Theoretical Investigation of Interaction between 5-Fluorouracil Anticancer Drug with Various Nitrosamine Compounds

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We present detailed theoretical studies of the H-bonded complexes formed from interaction between 5-fluorouracil and various six-membered cyclic nitrosamine compounds. In this study, an investigation on intermolecular interactions in X-NU (X = CH_2, SiH_2, BH, AlH, NH, PH, O and S) complexes is carried out using density functional theory. The calculations are conducted on B3LYP/6-311++G** level of theory for optimization of geometries of complexes and monomers. Furthermore, quantum theory of ''Atoms in Molecules'' (AIM) and natural bond orbital (NBO) method are applied to analyze the H-bond interactions in respective complexes. The electron density (ρ) and Laplacian ($\nabla^2\rho$) properties, estimated by AIM calculations, indicate that O…H bonds possess low ρ and positive $\nabla^2\rho$ values which are in agreement with electrostatic character of the H-bonds. In addition, the examination of the H-bond in these complexes by quantum theory of NBO method supports the obtained results. Natural population analysis data, electron density, and Laplacian properties, as well as, the υ(C-H) and υ(N-H) frequencies of complexes, calculated at the B3LYP/6-311++G** level of theory, are used to evaluate the H-bond interactions. Several correlations between topological, geometrical and energetic parameters are also found.

INTRODUCTION

Hydrogen bonding is of great importance in chemical and biological systems. It is the strongest intermolecular force. The importance of the hydrogen bond cannot be overstated. Its chemical properties have both subtle and profound influences on the essential chemistry of life, crystal packing and engineering, self-assembly, solvation, catalysis, chelation, and a host of other important phenomena. Extensive research has been devoted to the nature of the hydrogen bond for nearly one century [1]. Intermolecular hydrogen bond systems are one of the key interactions that determine the structure, functionality, and dynamic processes in a large variety of systems. Intermolecular hydrogen bonds frequently occur in inorganic, organic, and biological chemistry. Therefore, the

understanding and comprehensive studies of the nature of hydrogen bonds is underpinning any insight into molecular bases of chemical and biological systems [2].

Uracil derivatives have registered their importance in pharmaceuticals [3], drug delivery, synthesis, polysaccharides, transportation, allosteric regulators [4] and pesticides [5]. Transformation of uracil into 5-fluorouracil significantly changes its chemical and spectroscopic properties, as well as its *in vivo* activity. The 5-fluorouracil can be considered as a derivative of a nucleobase thymidine where the methyl group is replaced by a fluorine atom. The fluorouracil is also used for the treatment of precancerous conditions such as solar keratosis [6], basal cell carcinoma and various cancer types such as colorectal, pancreatic, ovarian, cervical, bladder, breast and stomach cancer [7]. It interferes with the growth of cancer cells, which are eventually destroyed. In addition to cancer, it is also used for a variety of other pharmaceutical purposes including porokeratosis [8], and psoriasis, sun-damaged skin and

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genital warts [9]. Due to extensive medicinal importance it has been a topic of investigation for decades.

Nitrosamine compounds are potent carcinogens reported by the International Agency for Research on Cancer (IARC) [10]. The nitrosamines are formed readily from various nitrogen compounds (such as nitrite and their various derivatives) [11]. The parent nitrosammonia (NH2-NO), of particular interest in atmospheric chemistry, has been a subject for detailed studies [12]. The nitrosamine can form DNA adduct to cause cancer in the human body [13]. The human can be ethod such as drying and pan-frying [14]. The endogenous formations of nitrosamine compounds in the human body are possible to be one of the exposures [15].

The present study is directed to investigate the interactions of the 5-flourouracil (5FU) with various six-membered cyclic nitrosamine (XN) compounds [16,17]. In this work, characterization of the nature of intermolecular interactions in the X-NU (X-Nitrosamine…fluorouracil) complexes is estimated. As can be seen in Fig. 1, the complexes are named according to the nature of the substitutions (X) on the nitrosamine ring (CH_2-NU, SiH_2-NU, BH-NU, AlH-NU, NH-NU, PH-NU, O-NU and S-NU). The main objective of this article is to analyze the effects of these interactions on the geometrical parameters, the H-bonding energies and topological properties of mentioned complexes. For this analysis density functional theory (DFT) calculations are carried out and also AIM and NBO methods are applied.

METHOD

The calculations in the current paper have been performed by means of the Gaussian 03 program package [18], at B3LYP theoretical level with 6-311++G** basis function. Harmonic vibrational frequencies are evaluated at the same level to confirm the nature of the stationary points found and to account for the zero point vibrational energy (ZPVE) correction. Frequency calculations indicate that the analyzed complexes have particular local minima on PES and, therefore, are stable. For the investigated systems, the interaction energy (IE) is calculated by evaluating the difference between the total energies of complex and individual monomers as given in Eq. (1):

$$IE = E_{X\text{-}NU} - (E_{FU} + E_{XN}) \tag{1}$$

The interaction energies are corrected for the basis set superposition error (BSSE) by the Boys-Bernardi counterpoise technique [19]. NBO analysis [20] has been also performed with NBO program (version 3.1) implemented in the Gaussian 03 package at the B3LYP/6-311++G** level of theory to elucidate the intermolecular hydrogen bonding, intermolecular charge transfer (ICT) and delocalization of electron density. The quantum theory of atoms in molecules (QTAIM) is also applied here [21]; bond critical points (BCPs) and ring critical points (RCPs) are analyzed in terms of the following characteristics: the electron density at the critical point (ρ), its Laplacian ($\nabla^2\rho$) and the total electron energy density at the critical point $H(r)$. For the latter, its components are also considered; the potential electron energy density $V(r)$ and the kinetic electron energy density $G(r)$. There is a well-known relation (Eq. (2)) between Laplacian and the energetic characteristics of the critical point [22].

$$\frac{1}{4}(\nabla^2\rho) = 2\,G(r) + V(r) \text{ and } H(r) = G(r) + V(r) \tag{2}$$

RESULTS AND DISCUSSION

H-Bond Energies

The structures of the H-bonded complexes formed from interaction between 5-flourouracil (5FU) and the various nitrosamine compounds (CH_2-N, SiH_2-N, BH-N, AlH-N, NH-N, PH-N, O-N and S-N), are shown in Fig. 1. Figure 1 presents the 5FU and nitrosamine compounds offer R site for hydrogen bond formation. Because 5FU contains C=O as well as NH groups, it is expected to form a strong binary H-bonded complex with nitrosamine compounds which are not only a proton donor but also a proton acceptor. Therefore, all systems analyzed here are coupled through double hydrogen bonds and all of them are found to be in plane. With preferential interaction site (R) in the vicinity of the fluorouracil, eight cyclic complexes (X-UN) are found, with two intermolecular hydrogen bonds $O_{FU}\cdots HC_{XN}$ and $O_{XN}\cdots HN_{FU}$ involved in each of them. E_{HB} binding energies correspond to two hydrogen bonding interactions. Studied dimers are stabilized by double hydrogen-bonding (E_{HB1} and E_{HB2}). On the other hand, the stability of X-NU complexes

Nitrosamine (XN)

X = CH$_2$
X = SiH$_2$
X = BH
X = AlH
X = NH
X = PH
X = O
X = S

5-Fluorouracil (5FU)

CH$_2$-NU

SiH$_2$-NU

BH-NU

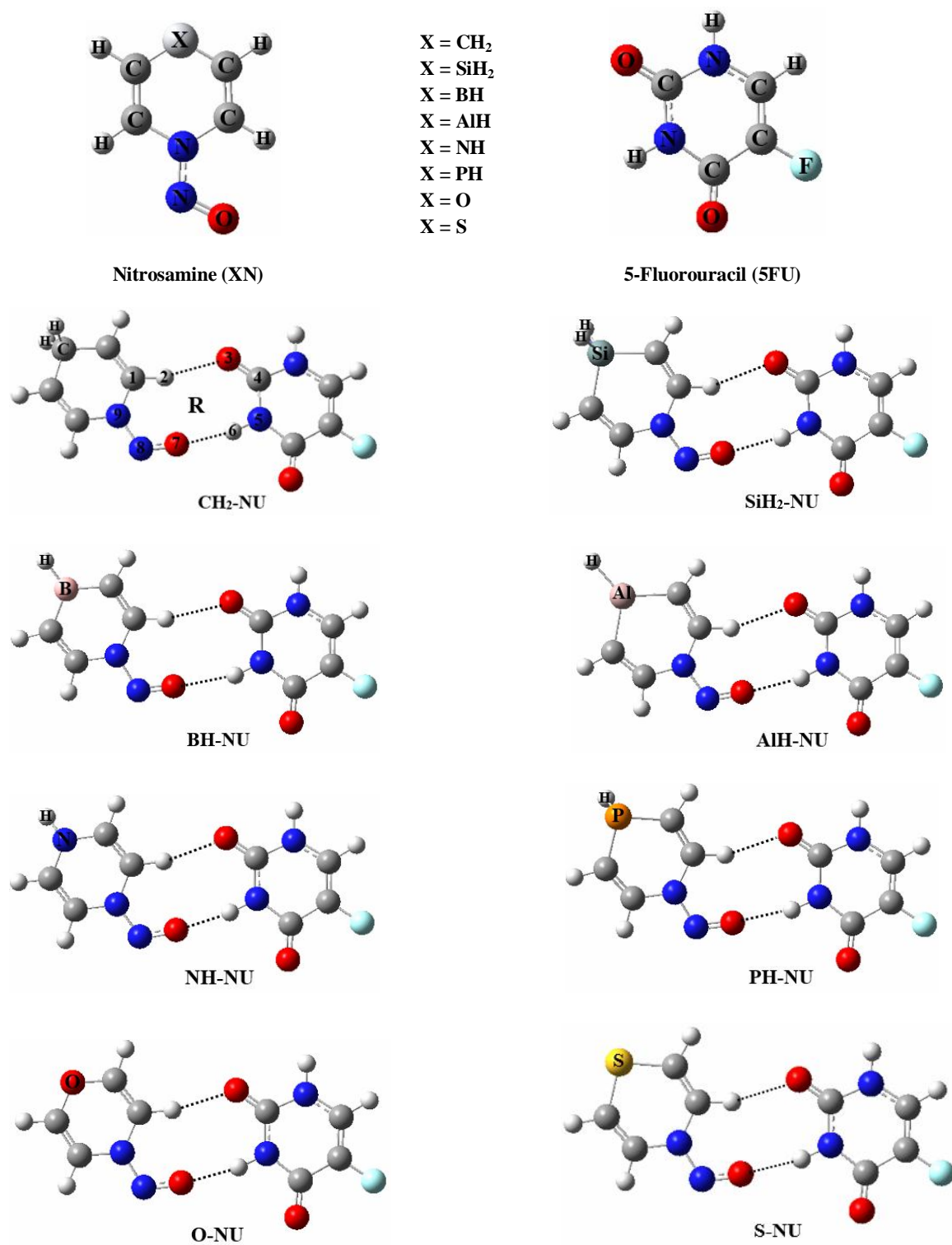**AlH-NU**

NH-NU

PH-NU

O-NU

S-NU

Fig. 1. The investigated complexes: The complexes of various six-membered cyclic nitrosamine compounds with 5-fluorouracil (X-NU).

is mainly due to the formation of intermolecular hydrogen bonding. In recent years, the main method of Espinosa [23] has been frequently applied for the estimation of the H-bond energy. It has been verified that the electron density at the H...Y BCP (Y is a proton acceptor for the X-H...Y H-bonds) correlates well with the H-bond energy. Theoretical studies are able to obtain a full description of both topological and energetic properties at critical points. It is possible to calculate such energetic parameters as the local kinetic energy density, G(r), and the local electron potential energy density, V(r) (see Table 3). Experimental studies of electron density do not provide the description of energetic properties of critical points. However, Abramov has proposed the evaluation of G(r) in terms of electron density ρ(r), its gradient $\nabla\rho$(r) and its Laplacian $\nabla^2\rho$(r) functions [24]. At the critical point, where $\nabla\rho$(r) = 0 the Abramov relation takes the form:

$$G(r_{cp}) = (\frac{3}{10})(3\pi^2)^{\frac{2}{3}}\rho^{\frac{5}{3}}(r_{cp}) + (\frac{1}{6})\nabla^2\rho(r_{cp}) \quad (3)$$

All the parameters in the above equation are expressed in atomic units. The local potential energy density $V(r_{CP})$ can be derived from the virial equation [24]:

$$2G(r_{cp}) + V(r_{cp}) = (\frac{1}{4})\nabla^2\rho(r_{cp}) \quad (4)$$

The simple relationship between H-bond energy and the potential energy density $V(r_{CP})$ at the critical point corresponding to $O_{FU}...H_{XN}$ and $O_{XN}...H_{FU}$ contacts was assigned to be $E_{HB} = 1/2\ V(r_{CP})$. V(r) designates the local electron potential energy density at the H...Y BCP, and Y designates the proton acceptor in X-H...Y hydrogen bond. We implemented this method to estimate the H-bond energies $O_{FU}...HC_{XN}$ (E_{HB1}) and $O_{XN}...HN_{FU}$ (E_{HB2}) for $O_{FU}...H_{XN}$ and $O_{XN}...H_{FU}$ contacts in X-NU complexes, the results are listed in Table 1. Theoretical results show that the lowest sum of the two H-bond energies E_{HB1} and E_{HB2} (*i.e.* $\sum E_{HB}$) is predicted for NH-NU while the highest $\sum E_{HB}$ is observed for the BH-NU complex. Furthermore, the obtained results in this study show that the complexes of O-NU and S-NU have energies near the lowest one.

Theoretical results show that the values of H-bonding energies also confirm the obtained interaction energies (IEs) results. The interaction energies of the analyzed complexes have been computed as a difference between the total energy of the complex and the energies of the isolated monomers and are further corrected for the zero-point vibrational energy (ZPVE) and basis set superposition error (BSSE) by applying the counterpoise procedure. The interaction energies for X-NU complexes including the BSSE and ZPVE corrections at the B3LYP/6-311++G** level of theory are reported in Table 1. As can be seen in this table, the interaction energies lie in the range of -11.24 to -24.60 kJ mol⁻¹. The obtained results show that for all complexes, the values of interaction energies in the NH-NU, O-NU, and S-NU complexes have been reduced (in

Table 1. The Interaction Energies (IEs, in k Jmol⁻¹), the Energies of the Intermolecular Hydrogen-Bond (E_{HB} in k Jmol⁻¹) and Stretching Frequencies ($\Delta\upsilon$, in cm⁻¹) of N-H and C-H Groups Calculated at the B3LYP/6-311++G** Level of Theory

Complex	IE	E_{HB1} $O_{FU}...HC_{XN}$	E_{HB2} $O_{XN}...HN_{FU}$	$\Delta\upsilon_{C-H}$	$\Delta\upsilon_{N-H}$
CH₂-NU	-18.12	-9.64	-18.63	20.11	108.80
SiH₂-NU	-14.38	-9.09	-14.51	3.90	74.59
BH-NU	-11.24	-8.90	-11.25	9.56	45.83
AlH-NU	-12.07	-7.89	-13.46	6.74	64.61
NH-NU	-24.60	-11.06	-24.62	32.00	170.35
PH-NU	-17.02	-10.12	-16.55	13.21	92.67
O-NU	-22.59	-12.35	-20.82	50.58	130.90
S-NU	-20.39	-11.36	-19.14	33.47	115.54

comparison with the corresponding values of the CH$_2$-NU complex) while these values in SiH$_2$-NU, BH-NU, AlH-NU and PH-NU complexes have been increased. Therefore, it is found that the NH-NU, O-NU and S-NU complexes are more stable than the other ones. Our theoretical results show the smallest IE for NH-NU complex while the greatest IE observes for the BH-NU complex. Relative stability order of the complexes can be predicted from the computed IEs. Although ZPVE correction has a significant effect on the IE of complexes, inclusion of ZPVE does not change the stability order of the complexes. Consequently, based on the predicted IEs, the relative stability of studied complexes increases in the order NH-NU > O-NU > S-NU > CH$_2$-NU > PH-NU > SiH$_2$-NU > AlH-NU > BH-NU.

The experimental gas phase proton affinities and acidities (defined according to the reaction U → U$^-$ + H$^+$) at various H-bonding sites of uracil have been given in literature [25]. As mentioned above, the complexes are formed when the XN interacts with FU. Both 5-fluorouracil and nitrosamine compound can simultaneously act as proton acceptor and proton donor. In these complexes O atom of NO group in XN and one C=O group of 5FU act as the proton acceptors while C-H and N-H bonds of XN and 5FU monomers, respectively, act as the proton donors (see Fig. 1). As seen in this figure, XN can be placed in R region in vicinity of FU (the intermolecular region). In this region, N-H bond has the highest acidity and O atom of NO has the lowest proton affinity. The highest H-bond energy is predicted when XN interacts with the FU in this region, in

which O atom of NO has the lowest proton affinity and N-H bond has the highest acidity. Thus, H-bond energy for the most stable complex depends more on the acidity of the proton donor than on the basicity of the proton acceptor [25]. Our results show that H-bond energy for SiH$_2$-NU, BH-NU, AlH-NU and PH-NU complexes is greater than that for NH-NU, O-NU and S-NU ones. Therefore, acidity of N-H bond of the former cases is smaller than that of the latter cases. Interaction between FU and XN for all of complexes takes place through the less acidic C-H bond. Therefore, it is expected that the O$_{XN}$…HN$_{FU}$ H-bond energy for these complexes to be smaller than the O$_{FU}$…HC$_{XN}$ H-bond energy. Proton donor site of FU in studied complexes is N-H bond and that of XN is C-H one.

Molecular Geometry

The most important structural parameters calculated at B3LYP/6-311++G** level of theory for studied complexes are given in Table 2. As can be seen, the O$_{FU}$…HC$_{XN}$ and O$_{XN}$…HN$_{FU}$ H-bond angles are nearly linear. The O$_{XN}$…HN$_{FU}$ angles ranging from 163.7° to 171.4° are greater than O$_{FU}$…HC$_{XN}$ angles varying from 158.8° to 167.3°. Consequently, deviation from linearity for O$_{XN}$…HN$_{FU}$ angle is smaller than that for O$_{FU}$…HC$_{XN}$ one. Besides, this linearity for the NH-NU complex is greater than the others. The small interaction energy calculated for NH-NU probably results from a more linear arrangement of the hydrogen bonds. In addition, in all studied systems, fluorouracil is donating an H-bond to the oxygen of various

Table 2. The Geometrical Parameters (Bond Lengths is in Å and Bond Angles in °) Calculated at the B3LYP/6-311++G** Level of Theory

Complex	C-H$_{(N)}$	H$_{(N)}$…O$_{(U)}$	C=O$_{(U)}$	C-N$_{(U)}$	N-H$_{(U)}$	H$_{(U)}$…O$_{(N)}$	N=O$_{(N)}$	N-N$_{(N)}$	C-N$_{(N)}$	O$_U$…HC$_N$	O$_N$…HN$_U$
CH$_2$-NU	1.081	2.280	1.217	1.382	1.020	1.983	1.224	1.347	1.413	165.4	168.9
SiH$_2$-NU	1.083	2.305	1.217	1.383	1.018	2.059	1.212	1.374	1.409	160.0	166.2
BH-NU	1.084	2.305	1.216	1.384	1.016	2.138	1.201	1.398	1.390	164.6	163.7
AlH-NU	1.085	2.355	1.216	1.384	1.017	2.082	1.207	1.388	1.407	158.8	165.4
NH-NU	1.079	2.234	1.219	1.381	1.024	1.898	1.241	1.330	1.424	165.8	171.4
PH-NU	1.083	2.267	1.217	1.383	1.019	2.019	1.219	1.361	1.410	161.3	167.5
O-NU	1.081	2.193	1.219	1.381	1.021	1.949	1.232	1.335	1.418	167.3	169.6
S-NU	1.082	2.227	1.218	1.382	1.020	1.975	1.228	1.350	1.414	162.1	168.3

nitrosamine compounds, while in the nitrosamine the H-bond is donated to the oxygen of the CO moiety in fluorouracil. The donor abilities of these two atoms (N and C) is different and therefore results in different H-bond strengths on this account as well. In our interested complexes, the intermolecular $O_{XN}\ldots HN_{FU}$ (H-bond between FU and XN) distances, ranging from 1.898 to 2.138 Å, are clearly shorter than those in $O_{FU}\ldots HC_{XN}$ ones which vary between 2.193 and 2.355 Å. The H-bond distances and the corresponding angles can be considered as a criterion of strength of H-bonding. Accordingly, $O_{XN}\ldots HN_{FU}$ H-bonds are much stronger than those for $O_{FU}\ldots HC_{XN}$. The H-bonding distances and the corresponding angles in the most stable complex NH-NU are, respectively, smaller and greater than the others. It is interesting to note that for the investigated complexes, the H-bonding distances correlate well with IEs. It is obvious from these data that X-NU complexes with the lowest H-bonding distance have the smallest interaction energy. A linear relationship between the IEs and the sum of H-bonding distances is shown in Fig. 2. From this figure, interaction energy decreases as the H-bond strength increases.

Interactions classified as the intermolecular resonance assisted hydrogen bonds (RAHBs) are also analyzed here. On the other hand, RAHB highlights the cooperatives between the π-electron delocalization and hydrogen bonds; the term was coined by Gilli and co-workers in the late 1980s, who have continued to refine their theory by publishing a series of papers [26]. In RAHB, the hydrogen bond donor and acceptor atoms are connected through π-conjugated double bonds, which were utilized in this work. All complexes have cyclic π-conjugated framework and exhibit the remarkable RAHB mechanism. One of the main features of RAHB is the strengthening of the hydrogen bond. As can be seen, influence of π-electron delocalization on the structural parameters of monomers is obvious. Owing to this, the largest changes are observed in the bonds (CN and CO bond of FU and NN and NO bond of XN) involved in the H-bonding.

It is worth mentioning that E_{HB} correlates with the geometrical parameters which are usually assumed to be good descriptors of the H-bond strength. It is well known that for the related systems the stronger is H-bond the
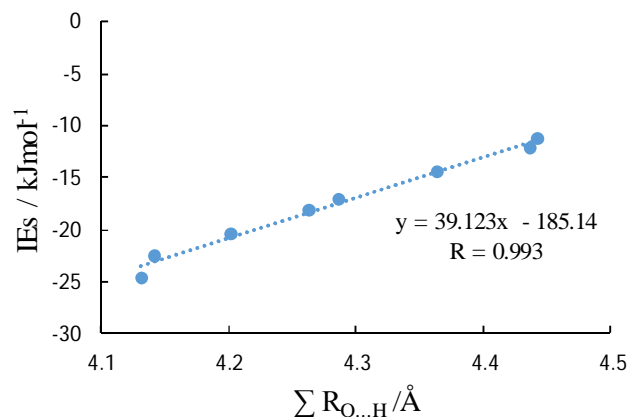

Fig. 2. Correlation between B3LYP/6-311++G** calculated electronic interaction energies (IEs) and sum of $O_{XN}\ldots H_{FU}$ and $O_{FU}\ldots H_{XN}$ distances (R) in the X-NU complexes.

greater is the elongation of the proton donating bond and the shorter is H…Y (Y is the proton acceptor) contact. Such situation is observed for the species studied here. There is a linear correlation between the sums of H-bonding energies (*i.e.* $\sum E_{HB}$) for $O_{FU}\ldots HC_{XN}$ (E_{HB1}) and $O_{XN}\ldots HN_{FU}$ (E_{HB2}) and sum of two H-bond distances $O_{FU}\ldots H_{XN}$ and $O_{XN}\ldots H_{FU}$ (*i.e.* $\sum R_{O\ldots H}$), the linear correlation coefficient is 0.991, with derived equation as:

$$\sum E_{HB} = 44.863 \sum R_{O\ldots H} - 219.6; \qquad (5)$$

where y corresponds to $\sum E_{HB}$ and x corresponds to sum of the H-bond distances ($\sum R_{O\ldots H}$). Here E_{HB} is a good description of the H-bond strength and reveals that the decrease in H-bond distances is accompanied by the reduction of H-bond energy values of corresponding intermolecular interactions.

Vibrational Frequencies

The geometric changes caused by the hydrogen-bonding formation are in line with the spectroscopic data. In assigning the calculated frequencies to approximate vibrational descriptor, the vibrational modes have been analyzed by means of the atom movements, calculated in Cartesian coordinates. Table 1 presents the stretching frequencies of the N(C)-H bond for the various X-NU complexes. The stretching frequency is calculated as a

difference between the frequency of the complex and the frequencies of isolated molecules. Inspection of the vibrational frequencies show that complex formation results in a marked change of vibrational frequency of N(C)-H (N and C atoms denotes donor) bonds involved in H-bonding. One can see the typical for conventional hydrogen bonds red-shift of the stretching mode with the exception of AlH-NU complex which indicates the blue-shift of C-H stretching vibrational frequency. The lengthening of the proton donating bond as an effect of the hydrogen-bonding formation is accompanied by this red shift of the corresponding mode. Our theoretical results show the greatest shifts for NH-NU, O-NU and S-NU complexes while the smallest shifts are observed for the other complexes. On the other hand, the amount of red-shift in the most stable complexes of X-NU are greater than that in other complexes. As a consequence, a substantial red-shift is observed for the fundamental N(C)-H stretching vibrational frequency. The red-shifts of N(C)-H stretching vibrational frequencies of FU monomer (and XN monomers) involved in interaction upon formation of the complexes are 3423.13 (3240.52) cm^{-1} for NH-NU, 3462.58 (3216.62) cm^{-1} for O-NU and 3477.94 (3200.16) cm^{-1} for S-NU at B3LYP/6-311++G** level of theory.

The results revealed that the red-shift of N(C)-H stretching frequencies of X-NU complexes relative to those of their monomers ($\Delta\upsilon$) is well correlated with the H-bond distances as a measure of strength of the $O_{FU}\ldots HC_{XN}$ and $O_{XN}\ldots HN_{FU}$ H-bonds. Therefore, vibrational frequencies can be easily evaluated from the H-bond distances, as follows:

$$\Delta\upsilon \text{ (N-H)}_{FU} = -505.84 \text{ dO}_{XN}\ldots HN_{FU} + 1118.6, \text{ R} = 0.986 \quad (6)$$

$$\Delta\upsilon \text{ (C-H)}_{XN} = -347.06 \text{ dO}_{FU}\ldots HC_{XN} + 807.59, \text{ R} = 0.975 \quad (7)$$

These red-shifted values reflect the strength of the H-bond interactions between the FU and various XN monomers. Our theoretical results also reveal that there is a linear relationship between the $O_{FU}\ldots HC_{XN}$ (E_{HB1}) and $O_{XN}\ldots HN_{FU}$ (E_{HB2}) H-bonding energies and their stretching modes. The corresponding correlation coefficients are equal
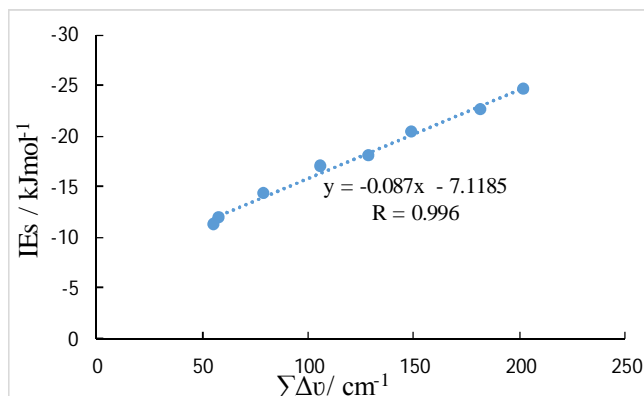

Fig. 3. Correlation between IEs and red-shift of N(C)-H stretching frequencies ($\Sigma\Delta\upsilon$) at B3LYP/6-311++G** level of theory.

to 0.934 and 0.999 with equations as:

$$E_{HB1} = -0.0846 \ \Delta\upsilon \text{ (C-H)} - 8.2573, \text{ R} = 0.934 \quad (8)$$

$$E_{HB2} = -0.1084 \ \Delta\upsilon \text{ (N-H)}_{FU} - 6.4904, \text{ R} = 0.999 \quad (9)$$
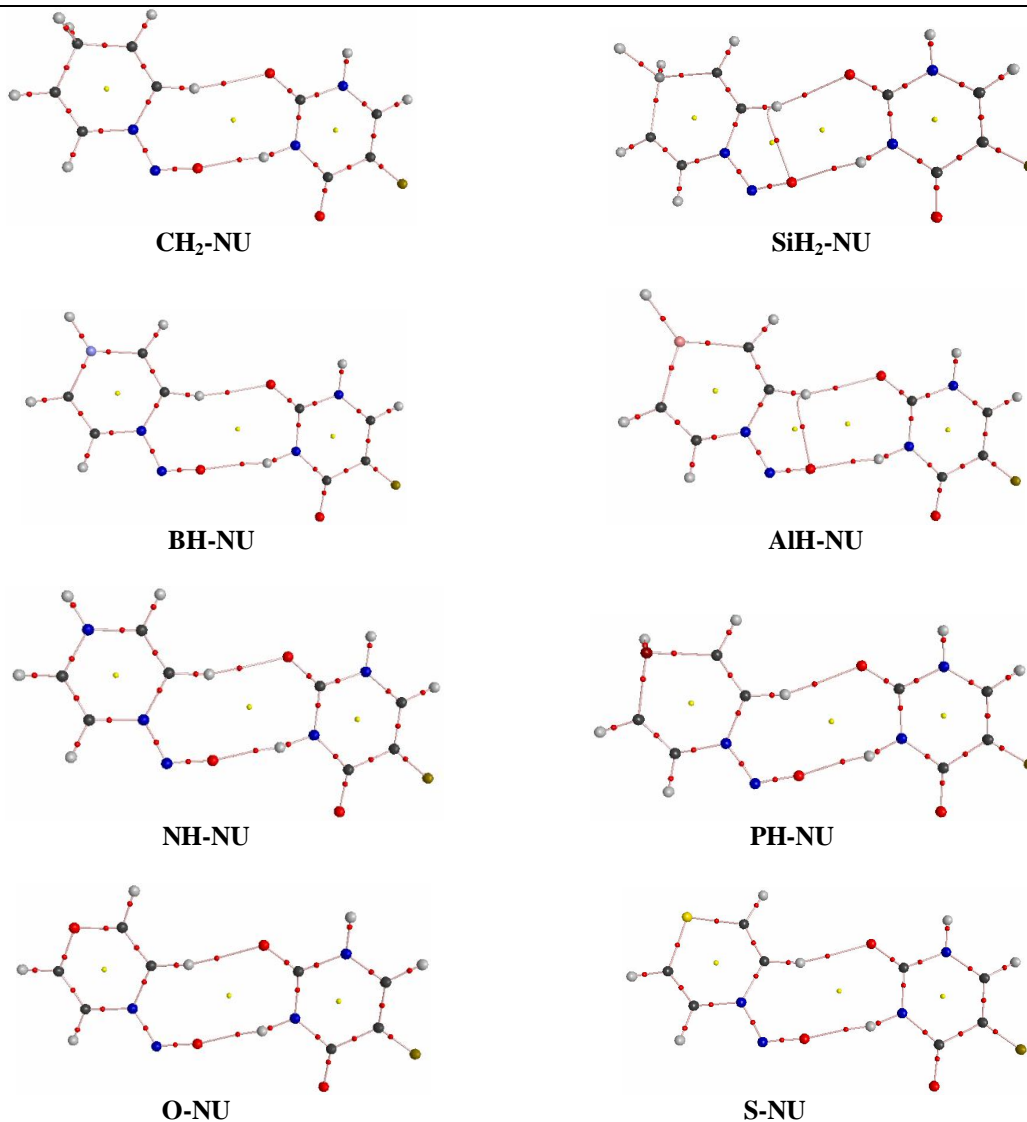
Furthermore, the results presented in Table 1 indicate a linear relationship between the sum of N(C)-H stretching frequencies ($\Sigma\Delta\upsilon$) and the interaction energies for the H-bonded complexes as a function of red-shift of υ with a good correlation coefficient 0.996 (see Fig. 3). Thus, stretching frequencies may be a useful parameter describing the interactions strength.

Aim Analysis

The calculated values of electron density, $\rho(r)$, Laplacian of electron density, $\nabla^2\rho(r)$, and electronic energy density, H(r), at the bond critical points (BCPs) at B3LYP/6-311++G** level of theory are listed in Table 3. The molecular graphs (including the critical points and bond paths) of all complexes are shown in Fig. 4. Besides, in all of the expected BCPs, the electron density reveals two additional BCPs in $O_{FU}\ldots HC_{XN}$ and $O_{XN}\ldots HN_{FU}$ distances and a ring critical point in intermolecular region. Therefore, interaction between FU and XN generates a cyclic system with a ring critical point (except for AlH-NU and SiH$_2$-NU complexes which create two cyclic systems with two ring

Table 3. The selected Topological Parameters of Investigated Complexes (in a.u.)

Complex	$O_{FU}...H-C_{XN}$					$O_{XN}...H-N_{FU}$						
	$\rho_{O...H}$	$\nabla^2_{\rho\,O...H}$	H(r)	G(r)	V(r)	$\rho_{O...H}$	$\nabla^2_{\rho\,O...H}$	H(r)	G(r)	V(r)	ρ_{RCP}	$\nabla^2\rho_{RCP}$
CH$_2$-NU	0.0123	0.0427	0.0017	0.0090	-0.0073	0.0183	0.0827	0.0032	0.0174	-0.0142	0.0040	0.0163
SiH$_2$-NU	0.0119	0.0405	0.0016	0.0085	-0.0069	0.0152	0.0686	0.0030	0.0141	-0.0111	0.0039	0.0163
BH-NU	0.0116	0.0401	0.0016	0.0084	-0.0068	0.0126	0.0560	0.0027	0.0113	-0.0086	0.0037	0.0155
AlH-NU	0.0108	0.0360	0.0015	0.0075	-0.0060	0.0143	0.0648	0.0030	0.0132	-0.0103	0.0039	0.0160
NH-NU	0.0136	0.0479	0.0018	0.0102	-0.0084	0.0226	0.1005	0.0032	0.0219	-0.0188	0.0042	0.0172
PH-NU	0.0128	0.0443	0.0017	0.0094	-0.0077	0.0168	0.0757	0.0032	0.0158	-0.0126	0.0040	0.0166
O-NU	0.0146	0.0526	0.0019	0.0113	-0.0094	0.0199	0.0894	0.0032	0.0191	-0.0159	0.0042	0.0170
S-NU	0.0138	0.0488	0.0018	0.0104	-0.0087	0.0187	0.0844	0.0033	0.0178	-0.0146	0.0042	0.0173

CH$_2$-NU

SiH$_2$-NU

BH-NU

AlH-NU

NH-NU

PH-NU

O-NU

S-NU

Fig. 4. Molecular graphs of the X-NU complexes. Nuclei and critical points (bond and ring) are represented by big and small circles, respectively.

critical points in intermolecular region). For AlH-NU and SiH$_2$-NU complexes, the obtained results clearly show an additional BCP between two oxygen (O) and hydrogen (H) atoms in nitrosamine monomer. The values of ρ_{BCP} and $\nabla^2\rho_{BCP}$, at these BCPs, are about 0.0200 and 0.0878 au for SiH$_2$-NU complex and 0.0211 and 0.0902 au for AlH-NU, respectively, which suggest the presence of a relatively strong interaction (see Fig. 4).

The electron density, $\rho(r)$, at the O$_{FU}$…HC$_{XN}$ H-bond CP (HBCP) varies from 0.0108 to 0.0146 au. The values of $\rho(r)$ also change from 0.0126 to 0.0226 au at the O$_{XN}$…HN$_{FU}$ HBCPs in the mentioned complexes. These values are within the range determined for the H-bonded complexes, which typically varies from 0.002 to 0.04 au [27]. As can be seen, the electron density for the O$_{FU}$…HC$_{XN}$ interactions are sensibly lower than those of the O$_{XN}$…HN$_{FU}$ ones in agreement with the smaller O$_{XN}$…HN$_{FU}$ H-bond distances compared to the O$_{FU}$…HC$_{XN}$ ones. Thus, O$_{XN}$…HN$_{FU}$ interaction in all complexes is stronger than that in O$_{FU}$…HC$_{XN}$. Furthermore, our theoretical results reveal that the sums of electron densities at both HBCPs are greater for NH-NU complex than other ones. There is a relationship between the B3LYP/6-311++G** calculated IEs and the sum of $\rho(r)$ at the O$_{FU}$…HC$_{XN}$ and O$_{XN}$…HN$_{FU}$ HBCPs. This dependency is illustrated in Fig. 5. This curve represents that the higher electron densities at the HBCPs are accompanied by the lower IEs.

The Laplacian of electron density, $\nabla^2\rho(r)$, varies from 0.0360 au to 0.0526 au at the O$_{FU}$…HC$_{XN}$ HBCP and 0.0560 au to 0.1005 au at O$_{XN}$…HN$_{FU}$ HBCP. These values are in the typical range of $\nabla^2\rho(r)$ (0.020-0.139 au) for the HB interactions. Investigating $\nabla^2\rho(r)$ in Table 3, we found a relationship between the B3LYP/6-311++G** calculated IEs and the sum of $\nabla^2\rho(r)$ at the O$_{FU}$…HC$_{XN}$ and O$_{XN}$…HN$_{FU}$ HBCPs (see Fig. 6). Data show that the largest $\nabla^2\rho(r)$ corresponds to the HBCPs in the most stable complex NH-NU. HBCP in BH-NU has the smallest $\nabla^2\rho(r)$.

The values of H(r) range from 0.0015 au to 0.0019 au at the O$_{FU}$…HC$_{XN}$ HBCP and 0.0027-0.0033 au at the O$_{XN}$…HN$_{FU}$ HBCP. As expected for closed-shell or weak interactions, the Laplacian of the electron density at HBCPs is positive, indicating a depletion of electron density from the interatomic surface toward the interacting nuclei. In
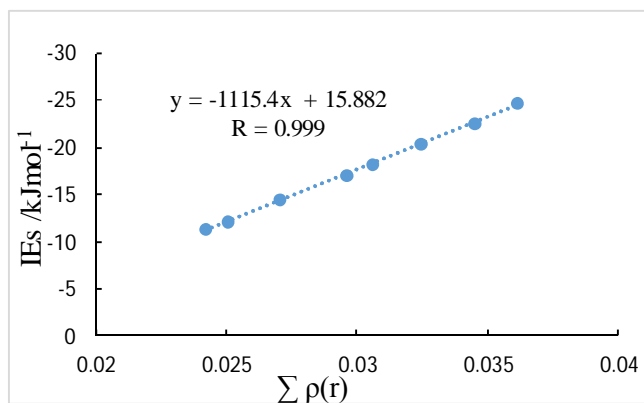

Fig. 5. Relationship between the B3LYP/6-311++G** calculated IEs and the sum of $\rho(r)$ at the O$_{XN}$…HN$_{FU}$ and O$_{FU}$…HC$_{XN}$ HBCPs.

accordance with small electron densities, positive values of $\nabla^2\rho(r)$ and H(r) at HBCPs indicate that the nature of the H-bonding in all complexes is electrostatic.

Another topic analyzed here is the existence of the ring critical point (RCP) for closed configurations. It has been mentioned recently that for the intermolecular H-bond, there is a correlation between the electron density at the bond critical point corresponding to the contact within the H-bridge and the electron density at the RCP [28]. For the systems investigated there are also good correlations among these parameters (*e.g.* ρ_{RCP} or $\nabla^2\rho_{RCP}$ and $\sum \rho_{O…H}$) with correlation coefficients of 0.941 and 0.914, respectively. Moreover, our theoretical results confirm that there is another correlation between ρ_{RCP} or $\nabla^2\rho_{RCP}$ and $\sum E_{HB}$ with correlation coefficients of 0.921 and 0.894, respectively, yielding the following relationship:

$$\sum E_{HB} = -30291\, \rho_{RCP} + 94.135 \tag{10}$$

$$\sum E_{HB} = -7891.4\, \nabla^2\rho_{RCP} + 102.9 \tag{11}$$

Our theoretical results also show that there are linear relationships between $\sum E_{HB}$ and sum of the two total energy of electrons (H) and its two components (G and V). The dependency between the $\sum E_{HB}$ and sum of H$_{RCP}$, G$_{RCP}$ and V$_{RCP}$ is given as follows:

$$y = -16985\ (-1238.4, 1313.1)\, x\ + 54.107\ (4.3758, 0.0073)$$

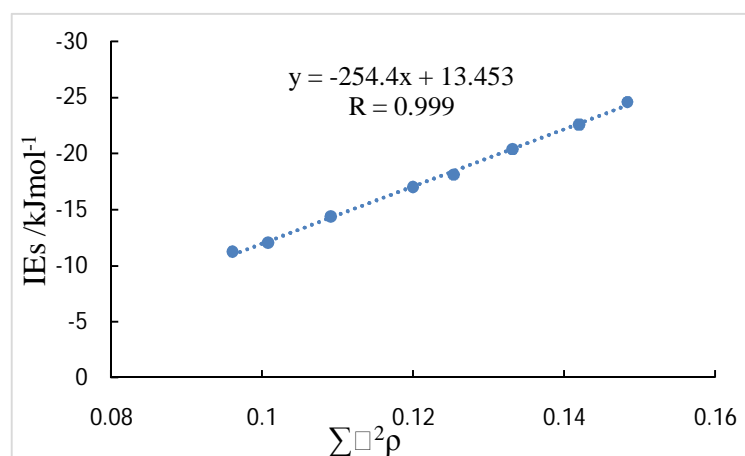$$R = 0.909\ (0.999, 1) \tag{12}$$

Fig. 6. Relationship between the B3LYP/6-311++G** calculated IEs and the sum of $\nabla^2\rho(r)$ at the $O_{XN}\cdots HN_{FU}$ and $O_{FU}\cdots HC_{XN}$ HBCPs.

Table 4. $E^{(2)}$ Corresponds to Charge Transfer Between the Oxygen Lone Pair and σ*C(N)-H Antibonds (in kcal mol^{-1}), Occupation Numbers (ON) of Mentioned Orbitals and the Charge Transfers (Q_{CT} in e) Computed at the B3LYP/6-311++G** Level of Theory

Complex	LP(O)$_{FU}$ → σ*(C-H)$_{XN}$	ON$_{(LP\,O)}$	ON$_{(σ*C-H)}$	LP(O)$_{XN}$ → σ*(N-H)$_{FU}$	ON$_{(LP\,O)}$	ON$_{(σ*\,N-H)}$	Q$_{CT}$
CH$_2$-NU	1.98	1.8453	0.0220	6.15	1.9785	0.0254	-0.065
SiH$_2$-NU	1.79	1.8445	0.0278	4.39	1.9813	0.0218	-0.052
BH-NU	1.66	1.8441	0.0259	3.10	1.9839	0.0193	-0.050
AlH-NU	1.44	1.8437	0.0320	3.94	1.9817	0.0209	-0.048
NH-NU	2.40	1.8466	0.0199	8.78	1.9734	0.0308	-0.064
PH-NU	2.08	1.8452	0.0268	5.24	1.9799	0.0236	-0.059
O-NU	2.66	1.8468	0.0212	7.08	1.9767	0.0273	-0.067
S-NU	2.43	1.8461	0.0256	6.33	1.9780	0.0256	-0.057

where y corresponds to $\sum E_{HB}$ and x corresponds to sum of the H_{RCP} (G_{RCP}, V_{RCP}) in kJ mol^{-1}. These imply that the properties of the ring critical point values could be very useful to estimate the strength of the intermolecular hydrogen bond. Their values permit us to have a better understanding of these novel correlations. The derived relationships from these correlations empower us to acquire other physically meaningful results.

Nbo Analysis

The formation of a hydrogen bond implies that a certain amount of the electronic charge is transferred from the proton acceptor to the proton donor molecule [29]. For several typical H-bonded systems, it has been demonstrated that the charge is transferred from the lone pairs of the proton acceptors to the antibonding orbitals of the proton donor [30]. The results of NBO analysis including charge transfer energy and the occupancy of NBOs in the complexes at B3LYP/6-311++G** level of theory are given in Table 4.

The NBO results show that the LP(O)$_{FU}$ → σ*(C-H)$_{XN}$ and LP(O)$_{XN}$ → σ*(N-H)$_{FU}$ donor-accep tor interactions are
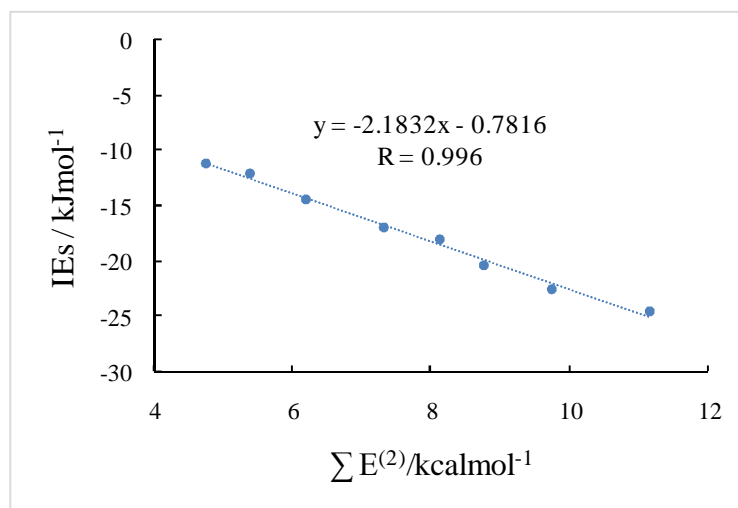
Fig. 7. Relationship between the IEs calculated at B3LYP/6-311++G** level and sum of charge transfer energies $E^{(2)}$ correspond to the $LP(O)_{FU} \rightarrow \sigma*(C-H)_{XN}$ and $LP(O)_{XN} \rightarrow \sigma*(N-H)_{FU}$ interactions in the X-NU complexes.
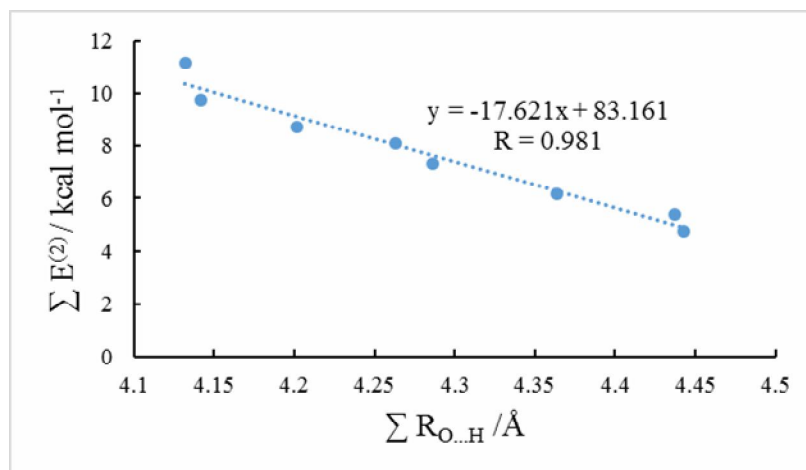

Fig. 8. Relationship between the sum of charge transfer energies $E^{(2)}$ and corresponding H-bonding distances at B3LYP/6-311++G** level of theory.

the most important ones. Sum of charge transfer energies $E^{(2)}$ corresponding to these interactions are 8.13, 6.18, 4.76, 5.38, 11.18, 7.32, 9.74 and 8.76 kcal mol^{-1} in CH_2-NU, SiH_2-NU, BH-NU, AlH-NU, NH-NU, PH-NU, O-NU and S-NU complexes, respectively. As can be seen, sum of charge transfer energies for NH-NU, O-NU and S-NU complexes are greater than that for the other ones. Sum of charge transfer energies for NH-NU is the greatest and that for BH-NU is the smallest. Figure 7 shows a linear

relationship between the IE and the sum of the energies of $LP(O)_{FU} \rightarrow \sigma*(C-H)_{XN}$ and $LP(O)_{XN} \rightarrow \sigma*(N-H)_{FU}$ donor-acceptor interactions in studied complexes. Increase in charge transfer energy is accompanied by the decrease in the values of interaction energy. Figure 8 depicts the relationship between the charge transfer energies $E^{(2)}$ and the H-bonding distances. This figure reveals that the increase in bond distance is accompanied by the decrease in $E^{(2)}$ of corresponding intermolecular interaction.

Furthermore, a comparison between the results of E_{HB} in Table 1 and $E^{(2)}$ in Table 4 shows that there is a linear relationship between values $\sum E_{HB}$ and $\sum E^{(2)}$. The corresponding correlation coefficient amounts to 0.998 (with equation as: $\sum E_{HB} = -2.5149 \sum E^{(2)} - 8.1063$).

The binding of FU to various XN compounds can be also explained by the amount of charge transfer. Charge transfer (Q_{CT}) term corresponds to the shift of electron charge between interacting subunits. Here, the charge transfer has been defined as the difference between the sums of the natural charges of each subunit. In addition, the values of charge transfer evaluated through natural population analysis are collected in Table 4. The reported values of Q_{CT} indicate that the amount of charge transfer depends on the nature of various XN π-systems. Population analysis shows that the charge transfer taking place from various XN monomers to FU in all complexes. In studied complexes, the large variation of charge values on X atoms (X = C, Si, B, Al, N, P, O and S) at different XN π-systems can be justified by large value of charge transfer from XN monomer to FU one in NH-NU, O-NU and CH_2-NU complexes. As a result, it is interesting to note that the obtained results at the NBO basis are completely accordant with the results obtained in the AIM framework.

CONCLUSIONS

The quantum chemical calculations at B3LYP/6-311++G** level of theory is carried out to examine the structural, energetic, vibrational and topological features of the X-NU complexes. All complexes have doubly hydrogen bonding. In all studied systems, fluorouracil is donating a H-bond to the oxygen of various nitrosamine compounds, while in the nitrosamine, the H-bond is donated to the oxygen of the CO moiety in fluorouracil. Frequency, NBO and AIM analyses show that all $O_{FU}\cdots HC_{XN}$ and $O_{XN}\cdots HN_{FU}$ contacts are proper H-bonds. The $O_{XN}\cdots HN_{FU}$ H-bond energy for these complexes is smaller than the $O_{FU}\cdots HC_{XN}$ H-bond energy. The results obtained from DFT calculations and the topological parameters derived from the Bader theory suggest that the strongest interaction and the highest electron density at BCP are related to the NH-NU complexes, while the weakest interaction and the smallest electron density at the BCP correspond to the BH-NH

complex. Moreover, the calculated electron density properties show that these interactions have low ρ and are also characterized by positive ($\nabla^2 \rho_{BCP}$) values showing that these properties are typical for closed shell interaction.

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