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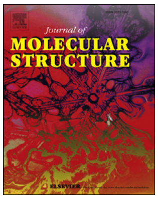

Molecular conformational analysis, reactivity, vibrational spectral analysis and molecular dynamics and docking studies of 6-chloro-5-isopropylpyrimidine-2,4(1*H*,3*H*)-dione, a potential precursor to bioactive agent

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ABSTRACT

FT-IR and FT-Raman spectra of 6-chloro-5-isopropylpyrimidine-2,4(1*H*,3*H*)-dione were recorded and analyzed. The vibrational wavenumbers were computed using DFT quantum chemical calculations and the data obtained from wavenumber calculations are used to assign the experimentally obtained bands. Potential energy distribution was done using GAR2PED software. The geometrical parameters of the title compound are in agreement with the XRD results. NBO analysis, frontier molecular orbital and first and second hyperpolarizability and molecular electrostatic potential results are also reported. The possible electrophile attacking sites of the title compound is identified using MEP surface plot study. Molecule sites prone to electrophilic attacks were identified using average local ionization energy surfaces, while further insight into the local reactivity properties of the title molecule has been gained by calculation of Fukui functions. Intra-molecular non-covalent interactions have been detected and visualized. Degradation properties based on autoxidation and hydrolysis have been investigated by calculation of bond dissociation energies and radial distribution functions, respectively. From the molecular docking study, the ligand binds at the active site of the substrate by weak non-covalent interactions and amino acids Leu89 forms alkyl interaction with the CH_3 groups and Glu90 amino acid forms π-anion interaction with the pyrimidine ring and Thr369 and Ser366 amino acids form H-bond interaction with the C=O and NH group, respectively. From the conformational analysis, the calculated structures show that the $C_6C_9C_{10}$ angle in the most stable form is about 8° smaller compared to the $C_8C_9C_{10}$ angle, indicating a higher repulsive force between the $(CH_3)_2HC-$ moiety and the chlorine atom due to the size of chlorine compared to oxygen atoms.

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1. Introduction

Pyrimidine-2,4-diones (uracils) and their related derivatives occupy a distinct and unique position in the field of chemotherapy. These heterocyclic moieties have great biological and medicinal significance. Large array of pyrimidine-related non-Nucleoside derivatives possess a variety of pharmacological properties. These properties include anticancer [1–6], antiviral [7–18], antimicrobial [19–24] and antimalarial [25,26] activities. 5-Alkyl-6-chloropyrimidine-2,4(1*H*,3*H*)-dione derivatives are frequently utilized as precursors for the synthesis of biologically-active pyrimidine derivatives [27–29]. Thus, the title compound was prepared as

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precursor for potential bioactive agents [27], its structure was established by ^{1}H, ^{13}C NMR and single crystal X-ray spectra [30]. In continuation to our ongoing interest on the vibrational spectroscopic studies of pyrimidine derivatives [31–33], we report herein the vibrational spectroscopic study of the title compound. Due to the diverse biological activities of the pyrimidine derivatives, the molecular docking studies of the title molecule are also reported. From the conformational analysis, the more stable form, which is predicted to be about 1 kcal/mol lower in energy than the other form, the $(CH_3)_2HC$— moiety orients itself such that the hydrogen atom eclipses the chlorine atom.

Improvement of experimental procedures for economical and efficient removal of organic pollutants is great challenge for scientific community. Great part of organic polluters is related to the pharmaceutical products based on biologically active molecules and so far these compounds have been detected in all types of water all around the world [34–36]. Their economical and efficient removal by conventional purification methods is not possible and in this regards advanced oxidation processes are seen as alternative approaches for the solution of these problems [37–39]. In order to develop methods for degradation of organic compounds it is necessary first to understand in details the reactive properties of target organic molecules. This is the part where DFT calculations and molecular dynamics (MD) simulations are vastly employed. Namely, employing DFT calculations it is possible to calculate bond dissociation energies (BDE) which can indicate molecule sites prone to autoxidation and show which bonds are the weakest. On the other side, MD simulations provide valuable information on the influence of solvent to the investigated molecule. Thus, beside fundamental reactive properties, in this work we have also employed above mentioned approaches in order to gain information significant for the understanding of degradation properties.

2. Experimental details

The title compound ($C_7H_9ClN_2O_2$) was prepared via the reaction of 5-isopropylbarbituric acid with phosphorus oxychloride and *N*,*N*-dimethylaniline to yield the 5-isopropyl-2,4,6-trichloropyrimidine, which was selectively hydrolyzed by heating in aqueous sodium hydroxide for 30 min to yield the target title compound in 74% overall yield [27]. In the title compound, the conformation is determined by intramolecular C—H⋯O and C—H⋯Cl hydrogen bonds. The isopropyl group is almost perpendicular to the pyrimidine ring with torsion angles of −70.8 and 56.3 [30].

The FT-IR (Fig. S1-supporting material) and FT-Raman (Fig. S2-supporting material) spectra were recorded using DR/Jasco FT-IR 6300 spectrometer and Bruker RFS 100/s spectrometer.

3. Computational details

Using Gaussian 09 software [40] and B3LYP/6-311++G(d,p)(5D,7F) [41,42] basis set, the molecular structure and vibrational wave numbers are predicted. A scaling factor of 0.9613 is used as scaling factor [43] for the predicted wave numbers to get better agreement with the experimental data. The optimized (Fig. 1) geometrical parameters (B3LYP) with XRD data are given in Table 1. The wave numbers are assigned by using GAUSSVIEW [44] and GAR2PED [45] programs.

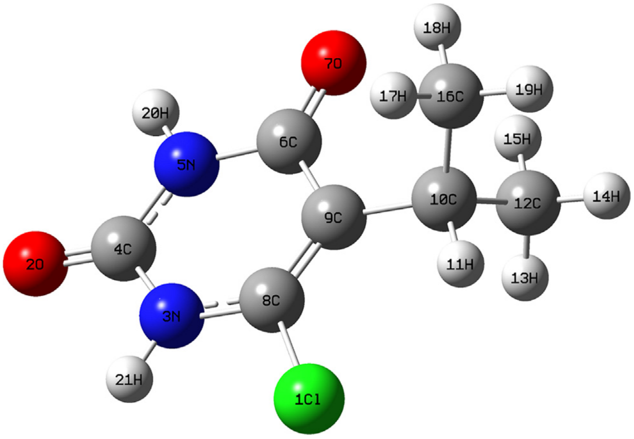

Fig. 1. Optimized geometry of 6-chloro-5-isopropylpyrimidine-2,4(1*H*,3*H*)-dione.

Table 1
Optimized geometrical parameters of 6-chloro-5-isopropylpyrimidine-2,4(*1H,3H*) dione with XRD data.

Bond lengths (Å) DFT/XRD			
C8—Cl1	1.7461/1.7200	C4—O2	1.2116/1.2222
C4—N3	1.3902/1.3642	N3—C8	1.3792/1.3702
N3—H21	1.0096/0.8320	C4—N5	1.3791/1.3602
N5—C6	1.4065/1.3862	N5—H20	1.0125/0.8430
C6—O7	1.2169/1.2262	C6—C9	1.4748/1.4572
C8—C9	1.3530/1.3423	C9—C10	1.5189/1.5162
C10—H11	1.0918/0.9530	C10—C12	1.5410/1.5073
C10—C16	1.5410/1.5003	C12—H13	1.0935/0.9600
C12—H14	1.0937/0.9600	C12—H15	1.0905/0.9600
C16—H17	1.0935/0.9600	C16—H18	1.0905/0.9600
C16—H19	1.0937/0.9600		
Bond angles (°) DFT/XRD			
C4—N3—C8	123.7/121.9	C4—N3—H21	116.0/117.6
C8—N3—H21	120.2/120.4	O2—C4—N3	122.9/122.6
O2—C4—N5	124.7/123.1	N3—C4—N5	112.4/114.3
C4—N5—C6	128.0/126.9	C4—N5—H20	116.1/116.1
C6—N5—H20	115.9/116.9	N5—C6—O7	119.2/119.2
N5—C6—C9	115.7/116.4	O7—C6—C9	125.1/124.4
Cl1—C8—N3	112.2/112.1	Cl1—C8—C9	123.9/123.2
N3—C8—C9	123.9/124.7	C6—C9—C8	116.2/115.6
C6—C9—C10	119.3/120.5	C8—C9—C10	124.4/123.8
C9—C10—H11	106.6/104.3	C9—C10—C12	111.9/114.4
C9—C10—C16	111.9/110.5	H11—C10—C12	107.2/106.3
H11—C10—C16	107.2/109.6	C12—C10—C16	111.7/111.5
C10—C12—H13	111.2/109.5	C10—C12—H14	109.6/109.5
C10—C12—H15	111.2/109.5	H13—C12—H14	107.8/109.5
H13—C12—H15	108.6/109.5	H14—C12—H15	108.3/109.5
C10—C16—H17	111.2/109.5	C10—C16—H18	111.2/109.5
C10—C16—H19	109.7/109.5	H17—C16—H18	108.6/109.5
H17—C16—H19	107.8/109.5	H18—C16—H19	108.3/109.5
Dihedral angles (°) DFT/XRD			
C4—N3—C8—C9	0.0/3.4	C4—N3—C8—Cl1	180.0/-175.5
C6—N5—C4—O2	180.0/-176.5	C6—N5—C4—N3	0.0/4.4
C8—N3—C4—O2	180.0/175.0	C8—N3—C4—N5	0.0/-5.8
C4—N5—C6—O7	180.0/179.3	C4—N5—C6—C9	0.0/-0.3
N3—C8—C9—C6	0.0/1.0	Cl1—C8—C9—C6	180.0/179.9
N3—C8—C9—C10	180.0/-175.2	Cl1—C8—C9—C10	0.0/3.6
O7—C6—C9—C8	180.0/177.9	N5—C6—C9—C8	0.0/-2.5
O7—C6—C9—C10	0.0/-5.7	N5—C6—C9—C10	180.0/173.9
C8—C9—C10—C16	−116.9/105.3	C6—C9—C10—C16	63.1/-70.8
C8—C9—C10—C12	116.9/-128.0	C6—C9—C10—C12	−63.1/-56.0

For the calculation of average local ionization energy (ALIE) surfaces, Fukui functions and BDE we have used Jaguar 9.0 [46] program, as implemented in Schrödinger Materials Science Suite 2015−4 [47]. In these DFT calculations B3LYP exchange-correlation functional [48] has been also used with 6−311++G(d,p) basis set for ALIE surface, 6-31 + G(d) for Fukui functions and6-311G(d,p) for BDE. For the MD simulations, after which radial distribution functions have been calculated, a Desmond [49–52] program, also as implemented in Schrödinger Materials Science Suite 2015-4, was used with OPLS 2005 force field [53] and NPT ensemble class. The pressure was set to be 1.0325 bar and temperature was set to be 300 K. Simulation time was 5 ns, while cut-off radius was set to

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