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A DFT analysis of the molecular structure, vibrational spectra and other molecular properties of 5-nitrouracil and comparison with uracil

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ABSTRACT

The four unit cells found in the crystals of the biomolecule 5-Nitrouracil were simulated as tetramer forms by density functional calculations. Four tetramer forms were fully optimized. Specific scale factors and scaling equations deduced from uracil molecule were employed in the predicted wavenumbers of 5-nitrouracil. The experimental FT-Raman and FT-IR spectra were recorded in the solid state. Comprehensive interpretation of the experimental FT-IR and FT-Raman spectra of the compound under study in the solid state is based on potential energy distribution. A good reproduction of the experimental wavenumbers is obtained and the % error is very small in the majority of cases. A complete vibrational assignment in the isolated state was also carried out aided by the theoretical harmonic frequency analysis and the results compared with those reported in Ar matrix. The scaled wavenumbers were used in the reassignment of several experimental bands. A comparison between the molecular structure and charge distribution of 5-Nitrouracil with related 5-uracil derivatives was presented. The effect of the nitro substitution in the 5th position of the pyrimidine ring was evaluated.

1. Introduction

The increasing interest in the spectroscopic studies of N-heterocyclic molecules is due mainly to their biological and pharmaceutical importance. Among these compounds uracil and its 5-substituted derivatives have demonstrated today many biological properties, including those as inhibitors of nucleic acid metabolism [1], and as clinical radiosensitizers of DNA in tumor cells [2], which are used to control damage to healthy tissues in radiation therapy. Also they have been used as antitumor [3,4], antibacterial [5] and antiviral drugs [6]. There is a selective recognition of uracil and its derivatives (including 5-nitrouracil) by the DNA repair enzyme UDG [7]. Also, 5-substituted uracils have been reported to be important core structure of diverse therapeutics. Herein, novel mixed ligand transition metal (Mn, Cu, Ni) complexes of 5-iodouracil and 5-nitrouracil have been synthesized [8].

Uracil contains consecutive hydrogen-bond-donor and acceptor groups. The effects of substituents on the pattern of H-bonding of uracil derivatives may contribute to explain the connection between the structure and the biological function of these nucleobasis [9]. We have studied 5-substituted uracils extensively [10–14], and we present now the results on 5-nitrouracil molecule.

Since the nitro radical is one of the strongest electron-accepting groups in the aromatic molecules, these compounds are found to be among the well-studied materials. Thus, the first thoroughly studied aromatic nitro compound has been 5-Nitrouracil (5-NU), discovered by Jerphagnon et al. [15] in 1971. 5-NU is currently of prime interest to the non-linear optical community [16–21] and is also of relevance to the biological and pharmaceutical sciences [22–25]. In the former case, the origin of the excellent structural properties of 5-NU is an extensive hydrogen bonding network in the crystal [26,27]. The proton-transfer process in the supramolecular structure of the molecular adducts formed by cytosine and 5-fluorocytosine with 5-nitrouracil have been investigated in detail [28].

In the latter case, 5-NU is an important biological compound; e.g. it is found to inhibit [24] the enzyme isoorotate decarboxylase

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(IDCase), which removes the carboxylate from isoorotate to yield uracil, and the thymidine phosphorylase [9]. 5-NU causes a significant growth inhibition of Neurospora crassa mold [29]. It is also one of the few substituted pyrimidines, reported to be active as chemotherapeutic and mutagenic agents, which is able to chelate trace metals [25]. Cu complex of 5-NU has been reported to be the most potent and promising cytotoxic compound [8]. The effectiveness of 5-NU as radiosensitizer has been related to the electron affinity of its nitro group [30]. Moreover, many derivatives of 5-NU have antibacterial activity, antitumor activity on leukemia cells and inhibitory effect on macrophage [31]. Therefore, many works concerning synthesis of new 5-NU derivatives are continously reported. Other applications of 5-NU includes the inhibition of the corrosion of steel [32].

From the spectroscopy point of view, although the NMR [33] and vibrational spectra of many uracil derivatives have been extensively reported [10–12,14], however, the vibrational analysis of 5-NU has only been studied by Stfpan'yan et al. [34] in argon matrix. In this study, the assignments of the bands have been carried out on the basis of MINDO/3 results, and thus some bands appear badly assigned. Therefore, the present investigation was undertaken to study the vibrational spectra of this molecule completely and rigorously for the first time in the isolated state, and to identify and correct the assignments of various normal modes. Previously, a short and first study on the hydration of this molecule was carried out by us [35]. Density functional calculations were performed to support our frequency assignments. Three procedures of scaling were performed. Specific scale factors were also deduced and employed for the prediction of the frequencies.

The other goal of present manuscript was the interpretation of the IR and Raman spectra of 5-NU in the solid state. The crystallographic data of 5-NU have been extensively studied by several authors [25,26,36–38]. The molecules tend to crystallize in different polymorphic structures, depending on the nature of the solvent and the crystallization conditions employed [39,40]. Four crystalline forms have been reported, namely, an optically active orthorhombic anhydrate (form I) [26], a monoclinic monohydrate (form II) [26,36], a monoclinic anhydrate (form III) [37], and a dimethyl sulfoxide-solvated (form IV) [37]. In aqueous solution growth grows a mixture of forms I to III. Thus, we have simulated as tetramer forms A-D the structure and vibrational spectra of the four unit cells found by X-ray.

2. Experimental

The spectrally pure sample of 5-NU (m.p.>300C, solid) was obtained from M/s Sigma Chemical Co, USA and used as such without any further purification. FT-IR spectrum was recorded in the region 400–4000 cm^{-1} on a Perkin Elmer FT-IR 1760 X instrument. Standard KBr pellet technique with 1 mg sample per 300 mg KBr was used for the spectrum. For the spectrum acquisition, 100 scans were collected at 1 cm^{-1} resolution.

The FT-Raman spectrum of solid 5-NU was measured on a Bruker IFS 66 NIR-FT instrument equipped with an integrated FRA 106 Raman Module. A Nd: YAG laser at 1064 nm with an output of 300 mW was used as the exciting source and the spectrum was recorded over 500 scans at a fixed temperature. The detector was a Ge-diode cooled to liquid nitrogen temperature. The upper limit for wavenumbers was 3500 cm^{-1} due to the detector sensitivity and the lower wavenumber is around 10 cm^{-1} due to Rayleigh line cut off by a notch filter.

3. Computational methods

Quantum chemical calculations based on the use of *ab initio* calculations and the density functional theory have been performed for 5-NU molecule. *Ab initio* geometry optimizations and wavenumber calculations were performed using MP2 [41] and density functional theory (DFT) [42] methods with B3LYP, along with the 6-31G(d,p) and 6–311++G(3df,pd) basis set. The presence of both polarization and diffuse functions in the basis set were necessary for a proper theoretical description of the molecular parameters. These procedures are implemented in the GAUSSIAN 09 [43] program package, which was utilized in the UNIX version with standard parameters. Among the DFT methods, B3LYP is the most popular, and it has been used satisfactorily in many studies of DNA components [44–49], of drug designing [50–53], and of other important molecules [54–58]. In DFT calculations the Becke's three-parameter exchange functional (B3) [59] with the non-local correlation functionals of Lee, Yang and Parr (LYP) [60] were selected as more appropriated [61,62].

The optimum geometry was determined by minimizing the energy with respect to all geometrical parameters without imposing molecular symmetry constraints. Berny optimization under the TIGHT convergence criteria was used. Four tetramer forms were simulated and the molecular geometry was built according to the X-ray diffraction data reported in the crystal unit cells. After the geometry is minimized, other properties were computed. The vibrational wavenumbers under harmonic approximation were calculated at the same level of theory of the respective optimization process, to characterize the stationary points and to evaluate the wavenumbers shifts due to tetramer formation. All the optimized structures showed positive harmonic vibrations only (true energy minimum). For the calculations of the zero-point vibrational energy (ZPE), the wavenumbers were retained unscaled. The natural NBO atomic charges were computed because they appear as the most accurate today to correlate properties.

Raman scattering activities (S_i) calculated by Gaussian 09 program were suitably converted to relative Raman intensities (I_i) using the following relationship derived from the basic theory of Raman scattering [63–65]:

$$I_i = \frac{f(\nu_0 - \nu_i)^4 S_i}{\nu_i[1 - \exp(-hc\nu_i/kT)]}$$

where f is the suitable chosen common scaling factor for all the peak intensities, ν_o is the laser exciting frequency (cm^{-1}); in this work we have used the exciting wavenumber $\nu_o = 9938.5$ (which corresponds to the wavelength of 1064 nm of a Nd:YAG laser), ν_i is the vibrational wavenumber of the ith normal mode, and h, c and k are universal constants.

4. Results and discussion

4.1. Geometry optimization

4.1.1. Isolated state

In the isolated state the optimized geometrical parameters in 5-NU using HF, MP2 and B3LYP methods and the 6-31G(d,p) basis set are listed in Table 1, in accordance with the atom numbering scheme given in Fig. 1. This molecule has a strong-acceptor group, the nitro group, and although its cyclic structure is considered nonaromatic, however, some interactions are expected to occur between the π electrons of the C=C double bond and the nonbonding electrons of the out-of-plane p_z orbital of the sp^2 hybridized nitrogen atoms belonging to the N–H groups. The nitro group may also interact with the electrons of the uracil ring [17].

In the isolated state, 5-NU molecule is planar by B3LYP, but by HF the planar conformation is a saddle point. In the optimum form by