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Vibrational spectra, tautomerism and thermodynamics of anticarcinogenic drug: 5-Fluorouracil

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ABSTRACT

The FT-IR and FT-Raman spectra of 5-Fluorouracil were recorded in the solid phase in the regions 400–4000 cm^{-1} and 50–4000 cm^{-1}, respectively. The vibrational spectra were analysed and the observed fundamentals were assigned to different normal modes of vibration. The experimental wavenumbers were compared with the scaled vibrational values using DFT methods: the Ar matrix data were related to gas phase calculations, while the values of the solid state spectra were compared to those with dimer simulations. The study indicates that some features that are characteristic of vibrational spectra of uracil and its derivatives are retained in the spectrum of 5-fluorouracil and it exists in ketonic form in the solid phase. The tautomerism was also studied and the spectra of the two most stable forms were simulated. The calculated wavenumbers have been employed to yield thermodynamic properties.

1. Introduction

It is well known that the vibrational spectra constitute an important characteristic of a molecule, and the common application of theoretical data and experimental results allow to draw detailed conclusions concerning the relation between the structure of a molecule and the exhibition of its specific properties in real conditions. The vibrational spectra also give important information for the effective investigation of H-bond formation [1].

Uracil and its derivatives, constituents of genetic materials play a pivotal role in basic biological processes. Their vibrational spectra have been studied extensively [2–13] by semiempirical [4,14] and ab initio [4,8–10,13] methods. Halogenated pyrimidines were synthesized in the 1957–1959s as potential anti-tumor agents after the successful discovery that certain tumors preferentially incorporated uracil rather than thymine into the DNA [15]. Transformation of uracil into 5-X uracil (X = halogen) significantly changes its chemical and spectroscopic properties, as well as its *in vivo* activity. They have been found to exert profound effects in a variety of microbial and mammalian agents and are used as antitumor, antibacterial and antiviral drugs. However, the mechanism of their biological activity is not fully understood and requires further studies.

5-Fluorouracil (5-FU), Fig. 1, a well-known anticancer drug, was first synthesized in 1957 [16] and it is being used since then for the treatment of solid tumors [17,18]. It belongs to the family of drugs called antimetabolite. It is a pyrimidine analogue. 5-FU was introduced in the early 1960s as topical chemotherapeutic agent and it has become increasingly accepted because of its efficacy, economy, and relative absence of side effects in treating many pre-cancerous conditions, certain benign and malignant tumors, and dermatoses [19]. However, despite its extensive therapeutic value, there are several side effects with usage of this drug [20]. 5-FU is inactivated by pyrimidine ring reduction carried out by dihydrouracil dehydrogenase, whose high turn over markedly impairs drug efficiency, thus forcing a high dosage and leading to serious cytotoxic effects [21,22].

The vibrational spectra (IR, Raman and FT-Raman) [2,3,13] and SERS [12] of 5-FU have been studied earlier. However, on account of medicinal importance of 5-FU and lack of consensus between the spectral data on it reported in literature, supplementary studies are required on the vibrational spectra of this compound. Therefore, in order to have more consistent interpretation of vibrational spectra, we have reinvestigated the FT-IR and FT-Raman spectra of 5-FU, especially in the solid state, and results are being reported in this paper. In addition the tautomerism in 5-FU was also studied and the spectra of the two most stable forms were simulated.

2. Experimental

5-Fluorouracil (solid state, white crystalline powder, m.p. 300 °C) of spectral grade was obtained from M/s Aldrich chemical (Milwanke, WI, USA) and used as such without any further purification.

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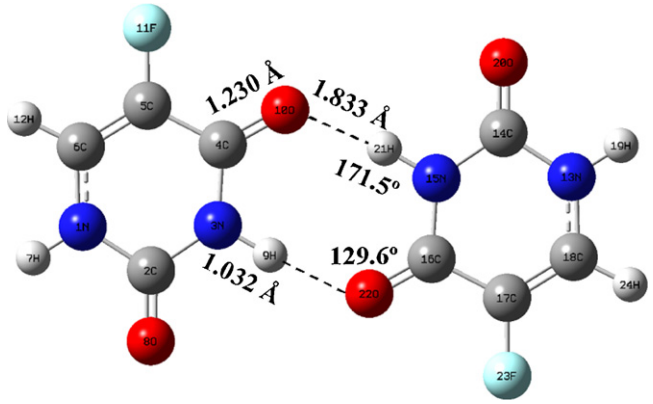

Fig. 1. Optimized dimer form of 5-fluorouracil, with the labelling of the atoms and several parameters of interest.

The mid infrared spectrum of 5-FU from 400–4000 cm^{-1} was recorded with Perkin Elmer FTIR model 1760X instrument using KBr technique with 1 mg sample per 300 mg KBr. For the spectrum acquisition, 4 scans were collected at 4 cm^{-1} resolution, Fig. 2b.

The FT-Raman spectrum of 5-fluorouracil was recorded at room temperature in the powder form in the region 50–4000 cm^{-1} on a Bruker IFS66 optical bench with an FRA 106 Raman module attachment. The sample was mounted on the sample illuminator using an optical mount and no sample pretreatment was undertaken. The NIR output (1064 nm) of an Nd: YAG laser was used to excite (the probe) the spectrum. The instrument was equipped with a liquid-nitrogen-cooled Ge detector. The laser power was set at 100 mW and the spectrum was recorded over 1000 scans at a fixed temperature. The spectral resolution was 6.0 cm^{-1} after apodisation (Fig. 4).

3. Calculations

Quantum chemical calculations using density functional methods (DFT) were performed, mainly with B3LYP, implemented in the GAUSSIAN 03 program package [23]. For the optimization process, 6-31G** and 6-311++(3df,pd) basis set, as well as DGDZVP were utilized. B3LYP was selected for its better accuracy in the wavenumber calculations [9,24]. Full optimization was performed with the option TIGHT and wavenumber calculations were carried out to asses that all the geometries correspond to stationary points (no negative eigenvalue) and as well to predict the theoretical IR and Raman spectra, Table 1 and Figs. 3 and 4.

In solid state 5-FU was simulated in a dimer form, Fig. 1. This dimer was the only one found in the crystal of 5-FU [25], and it is planar and symmetric. The calculated wavenumbers were collected in Table 2, while the simulated IR and Raman spectra with scaled wavenumbers were plotted for comparison purposes in Figs. 3 and 4.

4. Results and discussion

4.1. Isolated state

5-FU is a planar, six membered N-heterocyclic ring molecule, which exhibits 30 normal modes of vibrations, 21 of which are in-plane (a′ species) and 9 are out-of-plane (a″ species). Table 1 shows the reported FT-IR wavenumbers in Ar matrix [13], 10th column. In order to help in the analysis and assignment of the observed wavenumbers, DFT computations of the vibrational spectra were carried out and included in the first two columns of Table 1. The level of earlier [2] calculations was improved in the present paper with the B3LYP/6-311++G(3df,pd) level, the fourth column. We have demonstrated [8,9,24,26], that the computed wavenumbers at the B3P86 and B3LYP/6-31G** DFT methods yield fairly good wavenumbers.

The characterization of the local modes is shown by using the definition of the uracil ring normal modes [26], in 11th column of Table 1. The calculated % potential energy distribution (PED) of the different modes for each vibration appears in the last column of the same table. Contributions lower than 10% were not considered.

An improvement can be carried out in the computed wavenumbers by the use of scaling procedures. To scale the wavenumbers, the simplest procedure is using an overall scale factor, which is the procedure generally applied in the literature [24], but it leads to a high error in the scaled values and impede a clear and accurate assignment of modes. Thus to reduce this error and get a trustworthy assignment two accurate scaling procedures can be

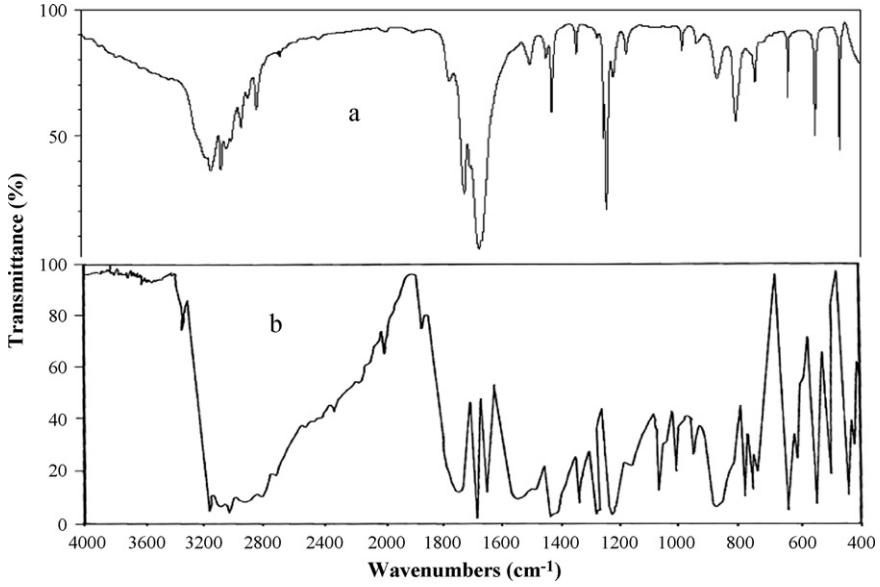

Fig. 2. Experimental IR spectra of 5-flurouracil: (a) from Ref. [42]. (b) Our spectrum at higher concentration of the sample.