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Experimental and DFT investigation of 5-para-nitro-benziliden-tiazolidin-2-tion-4-ona

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The molecular vibrations of 5pNBTT were investigated by FTIR and FT-Raman spectroscopies. 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 of 5pNBTT have been analyzed by theoretical methods and their relative stability is discussed. The vibrational IR and Raman spectra of the 5pNBTT molecule have been computed using DFT calculations and the experimental vibrational bands were assigned to the calculated normal modes. The molecular electrostatic potential of the molecule has been calculated and used for predicting site candidates of electrophilic attack. Overall, the very good correlation found between the experimental and theoretical vibrational data allows us to validate the structure and geometrical parameters of the molecule.

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1. Introduction

Since the discovery of the antibiotic action of tetracycline, a large number of different compounds and derivatives have been synthesized, aiming to obtain potent antibiotics without side effects. The title molecule (5-pNBTT) has been recently synthesized and the preliminary results proved that it is a very efficient antibiotic, having a superior activity to ampicillin used as a reference standard.

For a better understanding of the molecular properties of pharmacological compounds, FTIR and Raman spectroscopies are very useful tools, especially when they are coupled with theoretical approaches. DFT methods are increasingly applied to representative pharmacological compounds aiming to elucidate their molecular structures and electronic properties and further to investigate the influence of electronic and structural factors on the reactions in which these compounds are involved. These studies contribute to the recognition of structure-activity relationships and to the understanding of the system properties and 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 semiempirical to DFT approaches, are invaluable tools [1-3], each method having its own advantages. DFT methods, particularly those using hybrid exchange-correlation functionals [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] 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, 20-23] to provide an excellent compromise between accuracy and computational efficiency of vibrational spectra for large and medium-size molecules.

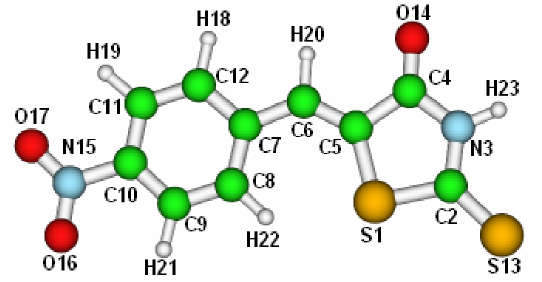


Fig. 1. Molecular structure and atom numbering scheme for 5-pNBTT.

Theoretical studies of bioactive compounds are of interest in order to gain a deeper insight into their action mechanism and consequently, for helping in the design of new drugs with therapeutic effects.

Molecular electrostatic potential (MEP) is related to the electronic density and is a very useful descriptor in understanding sites for electrophilic attack and nucleophilic reactions as well as hydrogen bonding interactions [14-17]. MEPs are also well suited for analyzing processes based on the "recognition" of one molecule by another, as in drug–receptor, and enzyme–substrate interaction, because it is through their potentials that the two species first "see" each other. Thus, the knowledge of physicochemical properties and sites of reaction of 5-pNBTT molecule will provide a deeper insight of its probable action.

2. Experimental

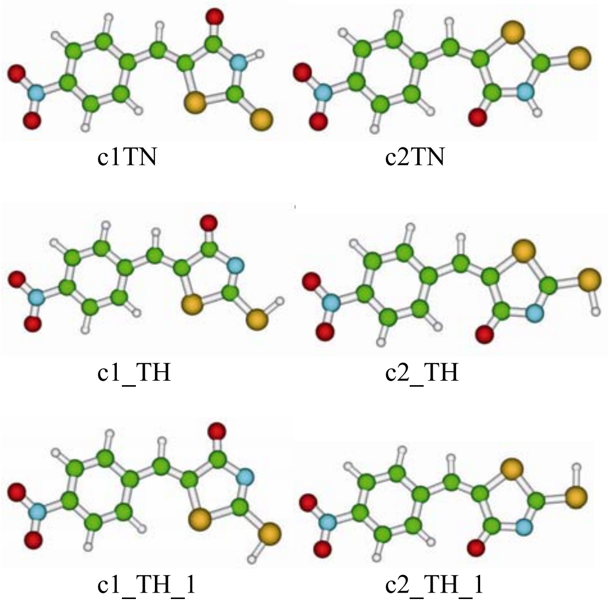
FTIR/ATR spectra for 5pNBTT powder sample were recorded at room temperature on a conventional Equinox 55 FTIR spectrometer, coupled with a Bruker Miracle ATR sampling device. FT-Raman spectra were recorded in a backscattering geometry with a Bruker FRA 106/S Raman accessory equipped with a nitrogen cooled Ge detector. 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 03W software package [10] by using DFT calculations with B3LYP functional, which has been previously shown to perform very well for calculations of different molecular properties [11]. The basis set used in these calculations is 6-31G(d). The geometries were fully optimized with the help of analytical gradient procedure implemented within Gaussian 03W program. Vibrational mode assignments were made by visual inspection of modes animated by using the Molekel program [12].

4. Results and discussion

Due to the presence of one benzenic and one thiazolidinic ring in the structure of 5-pNBTT molecule, two conformers are possible, one with oxygen atom O14 (see Fig. 1 for atom numbering scheme) in *trans* position with respect to the carbon C8 atom (c1 in Fig. 2) and the second with O14 in *cis* position relative to C8 (c2 in Fig. 2). Moreover, each conformer may exist in two tautomeric forms as thione and thiol, respectively.



c1TN c2TN

c1_TH c2_TH

c1_TH_1 c2_TH_1

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

The thiolic tautomers may exist also in two conformations (TH and TH1 in Fig. 2) depending on the orientation of SH bond with respect to thiazolidinic ring.

First we optimized the geometries of all the possible conformers and tautomers for 5-pNBTT molecule at B3LYP level of theory using the standard 6-31G(d) basis set. No imaginary frequencies were found for the obtained geometries and thus, all the optimized structures represent true minima on the potential energy surface. The optimized structures are given in Fig. 2, and their relative energies are given in Fig. 3.

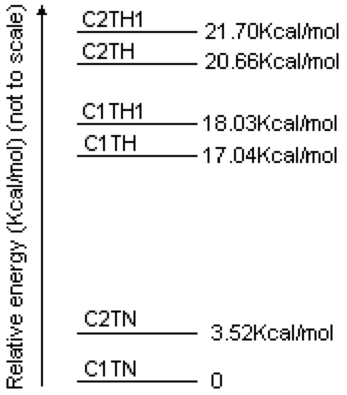


Fig. 3. Relative energies of the gas-phase conformers and tautomers of 5-pNBTT molecule.

According to theoretical results, c1 conformer in its thionic form represents the lowest energy conformer. The small difference between the energy of the two thionic conformers of 5-para-nitro-benziliden-tiazolidin-2-tion-4-ona (c1TN and c2TN) suggests 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 FT-IR/ATR spectra of 5pNBTT. Normal mode frequencies have been calculated with the Gaussian 03 program [10] using the hybrid B3LYP functional and the computed wave-numbers have been scaled by 0.9614 [13].

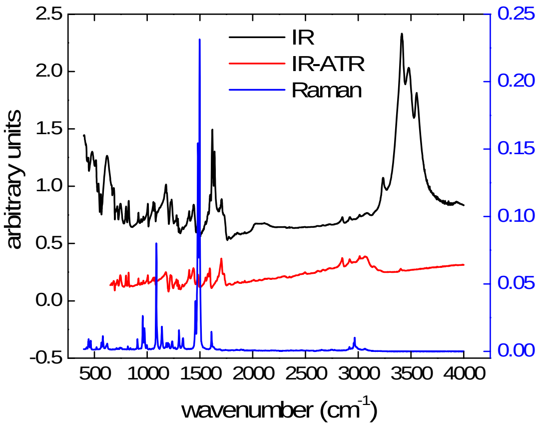


Fig. 4. Experimental vibrational spectra of 5-pNBTT; from top to bottom: FTIR, FTIR/ATR and FT-Raman spectra.

According to calculations, the experimental band at 3477 cm^{-1} in the IR spectrum corresponds to the ν(NH) stretching vibration. The corresponding theoretical value for the gas-phase molecule was found at 3475 cm^{-1} (using the B3LYP/6-31G(d) method), in good agreement with the experimental values. This fact supports the conclusion that in solid state the NH group does not participate in hydrogen bonding because in this case an important red shift of ν(NH) wave number should be expected. The ν(CH) vibrations were predicted by B3LYP/6-31G(d) calculations in very good agreement with the experimental data: the theoretical values are 3124 cm^{-1}, 3123 cm^{-1}, and 3043 cm^{-1}, and the corresponding experimental values are 3173 cm^{-1}, 3119 cm^{-1} and 3049 cm^{-1} respectively.

Another characteristic band is due to the ν(CO) vibration which is seen in the infrared experimental spectrum at 1717 cm^{-1}, while the calculated value is shifted to 1747 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 1607, 1588, and 1533 cm^{-1}, and the corresponding theoretical bands were found at 1605, 1581, and 1546 cm^{-1} respectively.

The most intense band in the experimental FT-IR spectrum is observed at 1344 cm^{-1}, while the B3LYP calculations predict the most intense band at 1340 cm^{-1}. It is due to the in-plane $\delta(NO_2)$ deformations coupled with δ(CH) bendings. The most intense band in the experimental Raman spectrum is located at 1588 cm^{-1} and according to calculations it corresponds to the ν(CC) and δ(CH) vibrational modes. The corresponding B3LYP calculated value is 1581 cm^{-1}, this band having also the largest theoretical Raman activity.

The experimental vibrational bands with contributions from δ(CCC) trigonal bending vibrations are located at 1236, 1191, 1097, 1009, 848, 769, 684, 620, and 571 cm^{-1} with corresponding calculated values at 1251, 1160, 1086, 1015, 843, 763, 683, 635, and 572 cm^{-1} respectively. The largest deviation between the experimental and theoretical wavenumbers is 49 cm^{-1} and it corresponds to the ν(CH) vibration. The whole Raman spectrum have been reproduced with a standard deviation of 11.8cm^{-1}, a value which confirms a safely and reliable assignment of this spectrum for 5-pNBTT molecule.

Molecular electrostatic potentials have been used extensively for interpreting and predicting the reactive behavior of a wide variety of chemical systems in both electrophilic and nucleophilic reactions, the study of biological recognition processes and hydrogen bonding interactions [18]. Unlike many of the other quantities used at present and earlier as indices of reactivity, *V*(r) is a real physical property that can be determined experimentally by diffraction or by computational methods. For the systems studied the MEP values were calculated as described previously, using the equation [19]:

$$V(r) = \sum_{A} Z_A / |R_A - r| - \int \rho(r') / |r' - r| dr'$$

where the summation runs over all the nuclei A in the molecule and polarization and reorganization effects are neglected, Z_A is the charge of nucleus *A*, located at R_A and $\rho(r')$ is the electron density function of the molecule.

To predict reactive sites for electrophilic and nucleophilic attack for the investigated molecule, molecular electrostatic potential (MEP) of 5-pNBTT molecule was calculated at the B3LYP/6-31G(d) level of theory, on the corresponding optimized geometries, and its 3D shape is given in Fig. 5. The negative regions of *V(r)* are related to electrophilic reactivity and the positive ones to nucleophilic reactivity. As easily can be seen in Fig.5, this molecule has several possible sites for electrophilic attack in which *V*(*r*) calculations have provided insights. Negative regions of V(r) are associated with O14, O16 and O17 atoms. The most negative V(r) value is associated with O14 with a value around –0.0907 a.u. while the O16 and O17 values are about –0.0799 au, and -0.0691 au respectively. Thus, it would be predicted that an electrophile will preferentially attack 5-pNBTT molecule at the O14 position. Alternatively, we found a maximum value of 0.12523 a.u. on the H23 atom on the positive regions of *V*(*r*) indicating that this site can be the most probably involved in nucleophilic processes.

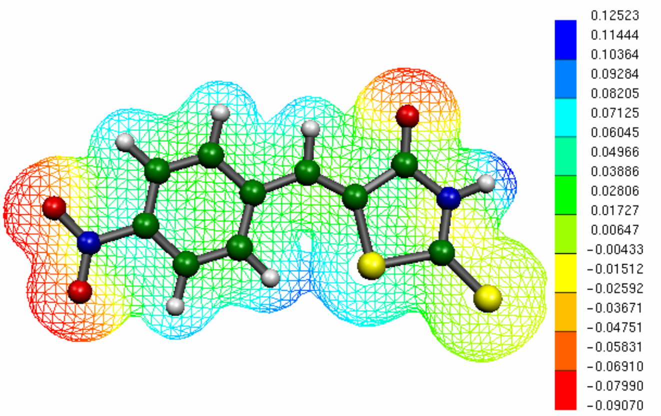


Fig. 5. Calculated 3D molecular electrostatic potential contour map of 5-pNBTT molecule in [au]. The electron density isosurface is 0.02a.u.

5. Conclusions

The most stable conformer of 5-para-nitro-benziliden-tiazolidin-2-tion-4-ona molecule is the thionic conformer with S1 atom in cis position with respect to C8 atom. Thiolic tautomers are significantly higher in energy than thionic conformers. The small energetic difference between the two thionic conformers suggests that in liquid or gas-phase both conformers could contribute to the vibrational spectrum of this molecule.

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

Molecular electrostatic potential calculations suggests that the most suitable atomic site for electrophilic attack or for metal coordination is the O14 atom, while the most probable site which could be involved in nucleophilic processes is H23 atom. Nitrogen atom in the pyrimidinic ring is also a possible site for electrophilic attack.

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