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Vibrational spectra and normal coordinate analysis of flucytosine

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A normal coordinate analysis on flucytosine has been carried out with a systematic set of symmetry coordinates following Wilson's F-G matrix method. The potential constants evaluated for the molecule are found to be in good agreement with literature values thereby confirming the vibrational assignments. To check whether the chosen set of vibrational frequencies contributes maximum to the potential energy associated with the normal coordinates of the molecule, the potential energy distribution has been evaluated.

Keywords : Normal coordinate analysis, FTIR and FT Raman spectrum, Flucytosine

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1 Introduction

Flucytosine is a fluorinated pyrimidine which is the only available antimetabolite drug having antifungal activity. It treats serious fungal infections found throughout the body. These include infections of the heart, blood, urinary tract, or lungs, and meningitis. It is chemically called as 4 -amino -5- fluoropyrimidin - 2(1H)-one[1]. Spectroscopic investigations on compounds of pharmaceutical importance have been carried out by many researchers [2, 3]. Among the biomolecules, N-heterocyclic compounds are of considerable importance as they are of considerable pharmaceutical importance. The characteristic vibrational frequencies of this drug have been identified and assigned on the basis of their relative intensity, characteristic positions and correlation of vibrational bands of related compounds. The properties of this compound like storage condition and interaction with other trace elements were studied in detail[4]. However, the normal coordinate analysis and the potential energy distribution (PED) associated with each vibrational mode of flucytosine have not been carried out so far. Hence in the present work, the vibrational spectral analyses have been carried out on flucytosine and using normal coordinate analysis. The potential energy constants have been evaluated on the basis of general valence force field, applying Wilson's *F–G* matrix method [5].

2 Experimental Details

High grade pure sample of flucytosine was procured from Sigma Chemical Company, USA and used as such. FTIR spectrum has been recorded in the region 4000 – 400 cm^{-1} in evacuation mode using KBr pellet technique (solid phase) with 4.0 cm^{-1} resolution. The FT Raman spectrum has been recorded in the region 4000 – 100 cm^{-1} in purge mode using YAG laser of 200 mW. Both the spectra were recorded using BRUKER IFS 66V spectrophotometer at Sophisticated Instrumentation Analysis Facility, IIT, Chennai, India. The FTIR and FT Raman spectra are presented in Figs 1 and 2, respectively.

3 Normal Coordinate Analysis

The compound under consideration, flucytosine has thirty three fundamental modes of vibration under C_s symmetry point group and are distributed as $\Gamma_{vib}=21A' +12 A''$. All the modes of vibration are active in both infrared and Raman. Of the 21 fundamental modes of vibration in A' species only 16 and all the 12 fundamental modes in A'' species are considered in the present work. The structure, orientation of the principle axes and the nomenclature of the parameters of the flucytosine molecule are shown in Fig. 3. The structural parameters have been taken from the Sutton table [6].

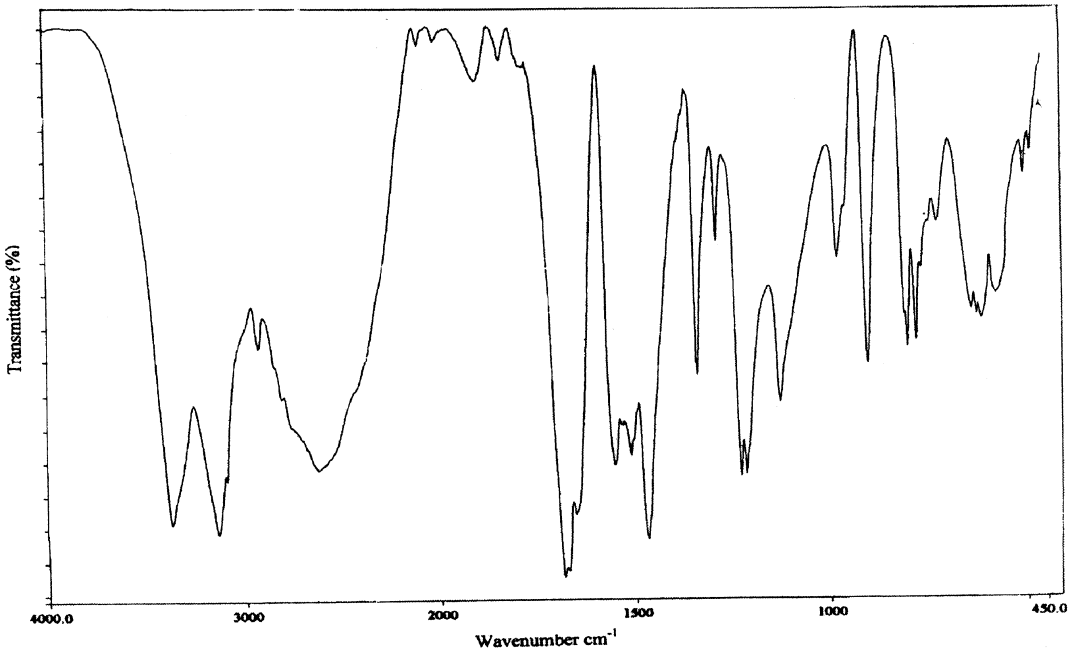

Fig. 1—FTIR spectrum of flucytosine

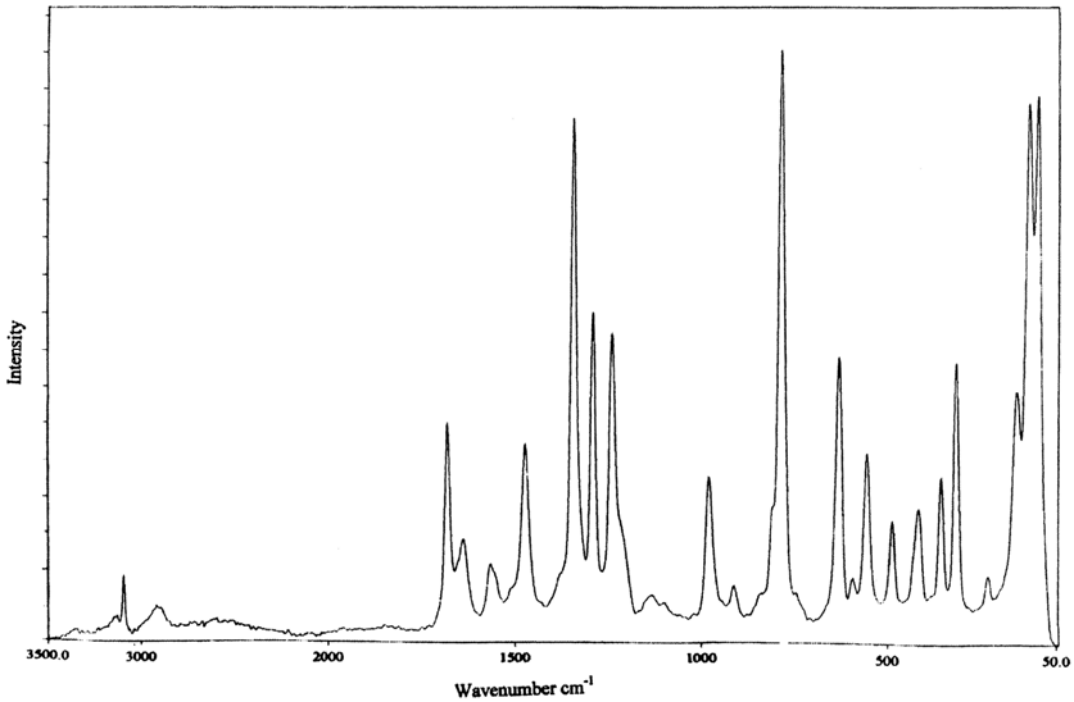

Fig. 2—FT Raman spectrum of flucytosine

3.1 Symmetry coordinates

The orthonormal set of symmetry coordinates for the molecule under study is constructed using the internal coordinates with the knowledge of the projection operator and with the help of the character table. The symmetry coordinates thus obtained are as follows:

A′ species

$S_1 = 1/\,2\,[\Delta a_1 + \Delta a_2 + \Delta a_3 + \Delta a_4]$

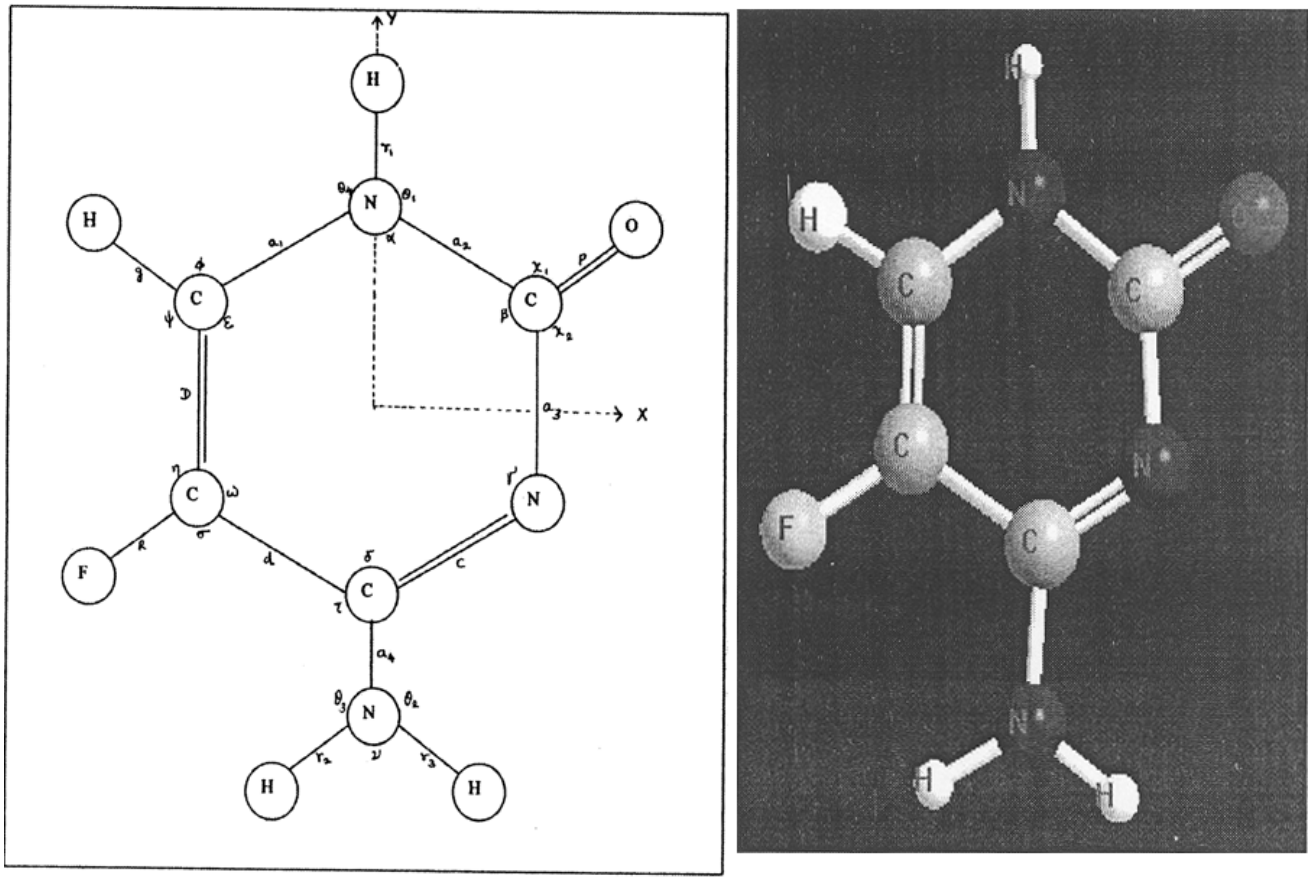

Fig. 3—Structure, nomenclature of parameters and the orientation of the principal axes and 3D view of flucytosine

$S_2 = 1/\sqrt{3}\ [\Delta r_1 + \Delta r_2 + \Delta r_3]$
$S_3 = \Delta D$
$S_4 = \Delta p$
$S_5 = \Delta c$
$S_6 = 1/2\ [\Delta\theta_1 + \Delta\theta_2 + \Delta\theta_3 + \Delta\theta_4]$
$S_7 = \Delta\alpha$
$S_8 = \Delta\phi$
$S_9 = \Delta\delta$
$S_{10} = \Delta\beta$
$S_{11} = \Delta\nu$
$S_{12} = 1/\sqrt{2}\ [\Delta\chi_1 + \Delta\chi_2]$
$S_{13} = \Delta\omega$
$S_{14} = \Delta\varepsilon$
$S_{15} = \Delta\Psi$
$S_{16} = \Delta\sigma$

A″ Species

$S_{17} = \Delta d$
$S_{18} = \Delta R$
$S_{19} = \Delta\sigma$
$S_{20} = 1/2\ [\Delta a_1 - \Delta a_2 - \Delta a_3 + \Delta a_4]$
$S_{21} = 1/\sqrt{6}\ [2\Delta r_1 - \Delta r_2 - \Delta r_3]$
$S_{22} = \Delta\nu$
$S_{23} = \Delta\tau$
$S_{24} = \Delta\eta$
$S_{25} = \Delta\pi$
$S_{26} = 1/2\ [\Delta\theta_1 - \Delta\theta_2 - \Delta\theta_3 + \Delta\theta_4]$
$S_{27} = 1/\sqrt{2}\ [\Delta\chi_1 - \Delta\chi_2]$

where Δ's represent the corresponding changes in bond distances and bond angles.

3.2 FTIR and FT Raman spectra and vibrational band assignment

The molecule under study is a heterocyclic compound, the vibrational frequency assignment in analogue with the vibrational frequencies of benzene, pyridine, and pyrimidine compounds. A satisfactory vibrational band assignment of the fundamental modes has been made according to the position,

Table 1—Vibrational spectral assignments, potential constants (10^2 N/m) and PED values of flucytosine

Symmetry Coordinate	Frequency (cm^{-1}) FTIR	FT Raman	Band assignment	Force constant (10^2 N/m)	PED %
A′ species					
S_1	1226 (s)	1238(s)	C – N symmetric stretching	6.9696	89
S_2	3093 (m)	3094(s)	N-H symmetric stretching	7.6313	97
S_3	1467 (m)	1472(m)	C=C stretching	7.7995	88
S_4	1683 (s)	1679(s)	C=O stretching	15.9011	83
S_5	1551 (m)	1565(m)	C=N stretching	14.9127	96
S_6	1336 (s)	1342(vs)	C-N-H symmetric bending	0.3509	99
S_7	420 (ms)	416(m)	C-N-C bending	0.6426	96
S_8	1450 (m)	-	N-C-H bending	0.5245	81
S_9	481 (s)	487(m)	C-C=N bending	0.8479	58
S_{10}	420 (s)	416(m)	N-C-N bending	1.1499	96
S_{11}	461 (m)	-	C-N=C bending	1.1387	54
S_{12}	609 (w)	-	N-C=O bending	1.2965	54
S_{13}	634 (m)	627(s)	C-C=C bending	1.1454	63
S_{14}	498 (s)	-	C=C-N bending	1.5396	57
S_{15}	***402 (w)***	-	C=C-H bending	0.4517	42
S_{16}	550 (w)	553(m)	C -C-F bending	1.2482	71
A ″ species					
S_{17}	1212(s)	-	C-C stretching	5.0401	84
S_{18}	1123(m)	1133(w)	C-F stretching	2.4522	99
S_{19}	2926 (ms)	2919(w)	C-H stretching	3.8906	83
S_{20}	1284 (m)	1290(s)	C-N asymmetric stretching	7.4044	88
S_{21}	3374 (w)	3370(w)	N-H asymmetric stretching	7.9567	96
S_{22}	1508 (s)	-	H-N-H bending	0.6654	52
S_{23}	440 (m)	-	C-C-N bending	1.4018	87
S_{24}	572 (w)	-	C=C-F bending	1.4333	51
S_{25}	1671 (m)	1679(s)	N=C-N bending	0.3196	53
S_{26}	1420(m)	-	C-N-H asymmetric bending	0.3399	77
S_{27}	717 (s)	725(w)	N-C=O asymmetric bending	1.6381	49

vs - very strong; s - strong; m - medium; ms – medium strong; w - weak

shape, nature and relative intensity. The qualitative study on the vibrational band assignments derived from FTIR and FT Raman spectra of flucytosine is presented in the paper. The vibrational spectral frequencies of flucytosine are summarised in the Table 1.

C-H *vibration*—The hetero aromatic structure shows the presence of C-H stretching vibrations[7] in the region 2990-2900 cm^{-1}. Hetero cyclic compound C-H vibration absorption bands are usually weak, in many cases, it is too weak for detection. In the present work, the bands observed at 2926 cm^{-1} is assigned to C-H stretching vibration, respectively.

C=C *and* C-C *stretching*—Pyrimidines absorb strongly in the region 1600-1450 cm^{-1} due to C=C vibration. This is evident of the presence of the bands around 1500 cm^{-1} in the spectra of the compounds [8]. In flucytosine , the band observed at 1467 cm^{-1} in the FTIR spectrum and the band at 1472 cm^{-1} in FT Raman spectrum are assigned to C=C stretching vibration and the band observed at 1212 cm^{-1} is assigned to C-C stretching mode of vibration, respectively.

C=N *stretching*—In the vibrational spectra of 2,3,4-substituted pyrazole-5 Zerbi *et al.*[9] identified stretching frequencies of C=N in the range 1620-1500 cm^{-1}. Referring to the work[9], the band observed at 1551 cm^{-1} in FTIR spectrum and the band at 1565 cm^{-1} in the FT Raman spectrum of flucytosine are assigned to C=N stretching mode of vibration.

N-H *stretching*—Primary aliphatic amines absorb in the region 3450-3250 cm^{-1} in solids or liquids and they are broad and of medium intensity. In solid and liquid phases, a band of medium intensity is observed in the range 3400-3300 cm^{-1} for secondary aromatic amines. The vibrational bands due to the N-H

stretching are sharp and weak than those of O-H stretching vibrations by virtue of which they can be easily identified[10]. In the present case, the compound chosen for study is hetero cyclic aromatic system of pyrimidine. By observing the position of the bands in the proper region, the vibrational bands present at 3093 cm^{-1} and 3374 cm^{-1} are assigned to N-H symmetric and asymmetric modes of vibration, respectively.

C-N *stretching*—Silverstein *et al.*[11] assigned C-N stretching absorption in the region 1342-1220 cm^{-1}. The spectra of benzene and pyridyl substituted compounds show the band in the region 1260-1210 cm^{-1}. In analogy with the previous work, the band appears at 1226 cm^{-1} and the band at 1284 cm^{-1} in the FTIR spectrum of flucytosine is assigned to C-N symmetric and asymmetric stretching mode of vibrations, respectively.

C-F *vibration*—In the vibrational spectra of related compounds, the band due to the C-F stretching vibration[12,13] may be found over a wide frequency range 1360-1000 cm^{-1}, since the vibration is easily affected by adjacent atoms or groups. Mono fluorinated compounds have a strong band in the frequency range1110-1000 cm^{-1} due to C-F stretching vibration. In the present work, the band observed at 1123 cm^{-1} has been assigned to C-F stretching mode of vibration, respectively.

C=O *stretching*—The pyrimidines and purines have been extensively studied on account of their intrinsic interest as important biological compounds. Due to tautomerism, pyrimidines substituted with hydroxyl groups are generally in the keto form and therefore, have a strong band due to carbonyl group. The carbonyl group shows a strong absorption band due to C=O stretching vibration and is observed in the region 1850-1550 cm^{-1}. Because of its high intensity[14,15] and the relatively interference-free region in which it occurs, this band is reasonably easy to recognize. In the present work, the bands observed at 1683 cm^{-1} in the FTIR spectrum and at 1679 cm^{-1} in FT Raman spectrum are assigned to C=O stretching mode of vibration, respectively.

C-N-H *bending*—Normally, the deformation modes of C-N-H occur in the region[16] 1450-1320 cm^{-1}. Hence, in the present study, the bands appear at 1336 and 1420 cm^{-1} in FTIR spectrum, are assigned to C-N-H symmetric and asymmetric bending modes of vibrations, respectively.

N-C-H *bending*—In the vibrational spectra substituted phenols and its derivatives N-C-H bending modes are observed in the region 1500-1425 cm^{-1} . The band appears at 1450 in the FTIR spectrum of flucytosine is assigned to N-C-H bending mode of vibration, respectively.

3.3 Method of kinetic constants

The method of kinetic constants has been successfully employed by many researchers for the structural elucidation of different types of molecules[17,18]. The determination of the symmetry force constants involved in the secular equation from the n_i vibrational frequencies has remained a mathematically unsolved problem. Therefore, any useful attempt to evaluate all the symmetry force constants associated with a problem of order $n_i > 1$ should involve the incorporation of at least $n_i\,(n_i-1)/2$ additional data other than n_i frequencies. The method of kinetic constants relates the off diagonal elements of the force constant matrix F, to its diagonal elements through the relation[16,17]

$$\frac{F_{ij}}{F_{jj}} = \frac{K_{ij}}{K_{jj}}, [i < j,\ i = j = 1,2,3,.....j]$$

Once the G and F matrices are obtained the secular equation $|FG-\lambda E| = 0$ has to be solved, where $\lambda = 4\pi^2C^2\nu^2$, and ν is the frequency assigned with the particular symmetry coordinate and E is the unitary matrix. The knowledge of the transformation matrix L (L is the transformation matrix obtained by $LL^T=G$) and the kinetic energy matrix K (G^{-1}) leads to the solution of the secular equation due to Wilson, yielding the elements of the force constant matrix F. The secular equation has been solved by fixing the initial set of force constants which are taken from the related molecules like benzene, pyridine, pyrimidine, etc.[16-20]. This set of force constants has been subsequently refined till the convergence takes place by giving suitable increments without fixing any of the force constants by iteration method using computer. In the present work, only the diagonal force constants have been considered.

The frequency assignment is verified by evaluating the potential energy distribution (PED) using the relation

$$PED = F_{ij}\, L_{ij}^{\ 2}/\lambda_j$$

where PED is the contribution to the potential energy of vibration of the symmetry coordinate whose frequency is ν_j, F_{ij} the force constant and L_{ij}, the L-matrix elements.

4 Results and Discussion

Wilson's F-G matrix method has been successfully employed in the normal coordinate analysis of flucytosine. The potential energy distribution for the fundamental modes of vibration is given in Table 1 and the force constants are summarised. The correctness of the frequency assignments has been checked by the PED calculation and it is seen that the PED calculation of all the fundamental vibrations is satisfactory. This is supportive of the frequency assignment and hence, the structure. The force constants of N-H stretching vibration of the compound are found to be around 7.6×10^2 N/m as expected and they contribute PED value of more than 96%. The symmetric and asymmetric C-N vibrations of the molecule show a force constant around 6.9×10^2 and 7.4×10^2 N/m, respectively, contributing to the PED value of more than 85%.

A PED value of around 84% is found to be calculated for C-C stretching vibrations whose frequency is assigned around 1212 cm^{-1}. The force constant of C-H stretching vibration is found to be around 3.89×10^2 N/m and they contribute PED value around 83%. Apart from these major stretching vibrations, the compounds also have a number of bending vibrations. The force constants for these vibrations have been evaluated to be around 0.8-1.2×10^2 N/m as expected and contribute to the PED values of 40-60%.

5 Conclusion

Thus, a complete vibrational band assignment of flucytosine has been carried out using infrared and Raman spectra on the basis of C_s point group symmetry. A systematic set of potential constants has been computed and they are found to be in good agreement with literature. The PED calculation regarding the normal modes of vibration provides a strong support for the frequency assignment.

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