

Vibrational structure of free and hydrogen bonded complexes of isoniazid: FT-IR, FT-Raman and DFT study

Introduction

At present, the accepted treatment of tuberculosis is achieved by drugs involving a combination of soniazid, pyrazinamide, ethambutal, rifampicin, etc. molecules. There are three main properties of antituberculosis drugs: bactericidal activity, sterilizing activity and the ability to prevent resistance. The essential antituberculosis drugs possess these properties to different extents. Isoniazid (INH) and rifampicin are the most powerful bactericidal drugs active against all populations of TB bacilli [1,2].

INH molecule can form complexes through its nitrogens and oxygen as a ligand. The NH_2 group hydrogens behave as donors and nitrogen and oxygen behave as acceptors. In this paper we report the molecular modeling study of isoniazid and its water complexes together with experimental FT-IR and FT-Raman spectra of INH. L.H. Jensen studied the crystal structure of INH [3], Yu Wang et al. studied the SER spectra of INH [4] and Silva et al. studied the experimental and theoretical structure characterization of two isoniazid derivatives [2]. The aim of this study is to determine the vibrational modes and wavenumbers of free and hydrogen bonded complexes of INH in the framework of the density functional method both at harmonic and anharmonic levels, to investigate the hydrogen bonding interactions by modelling three different water complexes of the molecule, the solvent effect on this molecule and to determine the wavenumbers that are scaled to get the best fit of the calculated wavenumbers to the observed ones and compare them with the anharmonic wavenumbers.

Experimental

The IR spectrum of the KBr disc of microcrystalline INH was recorded on a Jasco 300 FT-IR spectrometer in the range $400\text{--}4000\text{ cm}^{-1}$ (2 cm^{-1} resolution). The FT-Raman spectra of the microcrystalline and aqueous solution of INH were recorded on a DigiLab FTS 7000 FT-Raman instrument using 1064 nm excitation from an Nd:YAG laser. The laser power was 100 mW , the detector was a liquid nitrogen cooled Ge detector and 250 scans were accumulated at a resolution of 4 cm^{-1} . The SER and

Raman spectra of INH [4] were also obtained from literature for comparison.

Calculations

The geometry optimizations and vibrational wavenumber (both harmonic and anharmonic) calculations of INH and three H₂O-INH complexes (see Fig. 1a–d) were carried out with the Gaussian 03 package [5]. DFT method with Becke3Lyp functional [6] and 6-31 G++(d,p) Pople et al. basis set [7] has been used. (see Fig. 2). For the solvent effect calculation, the PCM (Polarizable Continuum Model) implemented in G03 was used as the solvent being water. The overall scaling factor for the molecule has been obtained and the scaled wavenumbers were compared with the anharmonic wavenumbers. The total energy distributions (TED %) of the vibrational modes have been calculated with the scaled quantum mechanics (SQM) method [8] by using parallel quantum solutions (PQS) program [9].

Conclusion

Vibrational analysis of isoniazid molecule together with its H₂O complexes have been performed based on DFT method with Becke3Lyp functional and 6-31G++(d,p) Pople and co-workers basis set both at harmonic and anharmonic levels and with solvent effect (Polarizable Continuum Model is chosen with the solvent as water) added. There is a reasonable overall agreement between the calculated results and those experimentally obtained. The results have been compared to those obtained by scaling factor method and the best agreement between the observed and calculated wavenumbers has been obtained when anharmonic corrections were taken into account. The H₂O complex analysis of the molecule has clearly shown that H bonding interactions exist in the crystal structure both through the N₁₃ - H₁₅ bond and the O atom in carboxyl group.