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MOLECULAR MODELLING, DIMER CALCULATIONS, VIBRATIONAL SPECTRA, AND MOLECULAR DOCKING STUDIES OF 5-CHLOROURACIL

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The structure and vibrational calculations of 5-chlorouracil (5-ClU) and its most stable dimer have been analyzed using the DFT method with B3LYP/6-31++G(d,p) and wb97xd/6-31++G(d,p), respectively. Vibrational calculations of the monomeric and dimeric forms were performed using both harmonic and anharmonic oscillator approximations with the same basis sets. A complete vibrational analysis of the molecule has been performed by combining experimental Raman, FT-IR spectral data and quantum chemical calculations. In addition, the DNA docking analysis of 5-ClU molecule was performed. 5-ClU molecule binds to the active site of DNA by hydrogen bonding interactions. The results show that the docked ligand formed a stable complex with DNA with binding affinity of –5.3 kcal/mol.

Keywords: *5-chlorouracil, dimeric structure, molecular docking, density functional theory, vibrational spectroscopy.*

МОЛЕКУЛЯРНОЕ МОДЕЛИРОВАНИЕ, РАСЧЕТЫ ДИМЕРА, КОЛЕБАТЕЛЬНЫЕ СПЕКТРЫ И ИССЛЕДОВАНИЕ МОЛЕКУЛЯРНОГО ДОКИНГА 5-ХЛОРУРАЦИЛА

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Методом теории функционала плотности (DFT) в приближении B3LYP/6-31 ++ G(d, p) и wb97xd/6-31 ++ G(д, р) осуществлены расчеты структуры и колебаний 5-хлорурацила (5-ClU) и его наиболее стабильного димера. Колебательные расчеты мономерной и димерной форм проводились с использованием приближений гармонического и ангармонического осцилляторов с одинаковыми базисными наборами. Полный колебательный анализ молекулы выполнен путем объединения данных комбинационного рассеяния, ИК-Фурье-спектроскопии и квантово-химических расчетов. Проведен анализ докинга ДНК с молекулой 5-ClU. Молекула 5-ClU связывается с активным центром ДНК посредством водородных связей. Показано, что закрепленный лиганд образует стабильный комплекс с ДНК со сродством связывания –5.3 ккал/моль.

Ключевые слова*: 5-хлорурацил, димерная структура, молекулярная стыковка, теория функционала плотности, колебательная спектроскопия.*

Introduction. As inhibitors of nucleic acid metabolism and as clinical radiosensitizers of DNA in tumor cells, substituted uracils show significant biological properties [1]. Among the 5-substituted uracils, the 5-halogenated uracils receive more attention since they exhibit pharmacological activities and so are used in antitumor, antibacterial, and antiviral drugs [2]. The 5-fluorouracil (5-FU) analog is a well-known anticancer drug for treatment of human malignancies, whereas 5-chlorouracil (5-ClU) is associated with inflammation [3] and has some antitumor properties. If the halogen atom is in position 5 on the uracil ring and if the methyl group is replaced by halogen atom, the structure is similar to that of thymine (T), indicating that 5-halogenated uracils may replace T in DNA *in vivo* easily [4].

Dobrowolski et al. interpreted the Ar-Matrix IR spectra of 5-halouracils by means of DFT/B3PW91/6-311G(d,p) calculations [5]. Dobrosz-Teperek et al. studied the vibrational spectra of 5-halouracils with the help of both HF/3-21G(d,p) and MP2/3-21G(d,p) levels on some selected frequencies [2]. Ortiz et al. carried out Raman and FT-IR study of 5-ClU and simulated the crystal structure as a tetramer form by density functional calculations [4]. Sun et al. studied both the equilibrium structures of the three 5-halogenated uracils and many of their excited-state properties like vertical excitation energies and the corresponding oscillator strengths of the first three singlet excited states [6]. Ortiz et al. studied the molecular structure, tautomerism, and solid-state simulation of 5- and 6- ClU together with their FT-IR and FT-Raman spectra [1]. Ten et al. calculated the relative Raman intensities of the title molecule via quantum chemical calculations [7]. Singh studied the FT-IR and Raman frequencies of 5-halosubstituted uracils [8]. Elkin et al. studied the vibrational wavenumbers of CH_3, NH_2, F, and Cl substituted uracil molecules both in their monomeric and dimeric forms by using the DFT/B3LYP method with adiabatic potential parameters [9].

Molecular docking is an important tool in molecular biology and computer-aided drug design. A study in 1993 by Morris et al. has shown that 5-ClU accumulation in DNA leads to sister chromatid exchanges and mutations [10]. Jiang et al. in 2003 found that chronic inflammation-mediated accumulation of modified bases may be related to cancer development [11]. In addition, the metal complex of the 5-ClU molecule has been synthesized by Rastrogi et al. because metal complexes function as antitumor agents against many types of tumors by inhibiting DNA and protein synthesis [12].

Although vibrational analysis has been done with different methods of calculation on the title molecule as a monomer, there is no structural and vibrational study on the dimers of the molecule except [9] where the calculations have been done with DFT/B3LYP method using adiabatic potential parameters, and only harmonic wavenumbers of some modes for the dimeric structure have been given. In this study, we calculated the energies for possible dimers of the title molecule and found the most stable dimeric structure and then we calculated vibrational wavenumbers using both harmonic and anharmonic oscillator approximations.

HOMO-LUMO analysis on this molecule have been studied relatively little and there is no molecular docking study on 5-ClU.

Experimental and computational details. *Experimental studies.* KBr disc of the sample was recorded on a Bruker Tensor 27 FT-IR spectrometer (1 cm^{-1} resolution) between 400 and 4000 cm^{-1} region. A Jasco NRS 3100 Raman spectrometer equipped with CCD detector was used for recording the micro-Raman spectra (1800 lines/mm grating) with the laser operating at 532 nm as the excitation source. All measurements were performed at room temperature in back-scattering geometry. The spectral resolution was 4.38 cm^{-1}.

Method of calculation. All calculations were performed using Gaussian 03 program [13]. The molecular structure of 5-ClU molecule as a monomer was optimized by using density functional theory (DFT) with Becke's three-parameter exchange functional and the gradient-corrected functional of Lee, Yang, and Parr, known as B3LYP [14]. For his purpose an initial geometry of the molecule was taken and optimized at DFT level with the 6-31++G(d,p) basis set. The optimized geometry was then used to calculate harmonic frequencies of the isolated molecule together with anharmonic corrections to these frequencies at the same theory level. The potential energy distribution (PED) analysis for the title molecule was done by the VEDA program [15]. HOMO-LUMO energies were also calculated by the same theory level. Docking analysis of 5-ClU molecule was performed by the AutoDock Vina program [16].

By combining two optimized monomers of the title molecule, all possible dimeric structures were formed as training dimers, and these dimeric structures (Fig. 1) were optimized using both B3LYP and wb97xd functionals with the 6-31++G(d,p) basis set. In this way we obtained nine different dimeric forms and optimized these structures by the DFT/wb97xd/6-31++G(d,p) method. Among them, the lowest energy form was chosen (dimer III) and vibrational wavenumbers of this form was calculated with the same method and basis set. The wb97xd is a hybrid functional [17, 18] that considers dispersion interaction as well as long and short range interactions in order to take into account the weak noncovalent interactions like charge transfer interactions and van der Waals interactions.

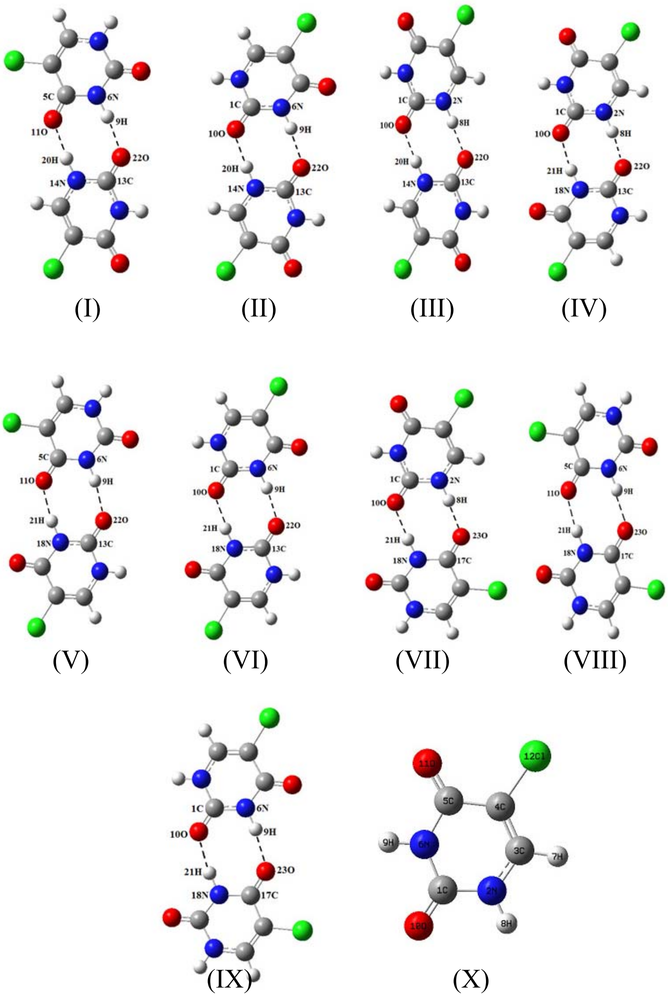
Results and discussion. *Molecular geometry.*The structural model and atom numberings of the 5-ClU molecule and its studied dimers are given in Fig 1. Table 1 gives the optimized structural parameters and corresponding experimental values of Sternglanz and Bugg [19] for monomeric and dimeric 5-ClU molecule. The calculated structural parameters are in accordance with the experimental data.

TABLE 1. Optimized Geometry Parameters (*R* in Å and *A* in degree) of 5-ClU and its Most Stable Dimer Compared to the Available Experimental Data

Atoms	Exp. Ref. [19]	Monomer B3LYP/ 6-31++G(d,p)	Dimer-III B3LYP/ 6-31++G(d,p)	Dimer-III wb97xd/ 6-31++G(d,p)
R (1,2)	1.363	1.391	1.373	1.366
R (1,6)	1.359	1.386	1.376	1.371
R (1,10)	1.227	1.219	1.238	1.232
R (2,3)	1.374	1.377	1.374	1.371
R (2,8)	1.03	1.011	1.034	1.033
R (3,4)	1.370	1.353	1.355	1.348
R (3,7)	0.96	1.083	1.083	1.083
R (4,5)	1.423	1.472	1.467	1.466
R (4,12)	1.715	1.733	1.733	1.724
R (5,6)	1.386	1.408	1.414	1.406
R (5,11)	1.238	1.218	1.217	1.211
R (6,9)	0.85	1.014	1.014	1.013
R (10,20)	1.99;1.77		1.775	1.757
R (8,22)	1.99;1.77		1.776	1.757
A (2,1,6)	115.4	112.9	114.6	114.8
A (2,1,10)	122.2	123.0	123.2	123.2
A (6,1,10)	122.5	124.1	122.2	122.0
A (1,2,3)	123.4	123.9	122.8	122.7
A (1,2,8)		115.3	116.5	116.7
A (3,2,8)		120.8	120.7	120.6
A (2,3,4)	119.3	121.5	121.9	121.9
A (2,3,7)		116.2	115.7	115.6
A (4,3,7)		122.4	122.4	122.4
A (3,4,5)	120.6	120.2	120.1	120.0
A (3,4,12)	120.6	121.5	121.7	121.8
A (5,4,12)	118.8	118.2	118.2	118.2
A (4,5,6)	114.9	112.8	112.5	112.6
A (4,5,11)	125.7	126.3	127.1	126.9
A (6,5,11)	119.4	120.9	120.5	120.6
A (1,6,5)	126.4	128.7	128.1	127.9
A (1,6,9)		115.5	116.2	116.2
A (5,6,9)		115.8	115.8	115.9

With the help of molecular electrostatic potential (MEP) analysis (Fig. 2), two optimized monomeric structures of the 5-ClU molecule have been combined to form the possible dimeric structures of the molecule. As the initial dimeric forms, the H-bonded structures given in Fig. 1 have been chosen. The optimal structures for these dimers have been obtained by both B3LYP and wb97xd methods using the 6-31++G(d,p) basis set. The calculated intermolecular H…O distances for these dimers are in the range of 1.775 –1.870 Å for B3LYP and 1.757 –1.838 Å for wb97xd. With dimerization, the elongation of the C=O bond is about 0.019 Å by B3LYP and 0.022 Å by wb97xd methods, and the elongation of the N-H bond is about 0.023 Å by B3LYP and 0.022 Å by wb97xd methods.

The relative and interaction energies of 5-ClU dimers (I–IX) are given in Table 2. As seen in this table, the lowest relative energy value belongs to dimer III. In this form, the H atom of the N-H group of 5ClU is involved in the H-bonding interaction with the O atom of the other 5ClU molecule, while the second H-bonding interaction occurs between the O atom of the first molecule and the H atom of the N-H group of the second molecule. As expected, the NH (N_2-H_8) and C-O (C_1-O_{10}) bonds that are involved in intermolecular H-bonding are affected by dimerization, whereas N_6-H_9 and C_5-O_{11} bonds that are not involved in hydrogen bonding are not.



(I) (II) (III) (IV)

(V) (VI) (VII) (VIII)

(IX) (X)

Fig 1. Numbering scheme used in this study and calculated monomeric and dimeric structures of 5-ClU molecule by DFT method.

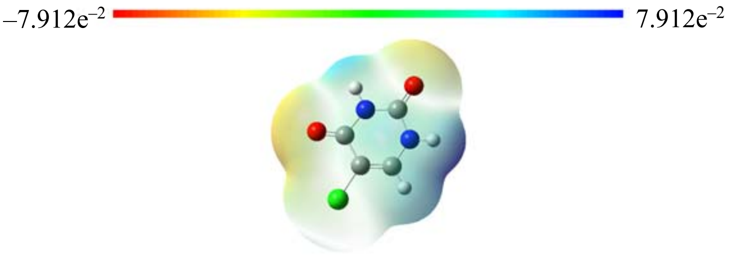


Fig 2. Molecular electrostatic potential (MEP) of 5-ClU molecule obtained by DFT/B3LYP/ 6-31++G(d,p) method.

When the optimized structural parameters and relative and interaction energies of the dimers I–IX are analyzed, it is determined that the dimers 1 and 7, 2 and 4, and 5 and 9 were symmetrically equivalent.

The interaction energies ($\Delta E = E_{\text{dimer}} - 2E_{\text{monomer}}$) of 5-ClU dimer-III are found to be –19.28 kcal/mol and –21.78 kcal/mol for the B3LYP/6-31++G(d,p) and wb97xd/6-31++G(d,p) methods, respectively. The dispersion correction contributes to the interaction energy significantly [20].

TABLE 2. Relative and Interaction Energies of the Dimers of 5-ClU (I–IX) Calculated by B3LYP/6-31++G(d,p) and wb97xd/6-31++G(d,p) Methods

Dimer	B3LYP/6-31++G(d,p)		wb97xd/6-31++G(d,p)	
	Relative energy of dimers (kcal/mol)	$\Delta E = E_{\text{dimer}} - 2E_{\text{mon}}$ (kcal/mol)	Relative energy of dimers (kcal/mol)	$\Delta E = E_{\text{dimer}} - 2E_{\text{mon}}$ (kcal/mol)
I	2.83	–16.45	2.81	–18.98
II	3.78	–15.49	3.75	–18.03
III	0.00	–19.28	0.00	–21.78
IV	3.78	–15.49	3.75	–18.03
V	6.46	–12.81	6.48	–15.30
VI	6.53	–12.75	6.50	–15.29
VII	2.83	–16.45	2.81	–18.98
VIII	6.18	–13.10	6.24	–15.54
IX	6.46	–12.81	6.48	–15.30

Molecular electrostatic potential. The molecular electrostatic potential surface (MEPs) of 5ClU is shown in Fig 2. The color code of this map is between –2.153 V (deepest red) and 2.153 V (deepest blue). The blue color indicates the minimum concentration of electrons, while the red color indicates the maximum concentration of electrons. According to these calculated results, the MEP map illustrates that regions with negative potential are concentrated on oxygen, whereas regions with positive potential are concentrated on hydrogen atoms of NH and CH groups. These active regions are clear evidence of biological activity in the title compound.

Vibrational analysis. The 5-ClU molecule contains 12 atoms and therefore has 30 modes of vibration. The calculated and experimental wavenumbers for these modes and their tentative vibrational assignments are presented in Table 3. These assignments were done based on calculated potential energy distributions (PED) and animated modes using Gaussian View [13]. The PED values are also given in Table 3. Figure 3 presents experimental IR and Raman spectra together with simulated IR and Raman spectra, which are plotted using Lorentzian band shapes (FWHM is 10 cm^{-1}).

TABLE 3. Comparison of the Calculated Harmonic and Anharmonic Wavenumbers with the Experimental Ar-matrix IR, Solid State IR, and Raman Spectra of 5-ClU Molecule Together with Calculated PED Values

No.	Ar matrix [5]	Solid (this study)		Monomer B3LYP/6-31++G(d,p)		Dimer III wb97xd/6-31++G(d,p)		PED%(≥10%)
		Raman	IR	Harm	Anh	Harm	Anh	
ν_1	3472	nd	3211	3646	3472	3303;3253	3009;2995	νNH(100)
ν_2	3426	nd	3171	3604	3443	3655;3655	3450;3448	νNH(100)
ν_3	–	3055	3060	3237	3088	3268;3268	2941;2942	νCH(100)
ν_4	1764	1712	1711	1810	1775	1809;1797	1757;1760	νCO(72)
ν_5	1729	1677	1682	1781	1749	1843;1841	1808;1812	νCO(79)
ν_6	1641	1625	1631	1675	1637	1719;1719	1678;1680	νring(67) + δCH(16)
ν_7	1461	1489	1490	1493	1457	1584;1580	1597;1581	δCH(42)+νring(25)+νCO(11)+δring(11)
ν_8	1393	1448	1442	1412	1374	1424;1423	1408;1407	δNH(26) + νring(22) + δring(10)
ν_9	1387	1407	1405	1401	1364	1493;1488	1468;1457	δring(54) + νring(23) + δCO(10)
ν_{10}	1333	1340	1340	1348	1324	1382;1379	1353;1352	δCH(49) + νring(20)
ν_{11}	1186	1227	1230	1198	1169	1264;1263	1251;1245	νring(45) + δNH(45)
ν_{12}	1161	1188	1184	1175	1147	1223;1220	1193;1189	νring(67) + δNH(10)
ν_{13}	1073	1083	1088	1079	1059	1107;1104	1086;1083	δring(50) + νCCl(23)
ν_{14}	964	943	945	973	956	1018;1010	1009;999	νring(32) + δring(29) + δNH(12)
ν_{15}	896	nd	866	909	896	933;932	906;903	γCH(79) + γring(10)
ν_{16}	nd	786	783	778	760	800;800	798;778	νring(37) + δring(33)
ν_{17}	758	754	757	757	750	763;763	757;756	γCO(86) + γCCl(11)
ν_{18}	751	nd	744	736	746	753;750	773;775	γCO(92)
ν_{19}	657	669	667	668	662	676;676	608;607	γNH(87)
ν_{20}	653	nd	680	662	651	686;680	676;667	δring(45) + νCCl(25)
ν_{21}	-	618	622	604	598	627;623	626;624	δCO(43) + δCCl(17) + δring(15)
ν_{22}	546	550	549	557	570	900;860	866;821	γNH(91)

Continue Table 3

No.	Ar matrix [5]	Solid (this study)		Monomer B3LYP/6-31++G(d,p)		Dimer III wb97xd/6-31++G(d,p)		PED%(≥10%)
		Raman	IR	Harm	Anh	Harm	Anh	
ν_{23}	533	nd	526	539	532	560;557	564;558	νring(26) + δCO(26) + δring(16)
ν_{24}	–	nd	447	404	401	445;423	458;421	δCO(41) + δring(14) + νCCl(14)
ν_{25}	–	425	418	384	389	401;400	392;393	γring(44) + γCH(18) + γCO(12)
ν_{26}	–	375	or	361	358	373;373	371;370	νCCl(23)+δCO(18)+δring(17)+νCN(12)
ν_{27}	–	323	or	289	292	308;307	315;313	γCCl(67) + γring(27)
ν_{28}	–	237	or	227	226	237;234	232;228	δCCl(73) + δring(10)
ν_{29}	–	nd	or	149	155	178;164	176;161	γring(93)
ν_{30}	–	nd	or	96	98	113;101	110;91	γring(91)

N o t e. nd: not determined, or: out of range.

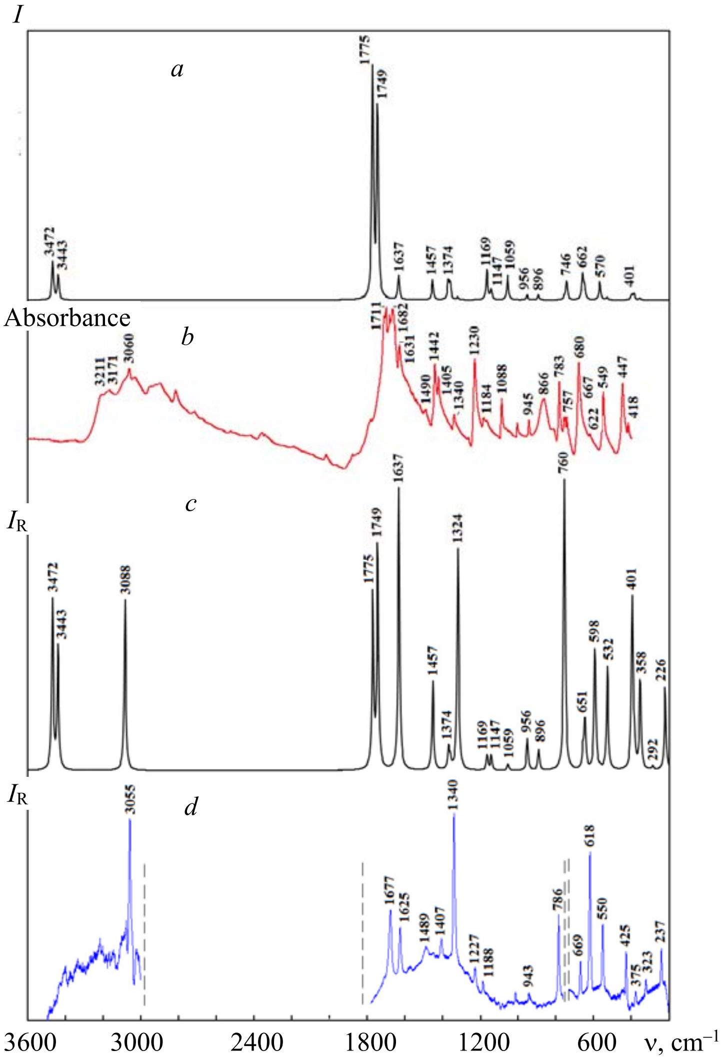


Fig. 3. Calculated (a, c) and experimental (b, d) IR spectra (a, b) and Raman spectra (c, d) of 5-ClU molecule.

N-H Vibrations. N-H stretching vibrations appear in the 3000–3500 cm^{-1} range in heterocyclic compounds, and they are pure vibrations. The PED for the two N-H stretching vibrations are both 100%. Ortiz et al. [4] have computed ν_{NH} frequencies for isolated 5-ClU with anharmonic corrections to be 3483 and 3434 cm^{-1}, and have assigned the frequency 3060 cm^{-1} in the IR spectrum to one of the ν_{NH} vibrations. Singh [8] has assigned the frequencies 3180 and 3160 cm^{-1} in the IR spectrum (nujol mull) and 3155 cm^{-1} in the Raman spectrum to ν_{NH} vibrations. Dobrosz-Teperek et al. [2] have reported the assignment for these modes at 3211 and 2718 cm^{-1} in the IR spectrum and at 3230 and 2823 cm^{-1} in the Raman spectrum, and they have calculated these modes to be 3542 and 3507 cm^{-1} by using the HF method. Dobrowolski et al. studied the Ar matrix IR spectrum of 5-ClU and have assigned the bands at 3472 and 3426 cm^{-1} to these vibrations, while they have calculated the anharmonic frequencies for the same modes to be 3481 and 3455 cm^{-1} by using B3PW91/6-311G(d,p) [5]. Elkin et al. have calculated these frequencies to be 3458 and 3438 cm^{-1} for the monomeric 5-ClU molecule and 3421, 3109, 3064, 3466, 3189, 3161, 3458, 3155, and 3122 cm^{-1} for various dimeric structures [9].

In this study, we have assigned the bands at 3211 and 3171 cm^{-1} in the solid IR spectrum to ν_{NH} vibrations and have calculated the anharmonic frequencies for these modes to be 3472 and 3443 cm^{-1} using B3LYP/6-31++G(d,p). For the dimer these modes have been calculated to be 3450, 3448, 3009, and 2995 cm^{-1} using wb97xd/6-31++G(d,p). The δ_{NH} vibrations are not pure, they are mostly mixed with ν_{ring} vibrations. The γ_{NH} vibrational modes are pure, and the anharmonic calculated frequencies are well in accord with the experiment (Ar-matrix).

C-H Vibrations. For C-H stretching vibrations the characteristic region is 3100–3000 cm^{-1} [21]. The obtained anharmonic frequency for ν_{CH} is 3088 cm^{-1}, and the experimentally observed frequency for this mode is 3060 cm^{-1} in IR and 3055 cm^{-1} in Raman. For the dimer, the anharmonic wavenumbers obtained for this mode are 2942 and 2941 cm^{-1}. The PED for the C-H stretching vibration is 100%. Ortiz et al. [4] have computed the ν_{CH} frequency for isolated 5-ClU with anharmonic correction to be 3089 cm^{-1}. Singh [8] has assigned the frequency 3060 cm^{-1} in the IR spectrum and 3060 cm^{-1} in the Raman spectrum to ν_{NH} vibration. Dobrosz-Teperek et al. [2] have reported the assignment for this mode at 3062 cm^{-1} in the IR spectrum and at 3059 cm^{-1} in the Raman spectrum, and they have calculated this mode to be 3106 cm^{-1} using the HF method. Dobrowolski et al. have calculated the anharmonic frequency for this mode to be 3088 cm^{-1} using B3PW91/6-311G(d,p) [5].

The in-plane δ_{CH} bending vibration appears to be distributed in modes ν_{10} (anharmonic frequency: 1324 cm^{-1}, PED value: 49%) and ν_7 (42% PED). The ν_{10} mode shows mixing of ν_{ring} vibration with dominance of δ_{CH}. For the dimer, the anharmonic wavenumbers obtained for this mode are 1597, 1581, 1353, and 1352 cm^{-1}. Dobrowolski et al. [5] have assigned experimental Ar-matrix IR frequency at 1333 cm^{-1} to this vibration and have calculated the anharmonic frequency to be 1315 cm^{-1}. Singh [8] has assigned the 1185 cm^{-1} band at IR spectrum to this vibration. Ortiz et al. [4] have calculated the anharmonic frequency for δ_{CH} to be 1323 cm^{-1} and have assigned the band at 1340 cm^{-1} in the IR spectrum and the band at 1339 cm^{-1} in the Raman spectrum to this mode. This band has been calculated to be 1319 cm^{-1} for the monomeric 5-ClU molecule and 1314 and 1308 cm^{-1} for the dimeric structures by Elkin et al. [9].

The γ_{CH} vibration is assigned to 866 cm^{-1} in the IR spectrum and also assigned to anharmonic frequency 896 cm^{-1} (79% PED). For the dimer, the anharmonic wavenumbers obtained for this mode are 906 and 903 cm^{-1}. Dobrowolski et al. [5] have assigned the experimental Ar-matrix IR frequency at 896 cm^{-1} to this vibration and have calculated the anharmonic frequency to be 894 cm^{-1}. Elkin et al. have calculated this band to be 896 cm^{-1} for the monomeric molecule and 907 and 890 cm^{-1} for dimeric structures [9]. Singh [8] has assigned the 955 cm^{-1} band in the IR spectrum to this vibration. Ortiz et al. [4] have calculated the anharmonic frequency to be 921 cm^{-1} and have assigned the band at 948 cm^{-1} in the IR spectrum for γ_{CH} vibration. It is worth noting that the difference between the Ar-matrix and the calculated anharmonic frequencies for these modes in this study is low.

C=O Vibrations. The bands in the IR spectrum due to C=O stretching vibrations in uracil and its derivatives are in general complex [2, 5]. When the Ar-matrix spectrum [5] (also the solid state FT-IR spectrum) of the molecule in the ~1700 cm^{-1} region is investigated, there seems to be a lot of $\nu_{C=O}$ bands (Fig. 3). This knotty pattern of the $\nu_{C=O}$ region is explained in terms of Fermi resonance (FR) [5]. The calculated anharmonic frequencies corresponding to C=O stretching vibration are 1775 cm^{-1} (72% PED) and 1749 cm^{-1} (79% PED). The bands at 1711 and 1682 cm^{-1} in the IR spectrum and the bands at 1712 and 1677 cm^{-1} in the Raman spectrum are assigned to C=O stretching modes. For the dimer, the anharmonic wavenumbers obtained for this mode are 1812, 1808, 1760, and 1757 cm^{-1}. Dobrowolski et al. [5] have assigned experimental Ar-matrix IR frequencies at 1769, 1764, 1736, 1729, and 1710 cm^{-1} to these vibrations and noted that these bands are involved in Fermi resonance. They have calculated the anharmonic frequencies to be 1812 and 1783 cm^{-1}. Ortiz et al. [4] have calculated the anharmonic frequencies for $\nu_{C=O}$ vibrations to be 1747 and 1758 cm^{-1} and have assigned one band at 1678 cm^{-1} in the IR spectrum and one band at 1700 cm^{-1} in the

Raman spectrum to one of these modes. Dobrosz-Teperek et al. [2] have reported the assignment for these modes at 1711 and 1666 cm^{-1} in the IR spectrum and at 1726 and 1658 cm^{-1} in the Raman spectrum, and they have calculated these modes to be 1740 and 1727 cm^{-1} using the HF method. Singh [8] has assigned the frequencies 1732 and 1705 cm^{-1} in the IR spectrum and 1735 and 1700 cm^{-1} in the Raman spectrum to $\nu_{C=O}$ vibrations. The in-plane bending vibrations $\delta_{C=O}$ are mixed with other vibrations (mostly with δ_{ring} vibrations) but the out-of-plane bending vibrations $\gamma_{C=O}$ are pure vibrations with PED values 86% and 92%. The $\gamma_{C=O}$ bands are also in good agreement with the Ar-matrix IR bands.

C=Cl Vibrations. For C-Cl stretching vibrations the characteristic region is 900–600 cm^{-1} [22]. The obtained anharmonic frequency for ν_{CCl} is 651 cm^{-1} (PED 25%), and the experimentally observed frequency for this mode is 680 cm^{-1} in IR. For the dimer, the anharmonic wavenumbers obtained for this mode are 676 and 667 cm^{-1}. Dobrosz-Teperek et al. [2] have reported the assignment for this mode at 669 cm^{-1} in the both the IR and Raman spectra, and they have calculated this mode to be 634 cm^{-1} using the HF method. Ortiz et al. [4] have assigned the band at 682 cm^{-1} in the IR spectrum and the band at 668 cm^{-1} in the Raman spectrum to this mode. Singh [8] has assigned the frequencies 1090 cm^{-1} in the IR spectrum and 1030 cm^{-1} in the Raman spectrum to ν_{CCl} vibration. Dobrowolski et al. [5] have calculated the anharmonic frequency to be 657 cm^{-1} (PED 31%) and have assigned the experimental Ar-matrix IR frequency at 653 cm^{-1} to this vibration. Elkin et al. have calculated this band to be 649 cm^{-1} for the monomeric 5-ClU molecule and 652 and 641 cm^{-1} for dimeric structures [9].

The calculated anharmonic in-plane bending vibration of the C-Cl bond is 226 cm^{-1}, and the observed Raman frequency for this mode is 237 cm^{-1}. For the dimer, the anharmonic wavenumbers obtained for this mode are 232 and 228 cm^{-1}. The same mode is calculated to be 227 cm^{-1} by Dobrowolski et al. [5], wich is observed at 180 cm^{-1} in the Raman spectrum by Singh [8]. The out-of-plane bending vibration of the C-Cl bond is calculated to be 292 cm^{-1} in this study and assigned to 327 cm^{-1} in the Raman spectrum. The same mode is calculated to be 293 cm^{-1} by Dobrowolski et al. [5].

HOMO and LUMO Energies. The frontier molecular orbitals play an important role in chemical reactions as well as in the electric and optical properties and UV-vis spectra. The energies of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) of 5ClU are calculated by the DFT method at the B3LYP/6-31++G(d,p) level of theory. In Fig. 4, the frontier molecular orbitals (HOMO and LUMO) are shown. As seen from Fig. 4, the HOMO levels are spread over the entire molecule, except one of the N-H groups in the ground state. The LUMO of the first excited state is almost uniformly distributed over the entire molecule.

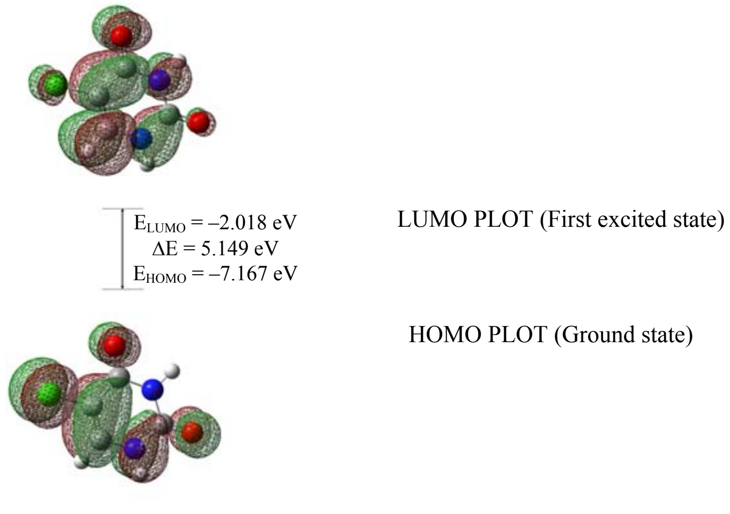


Fig. 4. Frontier molecular orbitals (HOMO and LUMO) of 5ClU calculated by the DFT method at the B3LYP/6-31++G(d,p) level of theory.

Molecular docking studies. Molecular docking is an important tool in molecular biology and computer-aided drug design. A study in 1993 by Morris et al. has shown that 5-ClU accumulation in DNA leads to sister chromatid exchanges and mutations [10]. Jiang et al. in 2003 found that chronic inflammation-mediated accumulation of modified bases may be related to cancer development [11]. In addition, the metal complex of the 5-ClU molecule has been synthesized because metal complexes function as antitumor agents against many types of tumors by inhibiting DNA and protein synthesis [12]. Docking analysis of the 5-ClU molecule was performed using the AutoDock-Vina program [16]. The 3D crystal structure of the DNA was obtained from the protein data bank (PDB ID: 1BNA) [23]. DNA was prepared for docking by removing the water molecules from the DNA and adding polar hydrogens to the DNA. The Kollman charges of DNA were also calculated. The gas-phase 5-ClU molecule was optimized with B3LYP/6-31++G(d,p) and made ready for docking. Partial charges of 5-ClU molecule were calculated using the Geistenger method. The active site of DNA was defined in a grid size of 40×40×40 Å. The 5-ClU molecule binds to the active site of DNA by hydrogen bonding interactions. The optimized structure of the 5-ClU molecule calculated by DFT/B3LYP/6-31++G(d,p) in the gas phase is bound by the intermolecular hydrogen bonds of DG10, DC15 and DG16 residues of DNA. The hydrogen bonds are observed between the residues DG16 and DG10 of the DNA and the oxygen atom of the 5-ClU molecule and between the DC15 and DG16 residues and the hydrogen atom of the 5-ClU molecule (Fig. 5). The results show that the docked ligand (5-ClU) formed a stable complex with DNA, and the binding affinity (ΔG) is -5.3 kcal/mol (Table 4).

Shahabadi et al. [24] studied the electropotential surface of DNA (see Fig. 5c) where the red regions and blue regions represented electronegative and electropositive regions of the DNA respectively. They have shown that the olanzapine molecule could dock to DNA through the electronegative region of DNA as given in Fig. 5c, and we have docked 5-ClU molecule to the DNA through the same region.

TABLE 4. The Binding Affinity Values of different Poses of the Title Compound Predicted by AutodockVina

Mode	Affinity (kcal/mol)	RMS distance from best mode (Å)	
		l.b.	u.b.
1	–5.3	0	0
2	–5.2	1.628	1.701
3	–5.2	1.997	3.243
4	–5.0	9.951	11.014
5	–4.9	21.752	22.819
6	–4.9	3.630	4.683
7	–4.9	4.084	4.814
8	–4.8	25.973	26.878
9	–4.8	22.655	23.685

RMS, l.b., and u.b. stand for root mean square, lower bound, and upper bound respectively.

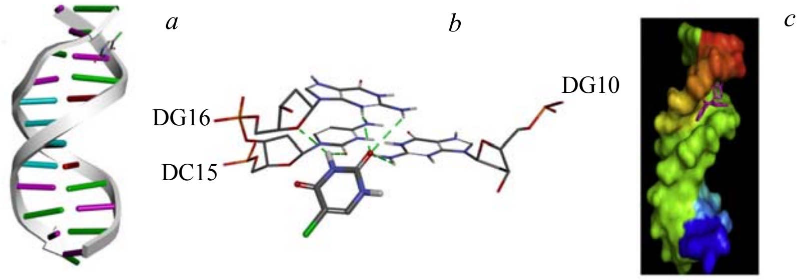


Fig. 5. (a) Docking of 5-ClU with DNA; (b) detailed interactions of the optimized structure of 5-ClU in the gas phase; (c) DNA electrostatic surface potential taken from [24].

Conclusion. The equilibrium geometry and wavenumbers (both harmonic and anharmonic) of 5-ClU molecule were calculated using quantum chemical methods. The identification of the bands presented in the solid state of 5-ClU were done using PED analysis. Calculations with the B3LYP method and with the 6-31++G(d,p) basis set appear in general to be useful for interpretation of the general features of the IR and Raman spectra.

To improve the calculated wavenumbers, anharmonic corrections to the wavenumbers were made. The agreement between the anharmonic wavenumbers and the experimental (Ar-matrix IR spectrum) values is very good. Thus, with the help of PED analysis and anharmonic corrections made on the wavenumbers, we believe that the assignments in this work are unambiguous.

The molecular electrostatic potential (MEP) map for 5-ClU illustrates that regions with negative potential are concentrated on oxygen, whereas regions with positive potential were concentrated on hydrogen atoms of NH and CH groups.

The dimeric structures of 5-ClU molecule were formed with the help of MEP analysis and optimized by the wb97xd/6-31++G(d,p) method. The lowest relative energy value belongs to dimer III. The harmonic and anharmonic wavenumbers were calculated for dimer III.

The HOMO and LUMO analysis of the 5-ClU molecule showed that the HOMO levels were spread over the entire molecule except one of the N-H groups in the ground state, while the LUMO state was almost uniformly distributed over the entire molecule.

The docking of 5-ClU molecule to DNA is studied for the first time. Results show that the docked ligand (5-ClU) formed a stable complex with DNA with binding affinity (ΔG) of –5.3 kcal/mol.

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REFERENCES

1. S. Ortiz, M. C. Alvarez-Ros, M. A. Palafox, V. K. Rastogi, V. Balachandran, S. K. Rathor, *Spectrochim. Acta A: Mol. Biomol. Spectrosc.*, **130**, 653–668 (2014).
2. K. Dobrosz-Teperek, Z. Zwierzchowska, W. Lewandowski, K. Bajdor, J. C. Dobrowolski, A. P. Mazurek, *J. Mol. Struct.,* **471**, No. 1-3, 115–125 (1998).
3. J. P. Henderson, J. Byun, J. Takeshita, J. W. Heinecke, *J. Biol. Chem.*, **278**, No. 26, 23522–23528 (2003).
4. S. Ortiz, M. A. Palafox, V. K. Rastogi, T. Akitsu, I. H. Joe, S. Kumar, *Spectrochim. Acta A: Mol. Biomol. Spectrosc.*, **110**, 404–418 (2013).
5. J. C. Dobrowolski, J. E. Rode, R. Kołos, M. H. Jamroz, K. Bajdor, A. P. Mazurek, *J. Phys. Chem. A*, **109**, No. 10, 2167–2182 (2005).
6. S. Sun, B. Alex, *J. Phys. Chem. A*, **119**, No. 17, 3961–3971 (2015).
7. G. N. Ten, T. G. Burova, V. I. Baranov, *J. Appl. Spectrosc.*, **73**, No. 4, 492–498 (2006).
8. J. S. Singh, *Spectrochim. Acta A: Mol. Biomol. Spectrosc.*, **87**, 106–111 (2012).
9. P. M. Elkin, V. F. Pulin, V. I. Berezin, *Izv. Saratov. Univ.*, *Fizika*, **13**, No. 2, 39–45 (2013) (In Russ.).
10. S. M. Morris, *Mutat. Res./Rev. Genet. Toxicol.*, **297**, No. 1, 39–51 (1993).
11. Q. Jiang, B. C. Blount, B. N. Ames, *J. Biol. Chem.*, **278**, No. 35, 32834–32840 (2003).
12. V. K. Rastrogi, H. P. Mital, C. B. Arora, U. Awasthi, In *Spectroscopy of Biological Molecules*, Springer, Dordrecht, 349–350 (1995).
13. M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, V. G. Zakrzewski, J. A. Montgomery, R. E. Stratmann, J. C. Burant, S. Dapprich, J. M. Millam, A. D. Daniels, K. N. Kudin, M. C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G. A. Petersson, P. Y. Ayala, Q. Cui, K. Morokuma, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. Cioslowski, J. V. Ortiz, A. G. Baboul, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, J. L. Andres, C. Gonzalez, M. Head-Gordon, E. S. Replogle, J. A. Pople, Gaussian 03, Revision B.1; Gaussian, Inc.: Pittsburgh, PA (2003).
14. A. D. Becke, *J. Chem. Phys.,* **98**, No. 7, 5648–5652 (1993).
15. M. H. Jamroz, Vibrational Energy Distribution Analysis VEDA 4.0, Drug Institute, Warsaw, Poland (2004).
16. O. Trott, J. O. Arthur, *J. Comput. Chem.,* **31**, No. 2, 455–461 (2010).
17. J. D. Chai, H. G. Martin, *Phys. Chem. Chem. Phys.*, **10**, No. 44, 6615–6620 (2008).
18. J. D. Chai, H. G. Martin, *J. Chem. Phys.,* **128**, No. 8, 084106 (2008).
19. H. Sternglanz, E. B. Charles, *Biochim. Biophys. Acta (BBA)–Nucleic Acids and Protein Synth.*, **378**, No. 1, 1–11 (1975).
20. E. I. Izgorodina, L. B. Uditha, R. M. Douglas, *J. Phys. Chem. A*, **113**, No. 25, 7064–7072 (2009).
21. J. Mohan, *Organic Spectroscopy: Principles and Applications*, CRC Press (2004).
22. G. Socrates, *Infrared and Raman Characteristic Group Frequencies: Tables and Charts*, John Wiley & Sons (2004).
23. H. R. Drew, R. M. Wing, T. Takano, C. Broka, S. Tanaka, K. Itakura, R. E. Dickerson, *Proc. Natl. Acad. Sci.*, **78**, No. 4, 2179–2183 (1981).
24. N. Shahabadi, B. Somayeh, *Spectrochim. Acta A: Mol. Biomol. Spectrosc.*, **136**, 1454–1459 (2015).