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Quantum chemical calculations on the geometrical, conformational, spectroscopic and nonlinear optical parameters of 5-(2-Chloroethyl)-2,4-dichloro-6-methylpyrimidine

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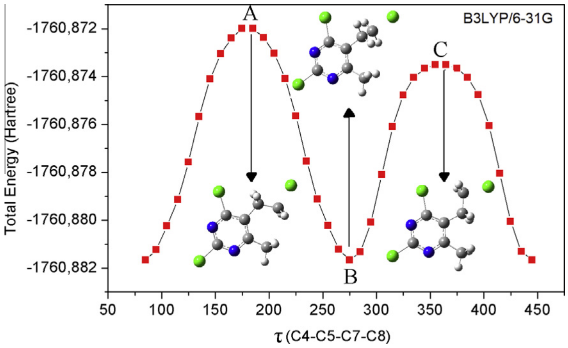
HIGHLIGHTS

- Structural and spectroscopic studies were performed by DFT and HF methods.
- Electric and electronic properties of the title compound were investigated.
- NBO analysis for the title compound was carried out.
- DFT and HF results are in good agreement with experimental ones.

GRAPHICAL ABSTRACT



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ABSTRACT

The optimized geometry, ^1H and ^{13}C NMR chemical shifts, conformational and natural bond orbital (NBO) analyses, thermodynamic parameters, molecular surfaces, Mulliken, NBO and APT charges for 5-(2-Chloroethyl)-2,4-dichloro-6-methylpyrimidine [$C_7H_7Cl_3N_2$] were investigated by the ab initio HF and density functional theory (DFT/B3LYP) methods with 6-311++G(d,p) basis set. The calculated structural parameters (bond lengths, bond angles and dihedral angles) and ^1H and ^{13}C NMR chemical shifts values are compared with experimental values of the investigated compound. The observed and the calculated values are found to be in good agreement. The energies of the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) were calculated, and the obtained energies displayed that charge transfer occurs in 5-(2-Chloroethyl)-2,4-dichloro-6-methylpyrimidine compound. In addition, the linear polarizability (α) and the first order hyperpolarizability (β) values of the investigated compound have been computed by using HF and DFT methods.

Introduction

The chemistry of heterocyclic compounds has a key role in the discovery of new drugs. This study field have gathered great attention over the past years, and a number of paper constructed by experimental techniques and theoretical methods have appeared in the literature. Various compounds such as alkaloids, essential amino acids, vitamins, hemoglobin, hormones, large number of synthetic drugs and dyes contain heterocyclic ring systems. There are large number of synthetic heterocyclic compounds, like pyrimidine, pyridine, pyrrole, pyrrolidine, furan, thiophene. It is well known that pyrimidines are biologically important molecules. 5-(2-Chloroethyl)-2,4-dichloro-6-methylpyrimidine compound was

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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) [1].

The title compound which contains both aliphatic and aromatic chlorine atoms possessed the most significant inhibitory effect. This compound inhibited colon carcinoma SW 620 in submicromolar range (IC50 = 0.4 lM). Influence of bromine in 2,4-dimethoxypyrimidine derivatives on antitumoral activity was also determined by Prekupec et al. [2]. Thus, pyrimidine derivative that bears one aromatic and two aliphatic bromine atoms showed the highest inhibitory activity against all tested malignant tumor cell lines. Inhibitory effect of the title compound was approximately 20-fold higher against SW 620 cell line than that of 5-FU. Besides, the title compound expressed better antiproliferative effects on SW 620 and MCF-7 cells than Ara-C. Recently, 5-(2-Chloroethyl)-2,4-dichloro-6-methylpyrimidine [$C_7H_7Cl_3N_2$] was synthesized and characterized with X-ray diffraction method and its structure was elucidated with ^1H and ^{13}C spectra (in the DMSO-d_6 solution) by Kraljevic et al. [1]. However, to the best of our knowledge, this is the first theoretical work that investigates the structural, spectroscopic electric and electronic properties of title compound.

The aim of the present study is to describe and characterize the results from HF/6-311++G(d,p) and DFT/6-311++G(d,p) calculations for the molecular geometry, ^1H and ^{13}C NMR chemical shifts values, conformational, natural bond orbital (NBO) and nonlinear optical (NLO) analysis, highest occupied molecule energy level (E_{HOMO}), the lowest unoccupied molecule energy level (E_{LUMO}), the energy gap (ΔE) between E_{HOMO} and E_{LUMO}, electronegativity (χ), hardness (η), softness (S), thermodynamic parameters, Mulliken, NBO and atomic polar tensor (APT) charges and molecular electrostatic potential (MEP) surfaces of investigated compound.

Computational details

All calculations were performed by using Gaussian 09W package program [3] and the output files were visualized by means of the Gaussian View 5 software [4]. The molecular structure of the title compound in the ground state was computed by performing both Hartree–Fock (HF) and the density functional theory (DFT) by a hydrid functional B3LYP functional (Becke's three parameter hybrid functional using the LYP correlation functional) methods [5,6] at 6-311++G(d,p) level. The HOMO–LUMO energy gap (ΔE), ionization potential (I), electron affinity (A), absolute electronegativity (χ) [7], absolute hardness (η) and softness (S) were computed using the frontier molecular orbital energies (E_{HOMO} and E_{LUMO}) at the B3LYP/6-311++G(d,p) and HF/6-311++G(d,p) levels of theory. ^1H NMR and ^{13}C NMR chemical shifts were calculated within the gauge-independent atomic orbital (GIAO) approach [8,9] which is one of the most common approaches for calculating nuclear magnetic shielding tensors, individual gages for atoms in molecules (IGAIM) and continuous set of gage transformations (CSGT) methods applying B3LYP and HF method. HF and DFT levels were also used to calculate the dipole moment (μ), the mean polarizability (<α>), the anisotropy of the polarizability ($\Delta\alpha$), and the total first static hyperpolarizability (<β>). The NBO analysis was performed to investigate the intra and intermolecular bonding and interaction among bonds and charge transfer or conjugative interactions in the title compound. 3D molecular surfaces were simulated by using B3LYP level so as to display the electrophilic and nucleophilic regions of the title compound. Finally, Mulliken, NBO and APT charges were calculated using HF and B3LYP level.

Results and discussion

Geometric optimization and conformational analysis

The 5-(2-Chloroethyl)-2,4-dichloro-6-methylpyrimidine [$C_7H_7Cl_3N_2$] synthesized by Kraljevic et al. has *Pbca* space group and orthorhombic system, with the unit cell parameters $a = 7.8128(4)$ Å, $b = 13.9748(5)$ Å, $c = 17.1690(6)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$ and $V = 1874.55(13)$ Å^3 [1]. The experimental molecular structure and numbering of atoms for the title compound are shown in Fig. 1a [1], and the optimized structure with B3LYP/6-311++G(d,p) are shown in Fig. 1b. The crystal structure of the title compound was taken from Cambridge Crystallographic Data Center (CCDC 749763). Obtained geometric parameters from HF and DFT levels along with the experimental data [1] were given in Table 1, and compared with each other. Correlation graphic for the calculated and experimental bond lengths, bond angles and dihedral angles are shown in Figure S1. The correlation between B3LYP and the experimental results are 0.9791, 0.9799 and 0.999 for bond lengths, bond angles and dihedral angles, respectively.

The N_1–C_2, Cl_1–C_2 and O_2–C_8 bond length were observed as 1.313, 1.736 and 1.699 Å [1]. In our calculations, these bond lengths were calculated as 1.320, 1.747 and 1.756 Å for B3LYP methods. The N_1–C_2–Cl_1 bond angle was found at 115.6° [1]. This angle has been calculated at 116.54° and 116.49° using HF and B3LYP methods, respectively. It should be noted that the experimental results belong to solid phase, while theoretical calculation, in this study can be classified as favorable, belong to gas phase. Considering this fact, it can be said that there is a good agreement between experimental and the calculated geometric parameters.

The conformational analysis has been performed to determine the most stable conformers of the title compound using the DFT/6-31G computational level. The minimum point structures located on the potential energy surface (PES) scan of title compound was submitted to optimization performed in the gas phase for the title

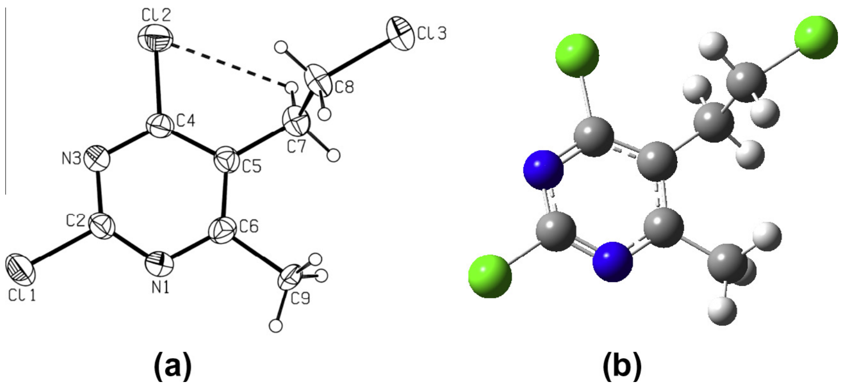

Fig. 1. (a) The experimental structure (b) The optimized geometric structure of the title compound obtained from B3LYP/6-311++G(d,p) level.