



Spectroscopic characterization of 4-[2-(5-Ethylpyridin-2-yl)ethoxy]benzaldehyde oxime and investigation of its reactive properties by DFT calculations and molecular dynamics simulations

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ABSTRACT

The molecular structure, vibrational wave numbers, NLO, NBO, MEP and HOMO, LUMO analysis of 4-[2-(5-Ethylpyridin-2-yl)ethoxy]benzaldehyde oxime were reported. The theoretically predicted geometrical parameters are in agreement with the XRD data. Using NBO analysis the change in the electron density in the anti-bonding orbital and stabilization energies have been calculated to give clear evidence of stabilization in the hyper-conjugation of hydrogen bonded interactions. The calculated first hyper-polarizability is 46.761 times that of the standard NLO material urea. From molecular electrostatic potential plot, phenyl ring, pyridine ring and oxygen atoms are the most electronegative regions and the hydrogen atom in the OH group is the most electropositive region. ALIE surfaces and Fukui functions have been calculated in order to obtain information related to the local reactivity properties of the title molecule. Intra-molecular non-covalent interactions have also been searched for. In order to investigate autoxidation and degradation properties we have calculated bond dissociation energies for all single acyclic bonds. To determine which atoms have the most pronounced interactions with water molecules we have conducted molecular dynamics simulations and calculated radial distribution functions. Molecular docking studies suggest that the title compound can be a lead compound for developing new anti-cancerous drug.

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1. Introduction

The title compound, 4-[2-(5-Ethylpyridin-2-yl)ethoxy]benzaldehyde oxime, is a key intermediate for the synthesis of biologically active compounds like, isoxazolines and isoxazoles [1,2]. Benzaldehyde oxime can be designated as an important part of pseudopeptides which show various bio-activities [3]. Isoxazole and isoxazoline ring systems show a variety of biological activities (insecticidal, antibacterial, antibiotic, antitumor, anti-fungal) [4] and they also

serve as prodrugs for an anti-arthritis agent [5]. For the synthesis of biologically active molecules, isoxazolines are used as important building blocks [5]. The single crystal XRD study of the title compound is reported in literature [6]. Xu et al. [7] reported the experimental and computational studies of the isomerization between Z and E isomers of benzaldehyde oximes.

In the present work the vibrational spectra of the title compound are investigated experimentally and theoretically. Using DFT calculations, the wave number assignments, geometrical parameters, NBO, MEP, frontier molecular orbital gap and hyper-polarizability values are studied. Molecular docking is also reported due to different potential biological activities of the title compound.

Understanding reactive properties of biologically active

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molecules, employing computational methods, is of great importance because it offers rationalization of experimental procedures. Principles of molecular modeling enables one to determine how some molecule reacts with other molecules by calculating quantities related to the global and local reactivity. Various quantities related to local reactivity also allow scientists to determine molecule's degradation properties, which is of great importance for problems related to environmental protection. This is especially important when we are speaking about biologically active molecules which are active components of pharmaceuticals. Due to their frequent usage biologically active molecules are becoming key pollutants of all types of water throughout the world and there is necessity for efficient and economic procedures for their removal [8–10].

Due to their persistent nature in aqueous mediums conventional methods for their removal are no longer adequate [11]. Even if some molecule is not considered to be persistent, its continuous usage and entering in water streams makes the same damage as if it is highly persistent [12]. Alternative approaches for the removal of organic pollutants have been proposed and one of them is certainly based on the photo catalytic properties of transition metal semiconductors [13]. Either way, in order to improve the development of removal procedures it is also necessary to understand degradation properties of organic pollutants, which is tedious scientific process. This is the moment when principles of molecular modeling can be very handy, since reactivity studies can produce results important for the proposals of degradation pathways.

In order to investigate local reactivity properties in this work we have also relied to the ALIE surfaces and Fukui functions in order to determine which molecule sites are prone to electrophilic or nucleophilic attacks. On the other side, in order to obtain information useful for understanding the degradation properties of title molecule, we have also calculated bond dissociation energies (BDF) and radial distribution functions (RDF). BDE results have been used in order to determine potential molecule's sites prone to autoxidation, while RDF served us to determine the atoms with pronounced interactions with water molecules.

2. Experimental details

The title compound was synthesized according to the protocol reported in literature [6]. The FT-IR spectrum (Fig. S1-supporting material) was recorded using KBr pellets on a DR/Jasco FTIR 6300 spectrometer with a spectral resolution of 4 cm^{-1} . The FT-Raman Spectrum (Fig.S2-supporting material) was obtained on a Bruker RFS 100/s, Germany. For excitation of the spectrum the emission of Nd:YAG laser was used with excitation wavelength 1064 nm and maximal power 150 mW; measurement were performed on solid samples. One thousand scans were accumulated with a total registration time of about 30 min. The spectral resolution after apodization was 2 cm^{-1} .

3. Computational details

Calculations of the title compound are carried out with Gaussian09 program [14] using B3LYP/6-311++G(d,p)(5D,7F) quantum chemical calculations methods to predict the molecular structure and vibrational wave numbers. The theoretically calculated wave numbers are scaled by using a scaling factor of 0.9613 for obtaining a better agreement with the experimental values [15]. The vibrational assignments are done by using potential energy distribution [16] and GAUSSVIEW program [17]. The NBO calculations [18] were performed at the B3LYP/6-31G(d) (6D, 7F) using the NBO 3.1 version as implemented in Gaussian software in order to understand the various second order interactions. The electronic

properties such as HOMO, LUMO energies, the first and second hyperpolarizabilities, molecular electrostatic potentials and NMR chemical shifts were calculated using the B3LYP/6-311++G(d,p)(5D,7F) basis set.

In this work for DFT calculations and molecular dynamics (MD) simulations we have also employed Jaguar 9.0 and Desmond programs, respectively, both as implemented in Schrödinger Materials Science Suite 2015-4 [19,20]. Jaguar 9.0 program was used for calculations of ALIE surfaces, Fukui functions and bond dissociation energies for single acyclic bonds (BDE) of the title compound using B3LYP exchange-correlation functional and 6-311G++(d,p), 6-31+G*(d) and 6-311G(d,p) basis sets, respectively.

To investigate interactions of title molecule with water molecules we have performed MD simulations in order to calculate radial distribution functions (RDF). For those purposes we have placed one molecule of title compound in cubic box with ~3000 water molecules and used OPLS 2005 force field [21] with ensemble class of NPT type. Simulation time was set to 5 ns, temperature to 300 K, pressure to 1.0325 bar, with cut-off radius of 12 Å. Simple point charge (SPC) model [22] was used for the treatment of solvent. Employing the method of Johnson [23,24], intramolecular noncovalent interactions have been investigated as well.

4. Results and discussion

In the following discussions, pyridine and phenyl rings are designated as PhI and PhII, respectively.

4.1. Geometrical parameters

The calculated geometrical parameters of the title compound (Fig. 1) with XRD data are given in Table 1.

For the title compound, the C–C bond lengths (DFT/XRD) of the phenyl ring are in the ranges 1.3841–1.4122/1.3872/1.4082 Å [59]. The C–C bond lengths (DFT/XRD) of the pyridine ring are in the ranges, 1.3893–1.4028/1.3902–1.4022 Å and CN bond lengths, C₁–N₆ = 1.3401/1.3512 Å, C₅–N₆ = 1.3393/1.3422 Å. For title compound the C–O bond lengths are, C₂₄–O₂₃ = 1.3598/1.3761 Å and C₂₀–O₂₃ = 1.4310/1.4379 Å and which are in agreement with the reported values [25,26]. For the title compound, the bond lengths (DFT/XRD) C₃₄ = N₃₆ = 1.2865/1.2842 Å and N₃₆–O₃₇ = 1.4079/1.4077 Å.

At C₃₁ position, the bond angles are, C₂₇–C₃₁–C₃₄ = 116.8/119.3°, C₂₇–C₃₁–C₂₉ = 117.5/117.9° and C₂₉–C₃₁–C₃₄ = 125.7/122.6° and the asymmetry in angles is due to the interaction between the phenyl ring and the C=N moiety. At C₂₄ position, the bond angles C₂₅–C₂₄–C₂₆ = 119.4/120.1°, C₂₅–C₂₄–O₂₃ = 115.8/115.7° and C₂₆–C₂₄–O₂₃ = 124.8/124.2° and the asymmetry in angles is due to the hydrogen bonding between H₂₈ atom and O₂₃ atom. Similarly at C₁ position, the bond angles are C₂–C₁–C₁₇ = 120.7/122.8°, C₂–C₁–N₆ = 121.7/121.2° and N₆–C₁–C₁₇ = 117.7/116.1° and the asymmetry in angles is due to the interaction between the CH₂ groups at C₁₇, C₂₀ with the pyridine ring. The steric repulsion between H₇, H₉ atoms and CH₂ group at C₁₀, CH₃ group at C₁₃ is given by the values of the bond angles, C₃–C₄–C₅ = 116.3/116.1°, C₃–C₄–C₁₀ = 122.1/122.8° and C₅–C₄–C₁₀ = 121.6/121.0°. The pyridine ring and the CH₂ groups are tilted slightly from each other as is evident from the torsion angles, C₃–C₂–C₁–C₁₇ = 179.6°, C₂–C₁–C₁₇–C₂₀ = 176.1°, C₅–N₆–C₁–C₁₇ = –179.6° and N₆–C₁–C₁₇–C₂₀ = –4.4° while the pyridine ring and the CH₂CH₃ groups are more tilted from each other as is evident from the torsion angles, C₂–C₃–C₄–C₁₀ = 178.5°, C₃–C₄–C₁₀–C₁₃ = –81.0°, N₆–C₅–C₄–C₁₀ = –178.5° and C₅–C₄–C₁₀–C₁₃ = 97.5°. The root mean square deviation is calculated and the RMSD values are 0.03143 for bond lengths; 10.31617 for bond angles and 18.90310 for dihedral angles.

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