and is used to treat nonmelanoma skin cancer, and osteoarthritis.[16,17] The objective of the present study is to analyze H-

http://doi.org/10.31788/RJC.2023.1618223

bonded complexes between nicotinamide and uracil and their derivatives like 5FU and 2TU to gain deeper insights into the nature and the strength of H-bond in these biomolecules as 5FU and 2TU have potential to act as anticancer agents. The present computational study may prove helpful to medicinal chemists in the molecular designing of promising anticancer agents.

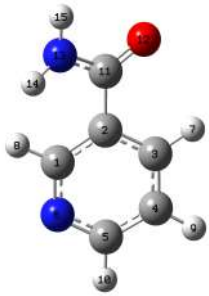
EXPERIMENTAL

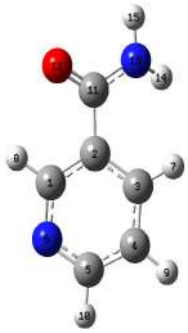
The geometries of isolated monomers and molecular complexes are optimized employing B3LYP/6-311++G** method through Gaussian 03 software.[18] Absence of imaginary frequency is used to characterize each stationary point to be global minima. The binding energies are obtained by taking the difference of energy of complex (AB) and the sum of energies of separated monomers A and B i.e. $\Delta E=E_{AB}-(E_A+ E_B)$. The counterpoise (CP) method of Boys and Bernardi is used to correct the basis set superposition error (BSSE) of binding energies.[19] Gauss view program is used to visualize the output of molecular structures. Natural bond orbital (NBO) analysis has been employed on the optimized structures to evaluate the atomic charges, FMO properties, dipole moments, second-order perturbation energies ($E^{(2)}$) values, the extent of charge transferred from proton donor to proton acceptor and hence to understand nature of H-bonding.[20] Analysis of topological features of electron density is carried out using AIM 2000 package.[21]

RESULTS AND DISCUSSION

Nicotinamide (NA) exists as a mixture of two conformers NA1 and NA2 (Fig.-1). The geometries of B3LYP/ 6-311++G** optimized conformers NA1 and NA2 differ in O12-C11-C2-C3 and N13-C11-C2-C1 dihedral angles to be 18.9˚ vs. -154.6˚ and 19.7˚ vs. -157.2˚ respectively in NA1 and NA2. Except for the above-mentioned torsion angles these two conformers share the same geometrical features. The calculated dipole moment of 1.9201 D for NA1 and 5.1795 D for NA2 differ significantly in magnitude and the NA2 is found to be more polar than NA1. The relative energy difference of these two forms is calculated to be 0.0014 hartrees or 0.92 kcal/mol at B3LYP/6-311++G**. Since NA1 is evaluated to be more stable out of the two conformers, further study of nicotinamide with uracil group (U, 5FU, and 2 TU) is carried out for this conformer only.

$\phi_{O12-C11-C2-C3}$=18.9˚
$\phi_{N13-C11-C2-C1}$=19.7˚





$\phi_{O12-C11-C2-C3}$=-154.6˚
$\phi_{N13-C11-C2-C1}$=-157.2˚

Fig.-1: Optimized Geometries of the Two Conformers of Nicotinamide (NA1) and (NA2) at B3LYP/6-311++G**

Hydrogen-Bonded Complexes

U, 5FU, and 2TU are placed at different preferential interaction sites in the vicinity of NA. For each uracil group, two configurations corresponding to energetic local minima are optimized and are presented in Fig.-2. The optimized structures are labeled as NAU1, NAU2 in the case of uracil, NAFU1, NAFU2 in the case of fluorouracil, and NATU1 and NATU2 in the case of thiouracil. Uracils and NA can act simultaneously as proton acceptors and proton donors toward each other. Two different intermolecular interactions are predicted to participate in the formation of the complexes, namely: conventional O…H-N and S…H-N H-bonds. All the complexes studied here are cyclic ones and are stabilized by two H-bonds and form eight-member rings. The dihedral angles of 180˚suggest that all the complexes are planar at the internal nitrogen of uracils. The planarity of the studied complexes is assigned to the enhanced electron resonance between participating atoms. The electronic properties of complexes depend on strength of donor and acceptor groups and the length of generated bridges between monomers. Also, it is well known that the closer the bridging H-bond angle to 180˚, the stronger the H-bond. The requisite geometrical parameters for describing H-bonding including H-bonding distances and the angle at bridging hydrogen

are evaluated for all the complexes using the B3LYP/6-311++G** level of theory and are mentioned in Fig.-2.

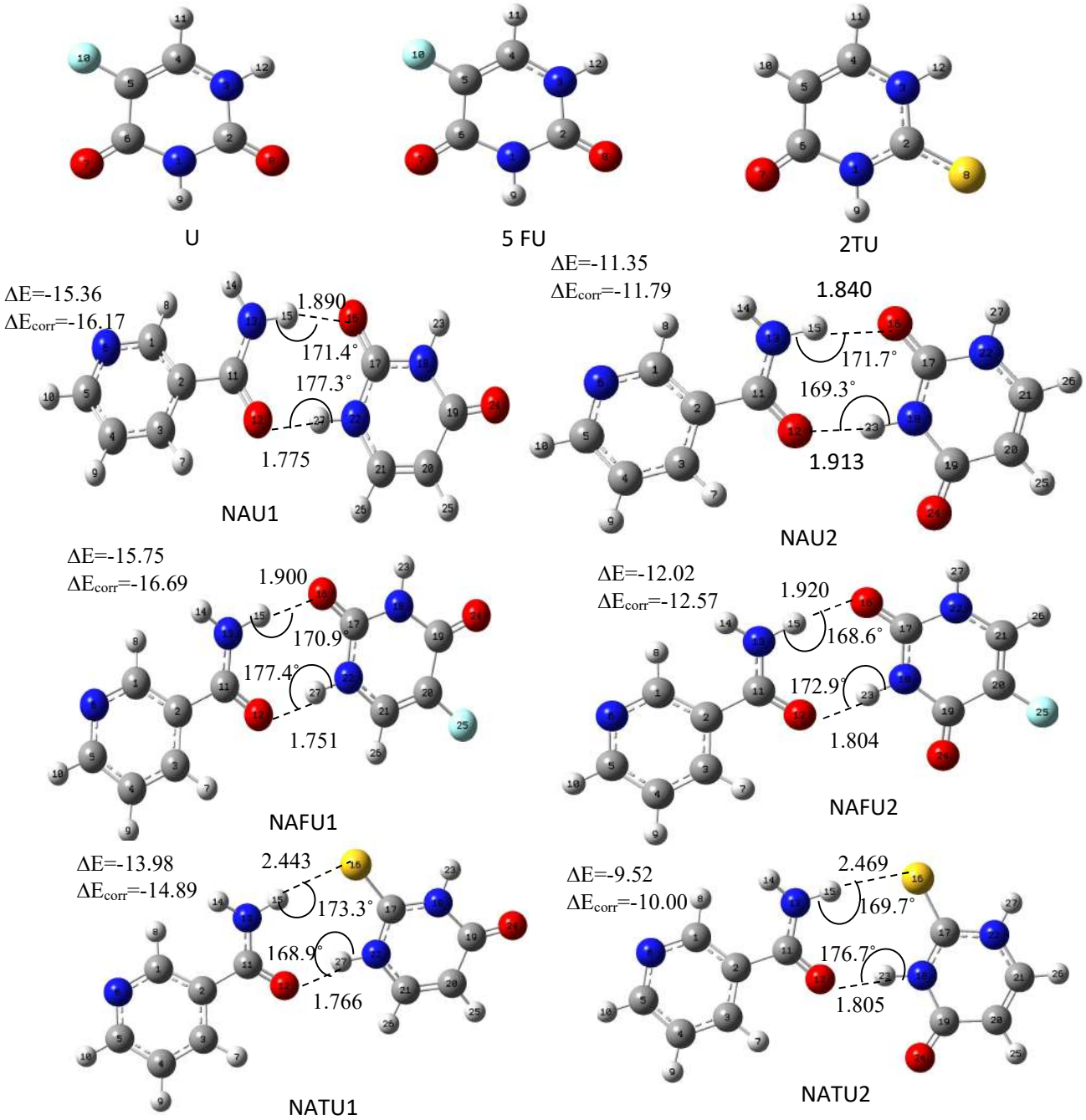


Fig.-2: Optimized Structures of Monomers and Complexes of Nicotinamide with Uracil, 5 fluorouracil, and 2 Thiouracil at B3LYP/6-311++G**. ΔE and ΔE_{corr} are in kcal/mol

The value of binding energies with BSSE correction (ΔE_{corr}) and without it (ΔE) and for all the structures calculated at B3LYP/6-311++G** are mentioned in Fig.-2. For each uracil group, the relative order of stability based on calculated binding energies is as follows: NAFU1>NAU1>NATU1> NAFU2>NAU2>NATU2. After BSSE correction, the complexes NAU1, NAFU1, and NATU1 are more stable than the others (NAU2, NAFU2, and NATU2). The predicted relative stability orders with BSSE correction and without it are identical in all complexes. The non-bonded $O_{(NA)}$…H-N $_{(U)}$ distance corresponding to NAU1, NAFU1, and NATU1 planar dimers are lowest where the highest one belongs to

NAU2, NAFU2, and NATU2, hence the strength of H-bond is maximum for former dimers with respect to latter. It can thus be concluded that the results of geometrical parameters corroborate well with the calculated S.E. Results indicate that the stability of complexes of NA with the U group depends on the electronegative nature of the atom. Most stable complexes are formed by 5FU followed by the uracil and least stable ones are formed by 2TU. The shortest H-bond contact O…H-N is of 1.751 Å in NAFU1 while the longest one is 2.443 Å for S…H-N in NATU1. The presence of two electron-withdrawing C=O(S) groups around the N-H donor bond of uracil and its derivatives decrease its H- bond donor strength in "2". The shorter H-bond length of N-H $_{(U)}$…O=C$_{(NA)}$ than N-H$_{(NA)}$…O=C $_{(U)}$ in NAU1, NAFU1, and NATU1 all indicate that uracil and its derivatives preferably act as better H-bond donor and NA act as better H-bond acceptor. In NATU1 and NATU2, it is revealed that the sulfur atom is a poor H-bond acceptor. The bigger size and largely diffused electron cloud of sulfur results in relatively longer H-bonds than formed by oxygen atoms. The lone pairs of sulfur atoms are perpendicular to the ring plane; hence wherever it acts as an H-bond acceptor it tends to form weak interactions. The H-bonds to oxygen are driven by charge-charge while in the case of sulphur, the stabilization results chiefly from interaction on acidic hydrogen with dipole and quadrupoles of sulfur. Furthermore, it is observed that H-bond lengths of bonds involved in H-bonding are increased in complexes relative to their monomers. Changes in H-bond donor bond length (Δd values) on complexation are calculated relative to monomers and reported in Table-1.

Table 1: The Dipole Moments (μ), Atomic Charges(q), Change in H-bond Donor Length (Δd) Binding Free Energy Change (ΔG), Enthalpy Change (ΔH), Intermolecular Delocalizations, Second Order Perturbation Energies ($E^{(2)}$) Values and Acceptor Orbital Occupancy in kcal/mol Calculated at B3LYP/6-311++G** Level

Species	Atomic charges		$\Delta d_{(N-H)}$	ΔG	ΔH	Delocalizations	$E^{(2)}$	σ^*_{N-H}
NAU1	$(q_{O12})q_{H27}$	(-0.686)0.458	0.024	-3.02	-13.82	$n_{O12}\rightarrow\sigma^*_{H27-N22}$	21.9	0.057
μ=1.915	$(q_{O16})q_{H15}$	(-0.679)0.438	0.015			$n_{O16}\rightarrow\sigma^*_{H15-N13}$	13.3	0.035
NAU2	$(q_{O16})q_{H15}$	(-0.678)0.437	0.012	-0.22	-9.94	$n_{O16}\rightarrow\sigma^*_{H15-N13}$	11.6	0.031
	$(q_{O12})q_{H23}$	(-0.668)0.464	0.024			$n_{O12}\rightarrow\sigma^*_{H23-N18}$	17.0	0.048
NAFU1	$(q_{O12})q_{H27}$	(-0.687)0.460	0.027	-3.46	-14.25	$n_{O12}\rightarrow\sigma^*_{H27-N22}$	24.0	0.061
μ=5.421	$(q_{O16})q_{H15}$	(-0.677)0.438	0.015			$n_{O16}\rightarrow\sigma^*_{H15-N13}$	12.8	0.034
NAFU2	$(q_{O12})q_{H23}$	(-0.670)0.466	0.027	-0.33	-10.63	$n_{O16}\rightarrow\sigma^*_{H15-N13}$	11.3	0.030
	$(q_{O16})q_{H15}$	(-0.676)0.436	0.011			$n_{O12}\rightarrow\sigma^*_{H23-N18}$	19.7	0.053
NATU1	$(q_{O12})q_{H27}$	(-0.685)0.462	0.024	-2.14	-12.57	$n_{O12}\rightarrow\sigma^*_{H27-N22}$	22.5	0.061
μ=5.646	$(q_{S16})q_{H15}$	(-0.236)0.420	0.013			$n_{S16}\rightarrow\sigma^*_{H15-N13}$	11.5	0.045
NATU2	$(q_{O12})q_{H23}$	(-0.665)0.469	0.026	-1.42	-8.26	$n_{S16}\rightarrow\sigma^*_{H15-N13}$	9.7	0.038
	$(q_{S16})q_{H15}$	(-0.294)0.420	0.010			$n_{O12}\rightarrow\sigma^*_{H23-N18}$	19.4	0.054

The values show elongation of N-H of both the NA and U group. However larger elongation of N-H of U/5FU/2TU than N-H of NA is observed in all the complexes indicating the uracil group to be a strong donor than NA. The results clearly show that out of the two H-bonds of eight member ring structure, the O$_{(NA)}$…H-N $_{(U/5FU/2TU)}$ are stronger than that of O$_{(U/5FU/2TU}$….H-N$_{(NA)}$. Thus, it can be concluded that increased N-H bond length is accompanied by increasing H-bond strength in the related complexes. For stronger H-bonding, the complexation leads to a) Elongation of N –H bond lengths as a proton donor and b) increased O(S)…H-N and S…H-N angles. The charge analysis of atoms participating in H-bonding depicts that the presence of electronegative atoms facilitates H-bonding interactions of NA and uracils. In all the complexes the hydrogen atoms of U/5FU/2TU show the highest positive charge due to bonding with highly electronegative oxygen and nitrogen atoms. For the most stable complexes highest positive and negative charges are present on hydrogen atoms and oxygen of uracil and nicotinamide respectively. The sulphur atom in complexes of thiouracil bears a low negative charge. Hence electrostatic interactions are weaker, particularly for S…H-N hydrogen bond in complexes of thiouracil. The thermodynamic properties such as enthalpy (ΔH) and Gibbs free energy (ΔG) for all complexes and are also calculated at B3LYP/6-311++G** level are listed in Table-1. The negative ΔG and ΔH for complexes indicate that the formation of such complexes is thermodynamically feasible. The order of ΔG is NAFU1 (-3.46)> NAU1 (-3.02)> NATU1 (-2.14) and this corroborates very well with ΔE and ΔE_{corr} and also with the order of ΔH

values. The greater negative ΔG values for NAFU1, NAU1, and NATU1 complexes show that these complexes have stronger interactions than NAFU2, NAU2, and NATU2. The highest ΔG of -3.46 kcal/mol and ΔH of -14.25 kcal/mol are observed for NAFU1. The ΔG values suggest NAFU1 is more stable than NAU1 by 0.44 kcal/mol. A similar difference in the free energy of NAFU1 and NATU1 is 1.32 kcal/mol in favor of NAFU1.

Dipole Moments and NBO Analysis

The molecular dipole moments of monomers and their complexes are calculated using B3LYP/6-311++G**. Results show that the predicted dipole moment of NA is 1.92 debye which is found to be much smaller than uracil monomers (U=4.66, 5FU=4.35, 2TU=4.77) this shows that when NA interacts with different sites of drug, the dipole moment of the molecule increases (Table-1). The high dipole moment values point towards the high reactivity of molecules. The increased dipole moment is due to charge redistribution and the movement of charges from one region of the molecule to the other leading to intermolecular interactions between NA and uracils. The values of the dipole moment of thiouracil and its complexes are slightly larger than uracil and fluorouracil complex Second-order interaction energies $E^{(2)}$ values associated with electron delocalizations between H-bond donor and acceptor orbitals and acceptor orbital occupancies calculated at B3LYP/6-311++G** level determined using NBO analysis and are presented in Table-1. The larger the $E^{(2)}$ value, the stronger the interactions of donor and acceptor orbitals and hence leading to larger stabilization energy (S.E). For most stable complexes, the sum of $E^{(2)}$ values for both H-bonds is 36.8,35.2,33.9 kcal/mol for NAFU1, NAU1, and NATU1 respectively is in agreement with binding energies order. The most stable complex NAFU1 has the largest $E^{(2)}$ value of 24.03 kcal/mol for $n_{O\ (NA)} \rightarrow \sigma^*_{N\text{-}H\ (FU)}$ delocalization. The $E^{(2)}$ values show significant charge transfer between NA and U/5FU/2TU groups. The occupancy of the acceptor orbital increases on receiving electron density. It is widely accepted that for H-bond type Y…X-H, the transfer of electron density from lone pair (n) of H-bond acceptor (Y) to antibonding σ* of H-bond donor (X-H) increases X-H bond length. As evident from Δd evaluated earlier, all the H-bond acceptor length increase. For most stable complexes NAU1, NAFU1, NATU1 the $E^{(2)}$ is higher for $n_{(NA)} \rightarrow \sigma^*_{N\text{-}H\ (U/FU/TU)}$ delocalization over $n_{(U/FU/TU)} \rightarrow \sigma^*_{N\text{-}H\ (NA)}$. It indicates a greater contribution of the former bond towards S.E. than the latter one. It also concludes uracil is to be an H-bond donor and NA act as an H-bond acceptor. High $E^{(2)}$ for delocalization in all the NAFU1, NAU1, and NATU1 shows that the acidic character of N-H of U/FU/TU is larger than NH of nicotinamide. Although the charge on sulphur of complexes of thiouracil is low, yet strong charge transfer interaction leads to significant S.E. of these complexes. NBO charges show enhancement of negative charge on H-bond acceptor atom and positive charge on hydrogen upon H-bonding.

Atoms in Molecules (AIM) Analysis

Bader's Atoms in molecule (AIM) theory based on a topological study of electron density (ρ) and its laplacian ($\nabla^2\rho$) at the bond critical point (BCP) is an elegant tool to study intermolecular interactions like H-bonding and van der Waal interactions. AIM analysis at the B3LYP/6-311++G** level is carried out on the optimized complexes to calculate various topological parameters and the results are listed in Table-2.

Table-2: The Electron Density (ρ), Laplacian of Electron Density ($\nabla^2\rho$) in a .u. at BCP and Ring Critical Point (RCP) for Considered Nicotinamide Complexes with Uracil and its Derivatives Obtained from AIM Analysis

Complex	Hydrogen Bond	BCP		Hydrogen Bond	BCP		RCP	
		ρ	$\nabla^2\rho$		ρ	$\nabla^2\rho$	ρ	$\nabla^2\rho$
NAU1	O12…H27	0.0376	0.0301	O16…H15	0.0280	0.0249	0.0050	0.0054
NAU2	O12…H23	0.0314	0.0268	O16…H15	0.0262	0.0241	0.0049	0.0051
NAFU1	O12…H27	0.0399	0.0311	O16…H15	0.0274	0.0244	0.0050	0.0055
NAFU2	O12…H23	0.0343	0.0284	O16…H15	0.0258	0.0238	0.0049	0.0052
NATU1	O12…H27	0.0384	0.0308	S16…H15	0.0180	0.0103	0.0044	0.0041
NATU2	O12…H23	0.0335	0.0286	S16…H15	0.0167	0.0101	0.0042	0.0038

The AIM molecular graphs of complexes are depicted in Fig.-3. According to Koch and Popelier criteria of H-bonding, the value of ρ at BCP falls in the span of 0.002-0.040 a.u., and the corresponding laplacian

of rho $\nabla^2\rho$ should lie in the range of 0.024-0.139 a.u.[22] The positive laplacian values indicate interaction to be closed shell type and the covalent character is related to its negative sign. All the complexes satisfy the H-bonding criteria of ρ and $\nabla^2\rho$ established by Koch and Popelier except $\nabla^2\rho$ of thiouracil-nicotinamide complexes where $\nabla^2\rho$ is below the lower limit of the range.

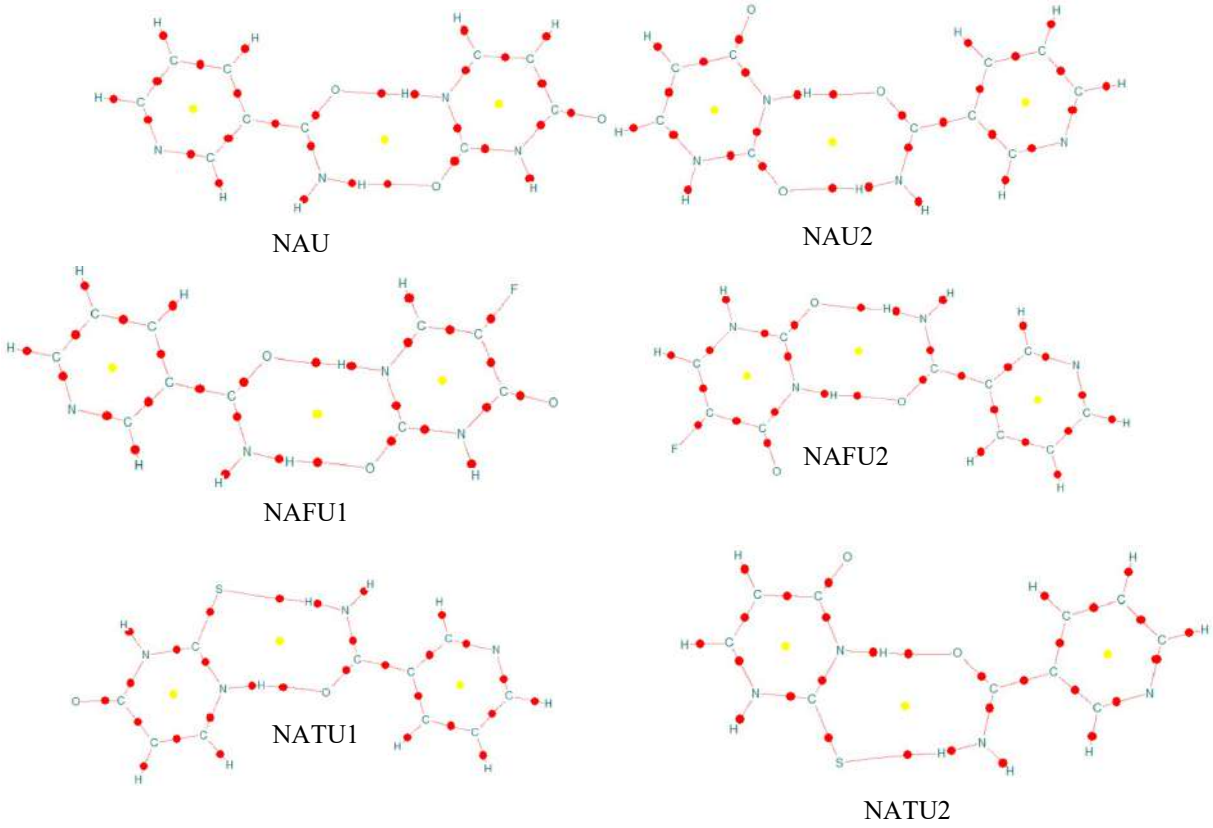


Fig.-3: AIM Molecular Graphs of Optimized Complexes, the BCP and RCP are Respectively Marked with Red and Yellow Balls

The ρ value at BCP is a measure of H-bond strength, the higher the value of ρ at BCP, the stronger the H-bond. The value of ρ_{BCP} in most cases is close to the upper limit of Koch-popelier established H-bond range leads to conclude that these H-bonds are of moderate strength. Further, the medium-strength H-bonds are characterized by $\nabla^2\rho > 0$ and $H < 0$. The higher values of ρ (0.0314-0.0399) for $(N\text{-}H)_{U/5FU/2TU}$ as an H-bond donor than ρ values of (0.0167-0.0280) or $(N\text{-}H)_{NA}$ substantiate the fact that N-H of uracil group serves as a better donor towards C=O of NA relative to N-H of NA to C=O (S) of uracil group molecules. In the most stabilized complex NAFU1, the two O12…H27-N22 and O16…H15-N13 interactions are retrieved, and the corresponding electron densities are 0.0399 a.u. and 0.0274 a.u. and the corresponding laplacian are 0.0311 a.u. and 0.0244 a.u. The ρ and $\nabla^2\rho$ at BCP is found to be highest for $N\text{-}H_{(5FU)}...O_{(NA)}$ and lowest for $S_{(2TU)}…H\text{-}N_{(NA)}$. The relationship of H-bond distance and topological parameters ρ_{BCP} and $\nabla^2\rho_{BCP}$ is examined for all optimized nicotinamide-uracil complexes. The variation of ρ_{BCP} and $\nabla^2\rho_{BCP}$ with H-bond distances is presented in Fig.-4.

Various properties like chemical potential, chemical hardness, chemical softness, electronegativity, and electrophilicity are calculated for NA, and the most stable complexes with the Uracil group (U, 5FU, and 2TU), are listed in Table-3.

The H-bond length is inversely related to both ρ_{BCP} and $\nabla^2\rho_{BCP}$. Hence it can be concluded that the shorter the H-bond length, the greater the electron density, and the more positive the laplacian at the BCP. The short contact distance results in increased orbital overlap leading to increased electron density along the bond path.

Frontier Molecular Orbital Analysis

FMOs are chief orbitals taking part in chemical reactions and are used to predict the most reactive sites in a conjugated system the corresponding energy level of FMOs for studied compounds are given in Fig.-5.

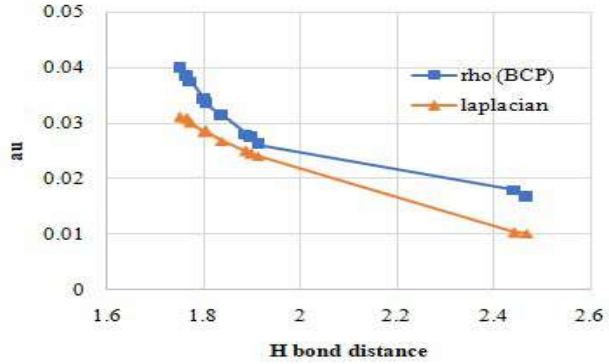


Fig.-4: Variation of the Electron Density (ρ_{BCP} in a.u. Rectangle Symbol) and its Laplacian ($\nabla^2\rho_{BCP}$ in a.u., Triangle Symbol) of the H-bond Formed in the Nicotinamide and Uracil and Derivatives Versus The H-Bond Distance (in Å)

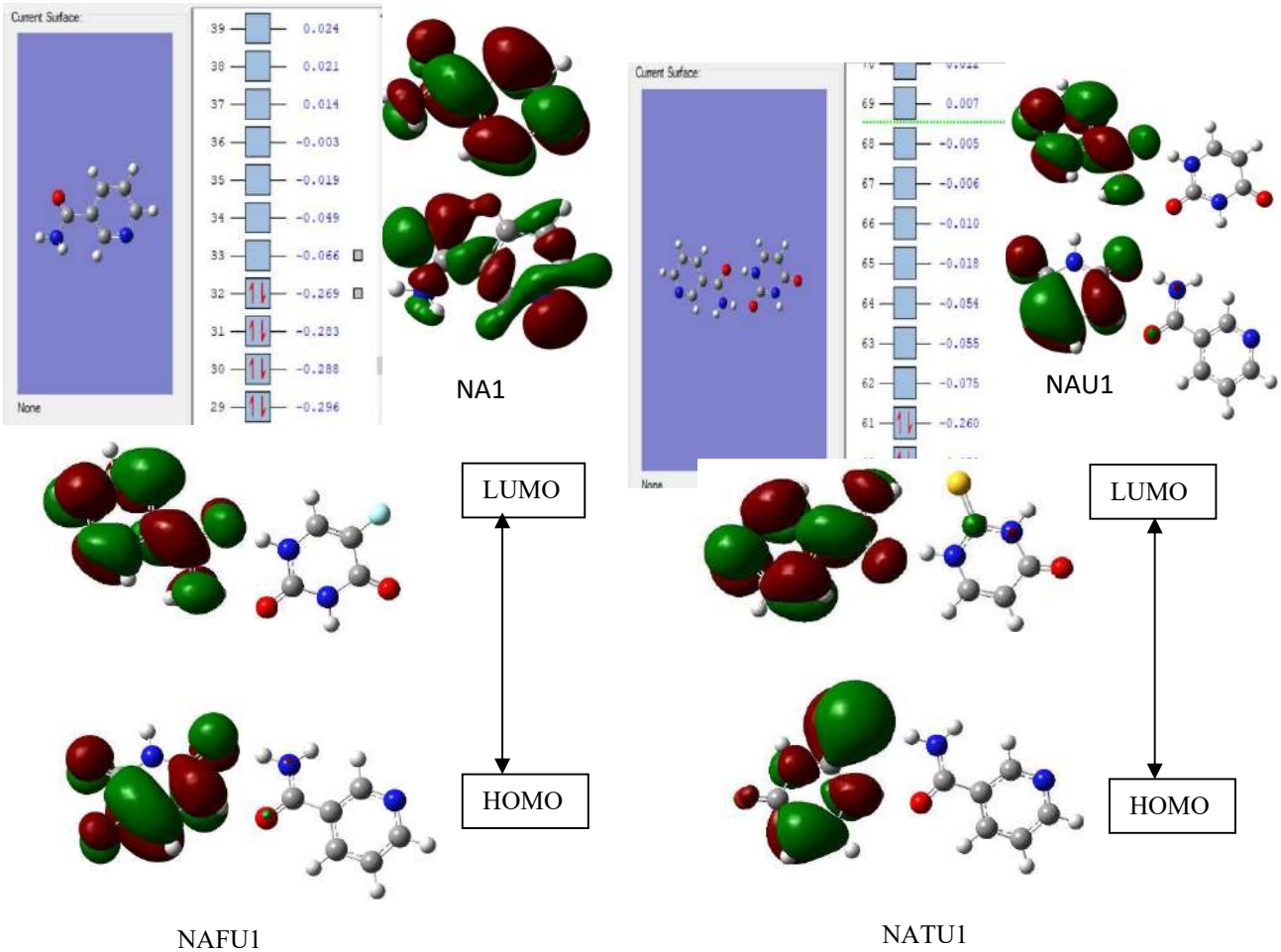


Fig.-5: Frontier Molecular Orbitals (HUMO and LUMO) of NA1, NAU1, NAFU1, and NATU1

Table-3: Frontier Orbital Energies and Description of Chemical Reactivity of the Nicotinamide and its Complexes with Uracil Group (U, 5FU, and 2TU) (in eV units) Calculated at B3LYP/6-311++G** Level

Chemical Properties		NA1	NAU1	NAFU1	NATU1
HOMO	-	-7.32	-7.07	-7.02	-6.56

LUMO	-	-1.79	-2.04	-2.12	-2.15
IP	$IP=-E_{HOMO}$	7.32	7.07	7.02	6.56
EA	$A=-E_{LUMO}$	1.79	2.04	2.12	2.15
BAND GAP	$E_{GAP}=IP-EA$	5.53	5.03	4.9	4.41
CHEMICAL POTENTIAL	$-(I+A)/2$	-4.55	-4.56	-4.57	-4.36
CHEMICAL HARDNESS	$\eta=(I-A)/2$	2.76	2.52	2.45	2.21
CHEMICAL SOFTNESS	$1/\eta$	0.36	0.40	0.41	0.45
ELECTRONEGATIVITY	$(I+A)/2$	4.55	4.56	4.57	4.36
ELECTROPHILICITY	$-\mu^2/2\eta$	3.75	4.13	4.26	4.30

For NA1, the average electronic energy (HOMO) expressed at 32 is measured at -0.269 Hartree's and the lowest electronic energy (LUMO) shown at 33 is measured at -0.066 Hartree's. Electron transfer occurs between HOMO and LUMO. The energy band gap was determined by taking the difference between HOMO and LUMO energy levels and for NA1, the band gap is 5.53eV. For NAU1, HOMO lies at 61 with an energy of -0.260 hartrees and LUMO at 62 with an energy of -0.075 Hartree's. The band gap for NAU1, NAFU1, and NATU1 is 5.0, 4.9, and 4.4 eV respectively. The decreased band gap shows easy excitation of the electron. The HOMO-LUMO bad gap, chemical hardness, and ionization potential are smaller for all H-bonded complexes relative to NA1. The chemical softness, electron affinity, and electrophilicity are found to increase in the studied H-bonded complexes. NA complex with 2FU viz. NAFU1 with the highest electronegativity is the best electron acceptor while thiouracil complex NATU1 with minimum electronegativity is the weakest electron acceptor. In complexes of NA with Uracil derivatives, the placement of HOMO on uracil while the placement of LUMO on NA indicates uracil to act preferably as an H-bond donor and NA to act as an H-bond acceptor. The results of the present investigation predict the preferred site of binding of uracil-based drugs with NA and also provide experimental chemists with the H-bond binding energies and other reactivity descriptors useful for drug designing.

CONCLUSION

Computational study of H-bonded complexes of nicotinamide with uracil, 2 thiouracils, and 5 fluorouracil is carried out at B3LYP/6-311++G**level. Optimized complexes are analyzed for geometrical and topological parameters, chemical reactivity descriptors, stabilization energies, binding free energy and enthalpy changes, NBO, and frontier orbitals. Enhancement of dipole moment on complexation, high delocalization energies (E^2 values), occupancy of acceptor orbitals, FMO, and NBO analysis all indicate significant charge transfer between NA and U/5FU/2TU.

While fluorouracil forms the most stable complex, the least stable complex with NA is formed by thiouracil. The geometrical parameters and $E^{(2)}$ values from NBO, all indicate uracil and its derivatives act preferably as H-bond donor while NA act as a better H-bond acceptor in their complexes. The order of S.E. of the most stable complexes is NAFU1> NAU1>NATU1 which is in tune with decreasing electro-negativity of F, O, and S atoms on U/5FU/2TU. Negative values of ΔG and ΔH for complexation suggest the formation of stable intercalation sites of uracil drugs with NA. As drug-vitamin interactions can positively or negatively impact human health, the present study is significant for medicinal chemists in designing novel anticancer drugs.

CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to the manuscript, participated in reviewing/editing, and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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[RJC-8223/2022]