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Molecular structure and vibrational spectroscopic studies of prothionamide by density functional theory

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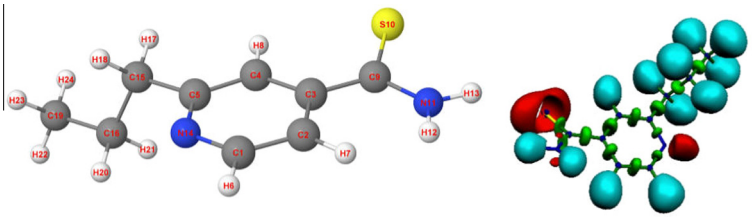
HIGHLIGHTS

- The most stable conformer of PTH was obtained by PES scan.
- FT-Mid IR, FT-Far IR and FT-Raman spectroscopy investigation have been carried out.
- The anharmonic and harmonic wavenumbers were calculated.
- The normal coordinate analysis was utilized.
- HOMO–LUMO, NBO and ELF basin analyses were performed.

GRAPHICAL ABSTRACT



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ABSTRACT

Prothionamide (PTH) is the secondary drug used against *Mycobacterium tuberculosis* bacteria and leprosy. The aim of this work was to investigate the potential energy surface map, anharmonic and harmonic vibrational spectra, NBO analysis and ELF (Electron Localization Function) of the title compound using DFT approach with the B3LYP (Becke, three-parameter, Lee–Yang–Parr) exchange–correlation functional with the 6-31G++(d,p) and the Z3POLX basis sets were employed. In the experimental part of this study, FT-Mid IR, FT-Far IR and FT-Raman spectra of the molecule were recorded in the regions 4000–450 cm^{-1}, 700–30 cm^{-1} and 4000–100 cm^{-1} respectively in the solid phase. The comparison between calculated and experimental vibrational spectra (infrared and Raman spectra) and assignments of fundamental vibrational modes were characterized by total energy distribution (TED). Theoretical spectra were seen to be in good agreement with those of the experimental ones.

1. Introduction

Tuberculosis (TB) is an infectious bacterial disease caused by *Mycobacterium tuberculosis* [1]. TB remains the leading cause of infectious disease-related mortality worldwide even in the 21st century. In addition, the levels of multi-drug resistant TB are increasing worldwide. Every year, more than 9 million people infected with TB and the deaths of nearly 1.5 million people [2–6]. PTH is used clinically effective in the treatment of *M. tuberculosis* [TB], *Mycobacterium leprae*, and *Mycobacterium avium* complex infections. [7–10].

PTH is a thionamide derivative which is structurally similar to isoniazid. The exact mechanism of action of PTH has not been clarified. Antibacterial activity and pharmacokinetics of PTH is similar to ethionamide, but PTH is said to be better tolerated. In case of the multidrug-resistant tuberculosis, prothionamide is used mostly in combination with other TB drugs [11–14]. The sample is in yellowish powder form, almost insoluble in water, unstable on exposure to light and called as 2-propylpyridine-4-carbothioamide.

In order to synthesize and to design new anti-tuberculosis drugs and to improve diagnosis and management of co-infection, it is very important to investigate anti-TB drugs at molecular level

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since their biological activities are directly linked to their structures [15,16].

The experimental and calculated vibrational spectra of similar compounds of PTH have been investigated in recent studies [17–20]. To the best of our knowledge, neither vibrational studies nor quantum chemical studies of PTH have been performed yet.

In this paper, conformational analysis and the vibrational spectra of PTH were examined by density functional theory (DFT). Moreover, the characteristics of the charge delocalization, electron localization and chemical bond characteristics of PTH were analyzed by using NBO and ELF. In addition, the FT-Mid IR, FT-Far IR and FT-Raman spectra of PTH were measured at room temperature in the solid state.

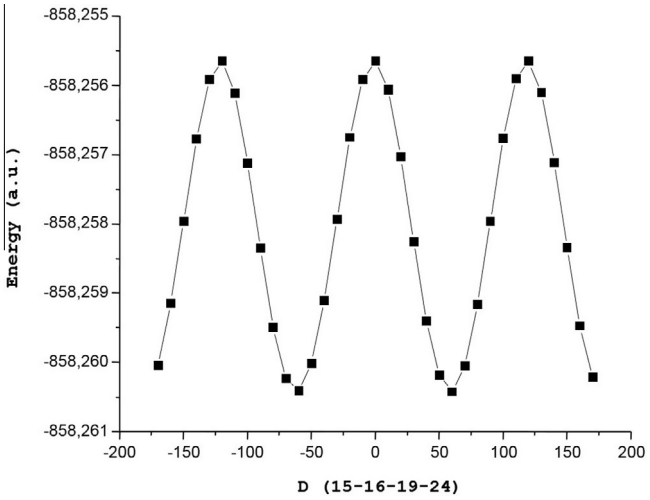

Fig. 1. 1-D PES scan plot for dihedral angle D[15-16-19-24].

2. Experimental details

The sample of PTH was obtained from Biofarma Pharmaceutical Industry Co. Inc and used without any purification. The FT-IR spectra of the title molecule were measured using an ATR unit (Pike Technologies, Gladi ATR, diameter of 3 mm, angle of incidence is 45°) by using Perkin Elmer Spectrum 400 FT-Mid IR and FT-Far IR system spectrometer in the ranges 4000–450 and 700–30 cm^{-1}, respectively. The spectral resolution was 4 cm^{-1} and 200 scans were performed. Deuteration was accomplished by repeated exchanges with D_2O at room temperature.

The FT-Raman spectrum of the powered sample was recorded on a Bruker RFS 100/S FT-Raman instrument using 1064 nm laser excitation source from an Nd:YAG laser. Ge detector was cooled by liquid nitrogen and 100 scans were accumulated. All spectra were recorded for PTH at room temperature.

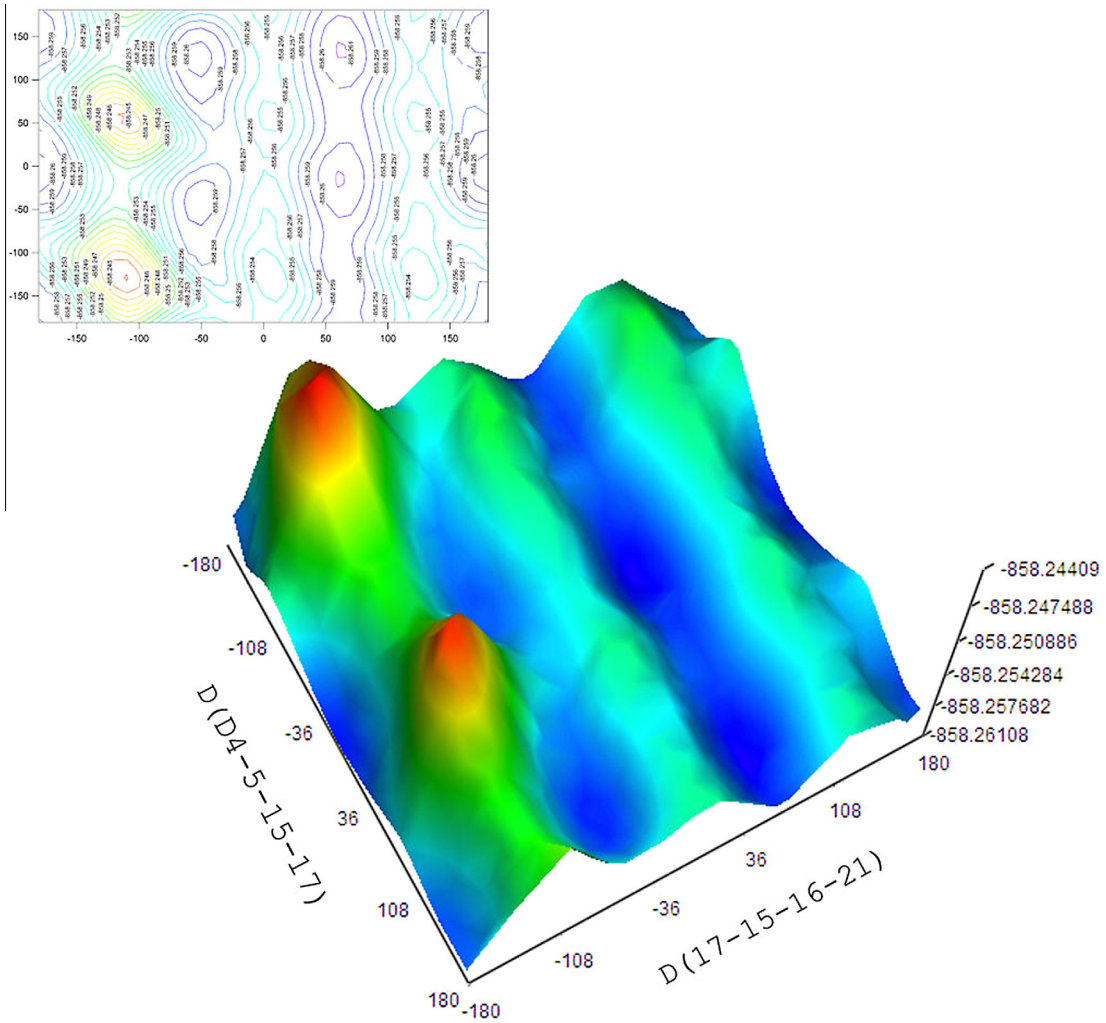

Fig. 2. 2-D PES scan plot for dihedral angles D[4-5-15-17] and D[17-15-16-21].