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Spectroscopic investigations, molecular interactions, and molecular docking studies on the potential inhibitor "thiophene-2-carboxylicacid"

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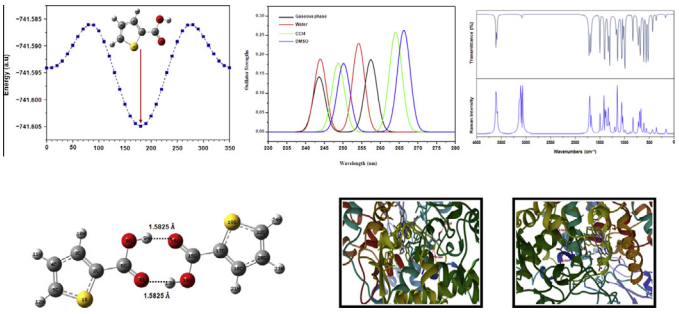
HIGHLIGHTS

- Vibrational FT-IR spectrum has been recorded and compared with simulated spectra.
- Charge transfer characteristics are analyzed by natural atomic orbital occupancies.
- Existence of dimer through carboxylic acid is discussed by NBO analysis.
- UV–Vis spectra of TCA in different solvents were simulated theoretically.
- The inhibition activities of TCA against 1CX2 and 1PTH have been discussed.

GRAPHICAL ABSTRACT



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ABSTRACT

Thiophene derivatives have been focused in the past decades due to their remarkable biological and pharmacological activities. In connection with that the conformational stability, spectroscopic characterization, molecular (inter- and intra-) interactions, and molecular docking studies on thiophene-2-carboxylicacid have been performed in this work by experimental FT-IR and theoretical quantum chemical computations. Experimentally recorded FT-IR spectrum in the region 4000–400 cm^{-1} has been compared with the scaled theoretical spectrum and the spectral peaks have been assigned on the basis of potential energy distribution results obtained from MOLVIB program package. The conformational stability of monomer and dimer conformers has been examined. The presence of inter- and intramolecular interactions in the monomer and dimer conformers have been explained by natural bond orbital analysis. The UV–Vis spectra of the sample in different solvents have been simulated and solvent effects were predicted by polarisable continuum model with TD-DFT/B3LYP/6-31+G(d,p) method. To test the biological activity of the sample, molecular docking (ligand–protein) simulations have been performed using SWISSDOCK web server. The full fitness (FF) score and binding affinity values revealed that thiophene-2-carboxylicacid can act as potential inhibitor against inflammation.

Introduction

In the last two decades, several thiophene derivatives were studied by researchers in the spectroscopic and medicinal field due to their remarkable pharmacological and biological activities.

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Generally, they are being used as a chemical intermediate for the preparation of drugs, dyes and aroma compounds [1,2]. In particular, a title molecule thiophene-2-carboxylicacid (abbreviated as TCA) was reported as potential inhibitors of HCV NS58 polymerase and HCV subgenomic RNA replication [3,4]. Moreover, TCA molecule exhibit antiporphyric activity in allylisopropylacetamide treated animals [5]. The inhibition activity of Carbazolothiophene-2-carboxylic acid derivatives against endothelin-1 has been reported by Babu et al. [6]. Inhibition of endothelin-1 prevents pulmonary vasculature constriction and thus decreases pulmonary vascular resistance. Deng et al. reported Thieno[3,2-b]thiophene-2-carboxylic acid derivatives as GPR35 agonists [7]. GPR35 is an inhibitor drug used for treatment of Parkinson's disease, inflammation, pain, cardiovascular diseases, and metabolic disorders [8,9].

Due to their high impact in the medicinal field, certain thiophene derivatives have been studied earlier [10–19]. The scaled quantum chemical force filed calculations and vibrational spectra of liquid thiophene and methyl substituted thiophene derivatives have been studied by Pasterny et al. and Hernández et al. [10,11], respectively. Theoretical DFT, experimental Raman and NMR studies on thiophene, 3-methylthiophene and selenophene have been performed by Kupka et al. [12]. The conformational stability and normal coordinate analysis of thiophene-2-aldehyde were investigated by Fleming et al. [13]. Singh et al. investigated solvation effects of thiophene in two different polar solvents and also performed vibrational assignments in both experimental and theoretical aspects [14]. Vibrational spectroscopic characterization of 2-Dicyanovinyl-5-(4-N,N-dimethylaminophenyl) thiophene has been studied by Hong et al. [15]. Recently, the spectroscopic investigation of thiophene-2-carbohydrazide and N′-(Adamantan-2-ylidene)thiophene-2-carbohydrazide have been reported [16,17]. The enzyme inhibition activity of organotin (IV) derivatives of thiophene-2-carboxylic acid has been evaluated by Abbas et al. [18]. The molecular docking studies along with antimicrobial evaluation of thiophene bearing sulfisoxazole moiety have been performed by Nasr et al. [19]. The tentative assignment without detailed interpretation of FT-Raman spectrum of thiophene-2-carboxylicacid has been proposed by Sarswat et al. [20]. In the present study, the detailed interpretation of vibrational spectra, molecular interactions, and molecular docking studies on thiophene-2-carboxylicacid have been reported.

Experimental and computational details

The thiophene-2-carboxylic acid with a stated purity of 98% was purchased from Sigma Aldrich Company, India. The infrared spectrum of the sample was recorded on a BRUKER FT-IR instrument with a spectral resolution of 1.0 cm^{-1} in the region 400 to 4000 cm^{-1}. A KBr pellet of solid sample was prepared from the mixture of KBr and the sample in 200:1 ratio using hydraulic press. Multi-tasking OPUS software was used for signal averaging, signal enhancement, base line correction and other spectral manipulations. The FT-Raman spectrum was recorded using BRUKER RFS 27 stand alone FT-Raman spectrometer as powder sealed in a capillary tube in the region 0–4000 cm^{-1}. The line 1064 nm of Nd:YAG laser was used as an exciting source with an output power of about 100 mW at the sample position. Spectrum was accumulated for 100 scans with a resolution of 2 cm^{-1}.

The implementation of theoretical computations usually gives us supportive evidence to the experimental results. In this work, theoretical density functional method has been approached to find the single point energy, geometry optimization, potential energy scan, vibrational frequencies and second order perturbation energies of the title molecule. The entire calculations have been carried out using Gaussian 03W software package with the internally stored DFT/B3LYP/6-31+G(d,p) basis set [21–23]. For spectrum simulations and isodensity plots, visualization interface Gauss View 3.0 has been used [24]. The vibrational frequency assignments of this molecule were carried out using MOLVIB program package [25]. The interactions of TCA with certain protein structures which are responsible for inflammation have been analyzed docking simulation. In this work, docking simulations have been performed by SWISSDOCK webserver and the docking results were viewed with the help of UCSF Chimera visualization program [26,27].

Result and discussion

Energy minimization of Monomer

In the present work, single point energy for various possible conformers of the title molecule is determined and is given in Fig. S1 (Supplementary material). Stationary point on the potential energy surface has been found by varying dihedral angle (C_2—C_6—O_8—H_9) of the minimum energy conformer. It is also found that dihedral angle positioned at 180° gives local minima (E_{min} = −741.6049 Hartree) of the title molecule. The stationary point energy for the other dihedral angle positions and their relative energy with the stable conformer are given in Table S1 (Supplementary material). The potential energy surface scan along with structure corresponding to local minima is given in Fig. 1. The optimized geometrical parameters of minimum energy conformer of the title molecule are collected in Table 1. It is worth mentioning that the C—C bonds in the five member ring vary from 1.3756 Å to 1.4200 Å. Typically, the C—C bonds to the carbons adjacent to the sulfur are about 1.34 Å, the C—S bond length is around 1.70 Å, and the other C—C bond is about 1.41 Å for thiophene [28]. The substitution of carboxylic acid group in the ring produces diverse effect on both bond lengths and bond angles. In the title molecule, the C—C bonds to the carbons adjacent to the sulfur calculated at DFT/B3LYP with 6-31+G(d,p) basis set are about 1.3759 Å (C_4—C_5) and 1.38 Å (C_2—C_3). The C—S bond lengths are about 1.7253 Å (S_1—C_5) and 1.7429 Å (S_1—C_2), and the other C—C bond in the ring is about 1.42 Å.

On the other hand, when we look into the bond angles, we can find a variation of 2° in comparison with that of thiophene. For thiophene molecule, the bond angle at the sulfur is usually around 93°, the C—C—S angle is around 109° and the other two carbons have a bond angle around 114°. In the title molecule, the calculated

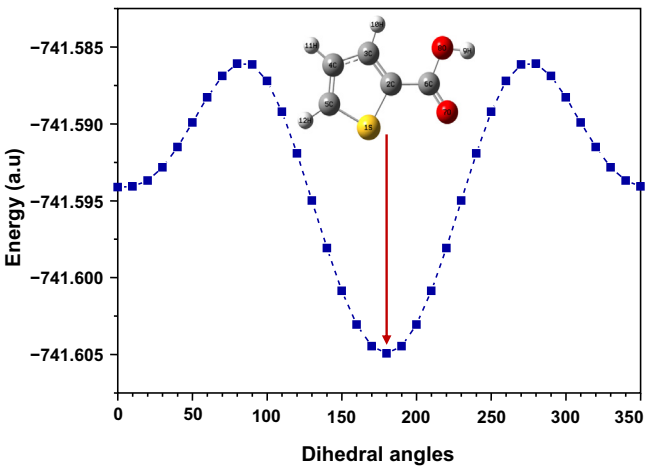

Fig. 1. Potential energy scan for the selected dihedral angle (C_2—C_6—O_8—H_9) of thiophene-2-carboxylicacid.