



Contents lists available at SciVerse ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

Theoretical investigation of 5-(2-Acetoxyethyl)-6-methylpyrimidin-2,4-dione: Conformational study, NBO and NLO analysis, molecular structure and NMR spectra

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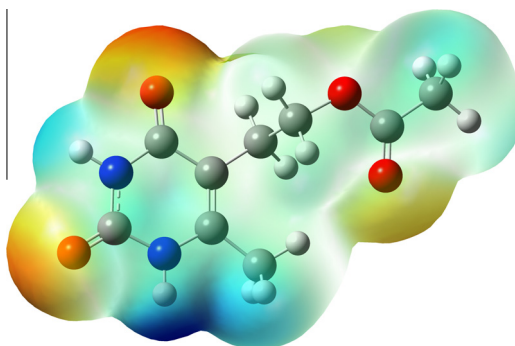
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HIGHLIGHTS

- The hyperconjugative interactions and charge delocalization has been investigated.
- The intramolecular charge transfer [$n \rightarrow \pi^*$, $\pi \rightarrow \pi^*$, $\pi^* \rightarrow \pi^*$] occurs in title compound.
- The compound exhibits strong effective intra- and intermolecular charge transfer.
- The compound shows large second-order nonlinearity.
- The 5,6-disubstituted pyrimidine systems are effective in the design of new bioorganic molecules.

GRAPHICAL ABSTRACT

The total electron density isosurface mapped with molecular electrostatic potential for 5-(2-Acetoxyethyl)-6-methylpyrimidin-2,4-dione (obtained from B3LYP level).



ARTICLE INFO

Article history:

Received 11 December 2012
 Received in revised form 25 February 2013
 Accepted 13 April 2013
 Available online 23 April 2013

Keywords:

5-(2-Acetoxyethyl)-6-methylpyrimidin-2,4-dione
 Conformational, NBO and NLO analysis
 HF and DFT
 NMR spectra
 HOMO–LUMO energies
 Molecular electrostatic potential (MESP) surfaces

ABSTRACT

Structural and conformational, natural bond orbital (NBO) and nonlinear optical (NLO) analysis was performed, and ^1H and ^{13}C NMR chemical shifts values of 5-(2-Acetoxyethyl)-6-methylpyrimidin-2,4-dione [$\text{C}_9\text{H}_{12}\text{N}_2\text{O}_4$] in the ground state were calculated by using Density Functional Theory (DFT-B3LYP/6-311++G(d,p)) and Hartree–Fock (HF/6-311++G(d,p)) methods. The NMR data were calculated by means of the GIAO, CSGT, and IGAIM methods. In addition, the molecular frontier orbital energies, thermodynamic parameters (in the range of 200–700 K), molecular surfaces, Mulliken charges and atomic polar tensor-based charges were investigated. Besides, the analysis of all possible conformational of the title compound, a detailed potential energy curve for $\tau_1(\text{C}_8\text{—O}_3\text{—C}_{10}\text{—O}_4)$, $\tau_2(\text{C}_8\text{—O}_3\text{—C}_{10}\text{—C}_{11})$ and $\tau_3(\text{C}_5\text{—C}_7\text{—C}_8\text{—O}_3)$ dihedral angles were performed in steps of 10° from 0° to 360° , and depicted to find the most stable form. Finally, the calculated HOMO and LUMO energies show that charge transfer occurs within the title compound.

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Introduction

Pyrimidines are biologically important molecules and valuable heterocyclic nuclei for the design of pharmaceutical agents [1].

Uracil derivatives which have significant status in the field of chemotherapy substituted either at C5 or C6 positions, as well as their nucleosides. Especially, 5-substituted uracil analogs have been extensively investigated to use in cancer [2,3] and viral

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chemotherapy [4,5], as enzyme inhibitors [6–9] and in the synthesis of modified nucleotides [10,11]. Lately, it is well known that some C5 and/or C6 substituted pyrimidine derivatives exhibited antiviral and cytostatic activities. Furthermore, 5-(2-Acetoxyethyl)-6-methylpyrimidin-2,4-dione molecule was evaluated for its cytostatic activities against human malignant tumor cell lines: acute lymphoblastic leukemia (Molt-4), colon carcinoma (HCT 116 and SW 620), breast carcinoma (MCF-7) and lung carcinoma (H 460) [12].

In the previous study, 5-(2-Acetoxyethyl)-6-methylpyrimidin-2,4-dione was synthesized and characterized with X-ray diffraction method and its structure was elucidated with ^1H and ^{13}C NMR spectra (in the DMSO- d_6 solution) by Kraljevic et al. [12]. The aim of the present work is to describe and characterize the molecular structure, conformational study, NBO and NLO analysis, NMR chemical shifts, the total energy, molecular frontier orbital energies (HOMO, HOMO-1, LUMO and LUMO+1), electronegativity (χ), hardness (η), softness (S), thermodynamic properties, Mulliken charges and APT charges, molecular electrostatic potential surfaces (MEPSs) and molecular surfaces of the title compound.

Computational details

The title compound was optimized based on the cif file belongs to the crystal structure. The optimized molecular structures of the title compound in the ground state (in vacuo) were computed by performing both HF and DFT by a hybrid functional B3LYP functional (Becke's three parameter hybrid functional using the LYP correlation functional) methods [13,14] at 6-311++G(d,p) level. The gauge-including atomic orbital (GIAO) [15–17], individual gauges for atoms in molecules (IGAIMs) [18], and continuous set of gauge transformations (CSGTs) [19] methods are three of the most common approaches for calculating nuclear magnetic shielding tensors [20–23]. In the present study, ^1H and ^{13}C NMR chemical shifts were calculated within GIAO, IGAIM, and CSGT approach applying B3LYP and HF methods with 6-311+G(d,p) basis set. The conformational studies, NBO and NLO analysis on the title compound were performed by using DFT and HF methods. Furthermore, Thermodynamic properties at various temperatures in the range of 200–700 K were evaluated. All calculations were performed by using Gaussian 09W program package [24], and the visualization parts were done with GaussView program [25] employing HF and B3LYP methods with 6-311++G(d,p) basis set.

Results and discussion

Structural and conformational analyses

5-(2-Acetoxyethyl)-6-methylpyrimidin-2,4-dione molecule [$\text{C}_9\text{H}_{12}\text{N}_2\text{O}_4$] has $P2_1/c$ space group and monoclinic crystal system

($a = 11.7336(6)\text{ \AA}$, $b = 5.0612(3)\text{ \AA}$, $c = 18.2071(10)\text{ \AA}$ and $\alpha = 90^\circ$, $\beta = 114.113(4)^\circ$, $\gamma = 90^\circ$) [12]. The title compound was synthesized by Kraljevic et al. [12], and the molecular structure and the numbering of atoms are shown in Fig. 1a [12]. The crystal structure of the title compound was taken from Cambridge Crystallographic Data Center (CCDC 749761) [26]. The optimized structure with B3LYP/6-311++G(d,p) level is shown in Fig. 1b. The calculated geometric parameters (bond lengths, bond angles and dihedral angles) at HF/6-311++G(d,p) and B3LYP/6-311++G(d,p) levels for title compound was compared with the experimental parameters [12] in Table 1.

In the title compound (Fig. 1), 2-acetoxyethyl chain is bonded to the C5 atom belongs to pyrimidine ring. The geometry of pyrimidine-2,4-dione is in a good agreement with similar structures in which alkyl chain bonded to C5 atom of the pyrimidine ring [12]. The planes of the C8/O3/C10/O4 atoms and pyrimidine rings' atoms are almost coplanar to each other. This planarity was supported by the conformational analysis for the τ_1 (C8–O3–C10–O4) and τ_2 (C8–O3–C10–C11) dihedral angles. Their mean planes form an angle of $5.28(11)^\circ$ [12].

The N1...O1 and N3...O3 hydrogen bonds in the compound is generated by O atoms which bonded to C(2) and C(4) [12]. These two N–H...O hydrogen bonds are reinforced by one C–H...O hydrogen bond, C9...O4, occurred between 2-acetoxyethyl chain and the pyrimidine ring. This phenomenon is a feature of self-organization processes, widely reported in the literature. The hydrogen-bonds were determined using symmetry transformations [12]. These bonds could be roughly signed using the optimized molecular structures obtained from DFT and HF methods. The calculated hydrogen-bond results are consistent with the experimental ones.

To make comparison with experimental results, we present linear correlation coefficients (R^2) for linear regression analysis of theoretical and experimental bond lengths and angles. These values are 0.9827 and 0.9857 (for bond lengths), and 0.9684 and 0.9691 (for bond angles) with HF and B3LYP levels, respectively. As one can easily see from above cited correlation coefficients, there are similar to each other for two levels. In Table 1, there is generally a good agreement between the experimental and theoretical geometric parameters results of the title compound. Minor differences show that the experimental results were observed in the solid phase while theoretical calculations were performed in the gas phase.

The minimum point structures located on the potential surface scan (PES) of the title compound was submitted to optimization using the HF/6-31G and B3LYP/6-31G computational levels of theoretical approximations were performed in the gas phase for the title compound. From the rotation of different groups, the minimum energy conformation and valuable structural information about compound are obtained. In order to reveal all possible conformational of

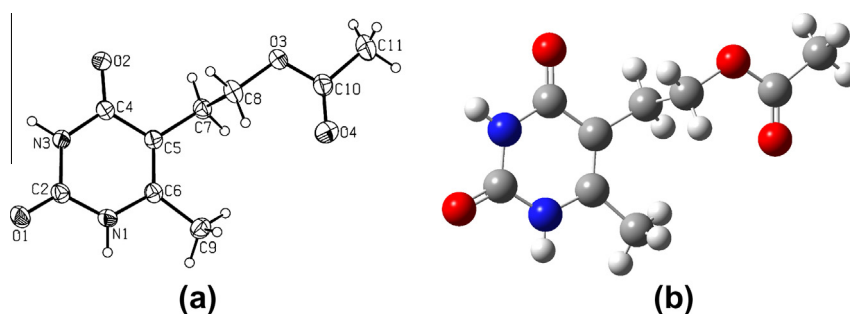


Fig. 1. (a) The experimental structure (b) the optimized geometric structure obtained using B3LYP/6-311++G(d,p) level of 5-(2-Acetoxyethyl)-6-methylpyrimidin-2,4-dione [$\text{C}_9\text{H}_{12}\text{N}_2\text{O}_4$] molecule.

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