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Experimental and theoretical investigation of 5-para-fluoro-benziliden-tiazolidin-2tion-4-ona

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The 5-para-fluoro-benziliden-tiazolidin-2-tion-4-ona molecule was recently synthesized in the Department of Pharmaceutical Chemistry, UMF “Iuliu Hatieganu” Cluj-Napoca, and it was shown to be a very efficient antibiotic that has a superior activity to ampicilin on beta-hemolytic Streptococcus. The molecular vibrations of 5pFBTT were investigated in polycrystalline sample, at room temperature, by Fourier Transform Infrared Spectroscopy (FT-IR), IR-ATR and FT-Raman spectroscopy. In parallel, quantum chemical calculations based on Density Functional Theory (DFT) are used to determine the geometrical, energetic and vibrational characteristics of the molecule. All the possible conformers and tautomers have been considered and analyzed by theoretical methods. All the experimental vibrational bands of 5pFBTT were assigned to normal modes on the basis of DFT calculations at the B3LYP and BLYP levels of theory in conjunction with the standard 6-31G(d) basis set. Using a uniform scaling of calculated frequencies, a very good correlation was obtained between the experimental and theoretical vibrational data.

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1. Introduction

DFT methods are increasingly applied to representative pharmacological compounds aiming to elucidate their molecular structures, electronic properties and bonds, the establishment of electronic and structural factors of selected reactions and their mechanisms.

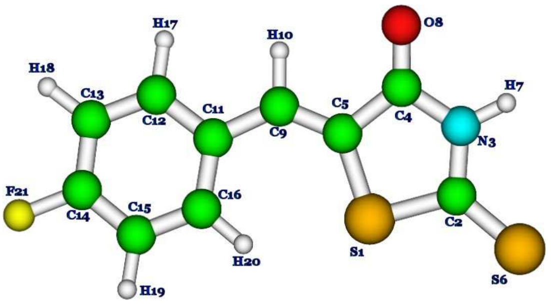

Fig. 1. Molecular structure and atom numbering scheme for 5 – para – fluoro - benziliden- tiazolidin-2-tion-4-ona molecule.

These studies contribute to the recognition of structure-activity relationships and to the understanding of the properties and system behavior. For a proper understanding of IR and Raman spectra, a reliable assignment of all vibrational bands is essential. For this purpose, the quantum chemical methods, ranging from semi-empirical to DFT approaches, are invaluable tools [1-3], each method having its own advantages. The semi-empirical calculations provide very fast, and in certain circumstances fairly good theoretical results, being applicable to large molecular systems. The Hartree-Fock *Ab Initio* methods are able to give good results provided a reasonable basis set and an appropriate correlation treatment is taken into account. On the other hand, DFT methods, particularly hybrid functional methods [4], have evolved to a powerful quantum chemical tool for the determination of the electronic structure of molecules. In the framework of DFT approach, different exchange and correlation functionals are routinely used. Among these, the B3LYP combination [5,6] is the most used since it proved its ability in reproducing various molecular properties, including vibrational spectra. The combined use of B3LYP functional and standard split valence basis set 6-31G(d) has been previously shown [7-9] to provide an excellent compromise between accuracy and computational efficiency of vibrational spectra for large and medium-size molecules.

2. Experimental

The experimental techniques used in the study of 5-para-fluoro-benziliden-tiazolidin-2-tion-4-ona molecule are: FT-IR/ATR and FT-RAMAN. FT-IR/ATR spectra for 5-pFBTT powder sample were recorded at room temperature on a conventional Equinox 55 FT-IR spectrometer equipped with an InGaAs detector, coupled with a Bruker Miracle ATR sampling device. The FT-Raman spectra were recorded in a backscattering geometry with a Bruker FRA 106/S Raman accessory attached to the FT-IR spectrometer. The 1064 nm Nd:YAg laser was used as excitation source, and the laser power was set to 400 mW. All spectra were recorded with a resolution of 4 cm^{-1} by co-adding 32 scans.

3. Computational details

The molecular geometry optimizations and vibrational frequencies calculations were performed with the Gaussian 98 W software package [10] by using DFT methods with B3LYP functional, which has been previously shown to perform very well for vibrational spectra calculations [11]. The basis set used in these calculations is 6-31G(d). The geometries were fully optimized without any constraint with the help of analytical gradient procedure implemented within Gaussian 98 W program. Vibrational mode assignments were made by visual inspection of modes animated by using the Molekel program [12]. The calculated molecular properties are: equilibrium geometries and vibrational spectra (IR and Raman).

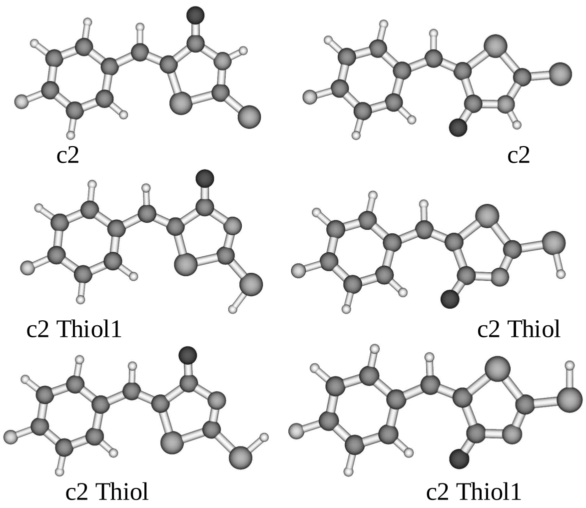

Fig. 2. Optimized geometries for the possible conformers and tautomers of 5-pFBTT.

4. Results and discussion

Due to its complexity, it is possible for this molecule to present more conformers. Moreover, each conformer may exist in two tautomeric forms as thion and thiol, respectively. First we optimized the geometries for all the possible conformers and tautomers for 5-pFBTT molecule. The optimized structures are given in Fig. 2 and their absolute and relative energies are summarized in Fig. 3.

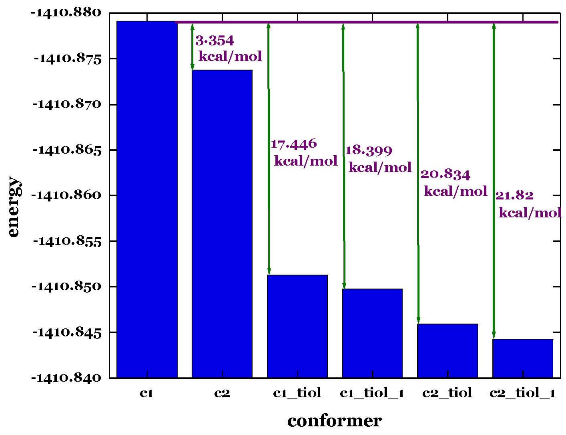

Fig. 3. Total and relative energies for the equilibrium geometries of the conformers and tautomers of 5-pFBTT molecule.

The geometries were fully optimized without any constraint at B3LYP/6-31G(d) level of theory. No imaginary frequencies were obtained for optimized geometries and thus, all the optimized structures represent true minima on the potential energy surface. Comparing the calculated energies for each conformer we found that the lowest energy conformer is C1 conformer in its thionic form, as shown in Fig. 3.

The small difference between the energy of the two thionic conformers of 5-para-fluoro-benziliden-tiazolidin-2-tion-4-ona (C1 and C2) suggest that very possible, the two conformers coexist in liquid phase, so that for a careful analysis of the solvent effects, the two contributions must be taken into account.

In Fig. 4 are given the experimental FT-Raman, FT-IR and ATR spectra. Normal mode frequencies have been calculated by using the Gaussian program [10] and the computed wave-numbers have been scaled by 0.9614 [13]. Theoretical values were obtained from calculations made on a single molecule of 5-pFBTT.

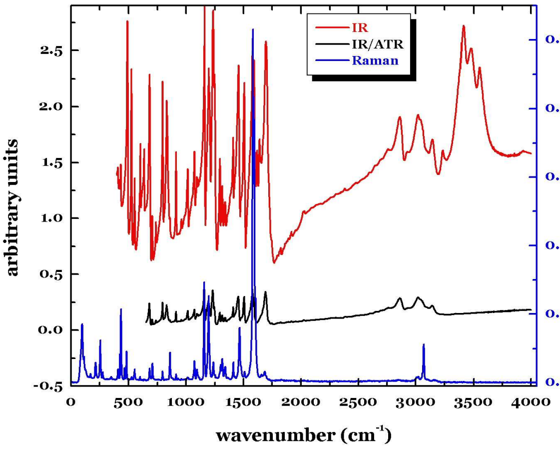

Fig. 4. Experimental vibrational spectra of 5-pFBTT. From top to bottom: FT-IR, FT-IR/ATR and FT-Raman spectra.

According to calculations, the experimental band at 3466 cm^{-1} in IR spectrum corresponds to the ν(NH) stretching vibration. The corresponding theoretical value for the gas-phase molecule is 3461 cm^{-1}, in very good agreement with experiment. The ν(CH) vibrations are predicted by B3LYP/6-31G(d) calculations in very good agreement with experiment: theoretical values are between 3110 cm^{-1} and 3045 cm^{-1}, while the experimental counterpart can be found between 3101 cm^{-1} and 3055 cm^{-1}.

Another characteristic band is that due to the ν(CO) vibration which is seen in the infrared experimental spectrum at 1746 cm^{-1}, the calculated value being 1742 cm^{-1}, and according to calculations, this mode is coupled with ν(CC), δ(NH) and δ(CH) vibrations. ν(CC) vibrations give rise to experimental bands at 1617, 1591, 1560 and 1294 cm^{-1} with theoretical counterparts at 1608, 1589, 1566 and 1293 cm^{-1}. Stretching vibrations of CN bond are seen in the experimental spectrum at 1384 and 1207 cm^{-1}, the calculated values being 1401 and 1213 cm^{-1}, respectively. The positions and infrared intensities of these bands are very well reproduced by B3LYP/6-31G(d) calculations.

The experimental vibrational bands for the δ(CCC) trigonal bending vibrations are located at 988, 808, 706 and 602 cm^{-1} with corresponding calculated values at 991, 812, 708 and 604 cm^{1}.

As resulted from this analysis, a very good overall agreement is obtained between the experimental and theoretical infrared spectrum of 5-pFBTT molecule and this fact confirms the assignment of vibrational spectrum of this molecule.

5. Conclusions

The main conclusions of our work can be summarized as follows:

i) the most stable conformer of 5-para-fluoro-benziliden-tiazolidin-2-tion-4-ona molecule is the thionic conformer with S1 atom in cis position with respect to C16 atom.

ii) the small energetic difference between the two thionic conformers suggest that in liquid or gas-phase both conformers could contribute to the vibrational and NMR spectrum of this molecule.

iii) the very good match between the experimental and calculated normal modes wave-numbers of 5-pFBTT molecule allow us to safely assign the vibrational spectrum of the molecule.

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