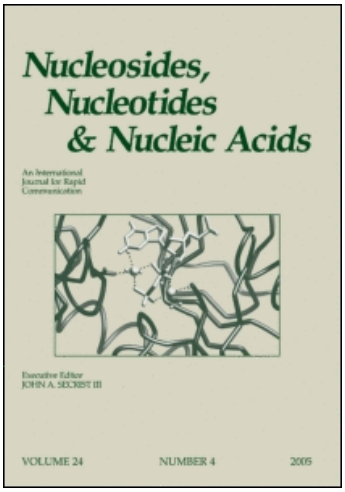

Nucleosides, Nucleotides and Nucleic Acids
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597286

Vibrational Study of a Nucleoside Analogue with Antitumoral and Antiviral Activity, 5-Fluoro-2'-deoxyuridine, FdU

L. Bailey[a]; A. Hernanz[a]; R. Navarro[a]
[a] Dept. Ciencias y Técnicas Fisicoquímicas, UNED, Madrid, Spain

To cite this Article Bailey, L. , Hernanz, A. and Navarro, R.(1997) 'Vibrational Study of a Nucleoside Analogue with Antitumoral and Antiviral Activity, 5-Fluoro-2'-deoxyuridine, FdU', Nucleosides, Nucleotides and Nucleic Acids, 16: 7, 1041 — 1044
To link to this Article: DOI: 10.1080/07328319708006128
URL: http://dx.doi.org/10.1080/07328319708006128

NUCLEOSIDES & NUCLEOTIDES, 16(7-9), 1041-1044 (1997)

VIBRATIONAL STUDY OF A NUCLEOSIDE ANALOGUE WITH ANTITUMORAL AND ANTIVIRAL ACTIVITY, 5-FLUORO-2'-DEOXYURIDINE, FdU.

L. Bailey, A. Hernanz* and R. Navarro

Dept. Ciencias y Técnicas Fisicoquímicas, UNED
Senda del Rey, s/n, 28040-Madrid, Spain

Abstract: The advantages of different methods for obtaining a reliable assignment of the vibrational spectra of the antitumoral and antiviral nucleoside analogue, 5-fluoro-2'-deoxyuridine, FdU, are evaluated as a basis for the study of FdU-containing polymers and drug-target interactions. The experimental FT-IR and FT-Raman spectra, are compared with theoretical frequencies obtained by a classical mechanics method and a semiempirical molecular orbital (MO) method, PM3.

Introduction

The antiviral and antineoplastic activity of 5-fluoro-2'-deoxyuridine, FdU, is related to thymidylate synthase inhibition by its mononucleotide FdUMP[1]and represents a classic in basic molecular biochemistry[2]. However, recent studies suggest that FdU may also be fraudulently incorporated into DNA and RNA leading to antimetabolite action at the primary genetic level[3]. For the rational development of drugs, the interaction processes between the drug and its biological targets should be known and a prerequisite for this knowledge is the description of the structural properties of the drugs as well as those of the interacting biological sites. Consequently, a greater understanding of the vibrational spectra of the fluorinated nucleoside is a useful basis in the study of both FdU-containing polymers and drug-enzyme interactions.

A comparison of the experimental FT-IR and FT-Raman spectra of FdU with theoretical frequencies obtained by a classical mechanics method and a semiempirical molecular orbital (MO) method, PM3, enables us to evaluate the advantages of both methods for obtaining a reliable assignment of the vibrational spectra. In this study, the force constants were not refined, nor scaling factors applied in either case, so that the harmonic frequencies predicted by different raw force fields could be compared. Previous normal coordinate analysis[4], partial *ab initio* MO calculations[5] and experimental spectra for the uracil base and 5-fluorouracil[6] are compared with our results.

Experimental

The FTIR spectra, Fig 1A, in the mid and far infrared regions have been obtained in a Bomem DA interferometer with effective apodized resolutions of 0.89 and 1.77 cm^{-1} respectively.The FT-Raman spectrum of FdU, Fig 1B, has been recorded with a Bruker Raman

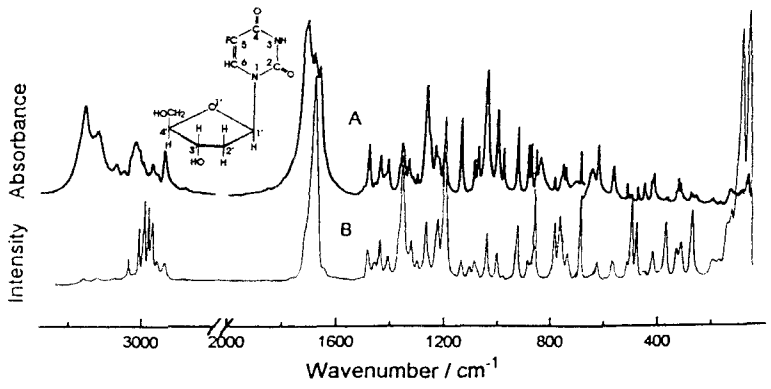

FIG.1. Spectra of polycrystalline FdU. A: Mid and far IR, B: FT-Raman.

RFS 100 spectrometer. A diode pumped Nd^{3+}:YAG laser (1064 nm) was the exciting source, and the apodized resolution was s = 4 cm^{-1} (Blackman-Harris apodizing function).

Computational Methods

The normal coordinate analysis is based on the Wilson GF method[7]. The cartesian coordinates were calculated from neutron diffraction data obtained by Harris et al[8]. The G matrix was written in internal coordinate representation and the eigenvalues of G provided a "symmetry" coordinate basis which was then applied to the F matrix in internal coordinates to yield a "symmetrized" F matrix. The GF product results in a secular equation whose eigenvalues give the 78 harmonic vibration wavenumbers (3N-6 internal coordinates corresponding to the 28 atoms of the FdU molecule).

The classical mechanics calculations were carried out using a specifically designed computer program, Bioviban[9]. Valence force constant values were transferred from simpler molecules [10-13] considered as FdU fragments according to the method described by Pulay[14].

Semiempirical MO calculations were carried out using the PM3 Hamiltonian[15]as implemented in the HyperChem™ program. Geometry optimization for the G matrix was carried out by obtaining the minimum on the potential energy hypersurface. The F matrix and subsequently the GF product, giving the vibrational frequencies, and their intensities were then calculated.

Results and Discussion

Mid- and far-infrared spectra of polycrystalline FdU in the 4000-750 and 770-40 cm^{-1} spectral regions and FT-Raman spectra are shown. The fundamentals calculated with the Bioviban program and the semiempirical PM3 method and assignment of the vibrational modes corresponding to FdU together with the PED are listed in Table 1, and compared with the experimental results.

In general, very good agreement was observed between experimental and calculated wavenumbers with the classical molecular mechanics method, Bioviban (~1% deviation in most cases). The agreement obtained with the semiempirical method was within 10%. The PED which gives

TABLE 1. Observed and calculated wavenumbers for polycrystalline FDU

Observed wavenumbers		Calculated wavenumbers		Potential energy distribution
FT-IR $\tilde{\nu}$/cm^{-1}	FT-Raman $\Delta\tilde{\nu}$/cm^{-1}	PM3 $\tilde{\nu}$/cm^{-1}	Bioviban $\tilde{\nu}$/cm^{-1}	PED/%
3132w		3904w	3149	99νO3'H
3089w	3092w	3385w	3102	97νN3H
3022w sh	3021w	3001vw	3015	96νC6H
2851w		2846w	2859	49νC2'H+47νC2'H'
1719vs	1688s	1946s	1696	15νC4O4+13δN3C4C5
1483m	1487w	1448w	1505	52δHC5'H'+15τHC5'4'H
1359m	1358m	1378m	1369	15δC1'C2'H+12δC3'C2'H'
1271m	1270w	1317w	1270	15τHC5'C4'H+13τH'C5'C4'H
1139m	1139w	1168w	1142	51δC5'O5'H
1045m	1042w	1066w	1044	19δC3'C2'H-13τO4'C1'C2'H
928w	928w	906vw	925	12τN3C2N1C6+11πO2C2N1N3
625w	627vw	675w	629	8δC5C4O4
568w	569vw	587vw	562	31πFC5C6C4+16πO4C4C5N3

information about the relative contributions of the force constants to the potential energy of a normal mode, is often limited only to the diagonal terms of the F matrix. Contributions of force constants for different in-plane and out-of-plane coupled vibrations are included in our calculations, providing off-diagonal elements, which are useful for refinement in the case of large molecules, such as FdU.

The semiempirical method, PM3, is helpful in the assignment of bands although there is less agreement with the wavenumbers of experimental spectra (10%). This is due to the fact that this method uses an optimized geometry for the isolated molecule in the gas phase and not the crystal structure obtained by X-ray diffraction, and also depends on the adequacy of the parameters used.

Acknowlegements. The authors thank the Universidad Nacional de Educación a Distancia for a postgraduate research grant to one of the authors (L.E.B.). We also wish to thank M. Delgue, C. Lehner and C. Boulou of Bruker for the use of their FT-Raman equipment for recording the FT-Raman spectra.

REFERENCES

1. Rossi, A.In *Nucleoside Analogues. Chemistry, Biology and Medical Applications*; Walker, R. T., DeClercq, E., Eckstein, F. Eds.; Plenum Press: New York, 1979; pp 409-436.
2. Harding, M. M.; Long, H. A. *Acta Cryst.* **1968**, *B24*, 1096-1102.
3. Broom, A. D. *J. Med. Chem.* **1989**, *32*, 2-7.
4. Aamouche, A.; Ghomi, M.; Coulombeau, C.; Jobic, H.; Grajcar, L.; Baron, M. H.; Baumruk, V.; Turpin, P. Y.; Henriet, C.; Berthier, G. *J. Phys. Chem.* **1996**, *100*, 5224-5234.
5. Person, W. B.; Szczepaniak, K.In *Vibrational Spectra and Structure*; Durig, J. R. Ed.; Elsevier: Amsterdam, 1993; pp 239-325.

6. Rastogi, V. K.; Mital, H. P.; Sharma, S. N.In *XI International Conference on Raman Spectroscopy*; Clark, R. J. H., Sharma, S. N. Eds.; J. Wiley: Chichester U.K. 1988; pp 87-88.
7. Wilson, E. B.; Decius, J. C.; Cross, P. C.In *Molecular Vibrations*; McGraw Hill: New York, 1955; pp 54
8. Harris, D. R.; Macintyre, W. M. *Biophys. J.* **1964**, *4*, 203-225.
9. Escribano, R. PhD Thesis **1976**.
10. Lagant, P.; Elass, A.; Dauchez, M.; Vergoten, G.; Peticolas, W. L. *Spectrochim. Acta* **1992**, *48A*, 1323-1333.
11. Reddy, B. V.; Rao, G. R. *Vibrational Spectrosc.* **1994**, *6*, 231-250.
12. Eyster, J.; Prohofsky, E. W. *Spectrochim. Acta* **1974**, *A 30*, 2041-2046.
13. Ghomi, M.; Taillandier, E. *Eur. Biophys. J.* **1985**, *12*, 153-162.
14. Pulay, P. *J. Mol. Struct.* **1995**, *347*, 293-308.
15. Stewart, J. P. *J. Comput. Chem.* **1989**, *10*, 209-220.