Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 98 (2012) 265–270

Contents lists available at SciVerse ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

Quantum chemical and experimental studies on polymorphism of antiviral drug Lamivudine

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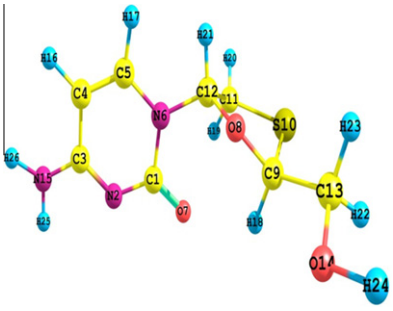
HIGHLIGHTS

- FT-IR and thermogravimetric analysis of Lamivudine in the solid state were recorded and analyzed.
- The optimized geometry and vibrational spectrum was computed using ab initio HF and DFT methods.
- The complete vibrational assignment and spectroscopic analysis have been carried out.
- Total atomic charges on the various atoms of molecule were obtained by Mulliken population analysis.
- The ^{13}C NMR chemical shift data assignment for Lamivudine have also been reported.

GRAPHICAL ABSTRACT

Polymorphism of HIV drug Lamivudine has been studied along with its structure in this article using a complete vibrational analysis performed by combining the experimental and theoretical information using ab initio and density functional theory based on scaled quantum chemical approach.



ARTICLE INFO

Article history:
Received 21 May 2012
Received in revised form 28 July 2012
Accepted 8 August 2012
Available online 17 August 2012

Keywords:
Lamivudine
Restricted Hartree Fock
Density functional theory
Infrared spectroscopy
Thermogravimetric analysis

ABSTRACT

Lamivudine, is chemically known as [4-amino-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin-2-one], is an anti-HIV agent belonging to the class of the non-nucleoside inhibitors of the HIV-1 virus reverse transcriptase. Spectral characteristics of Lamivudine have been studied by methods of FTIR, NMR and quantum chemistry. The FTIR and spectra of Lamivudine was recorded in the regions 4000–400 cm^{-1}. The thermal stability of Lamivudine was studied by the thermogravimetric analysis (TGA). The isotropic ^{13}C-nuclear magnetic shielding constants of this compound were calculated by employing the direct implementation of the gauge including-atomic-orbital (GIAO) method at the HF and B3LYP density functional theory using 6-31G(d,p) basis set. The optimized molecular geometry, bond orders, harmonic vibrational spectrum of anhydrous and hydrated Lamivudine were calculated by restricted Hartree Fock and density functional B3LYP method with the 6-31G(d,p) basis set using Gaussian 03W program.

Introduction

Acquired immunodeficiency syndrome (AIDS), which is now a plague in several countries, was first identified in California in 1981. It is a disease in which the body's immune system breaks down and is unable to fight off infections caused by human immunodeficiency virus (HIV). HIV infects human cells and uses the energy and nutrients provided by those cells to grow and reproduce

Abbreviations: DFT, density functional theory; HIV, human immunodeficiency virus; FTIR, Fourier transform infrared; NMR, nuclear magnetic resonance; RHF, restricted Hartree Fock; TGA, thermogravimetric analysis; GIAO, gauge including atomic orbital; DTGS, deutrated tri glycine sulphate; TMS, tetramethylsilane; HOMO, highest occupied molecular orbital; LUMO, lowest unoccupied molecular orbital.

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http://dx.doi.org/10.1016/j.saa.2012.08.013

and it is often necessary to take several medicines for prolonged periods. Lamivudine, [4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl-(1H)-pyrimidin-2-one], which is a 1,3-oxathiolane nucleoside analogue, has shown to possess antiviral activities. This reverse transcriptase inhibitor exists in two polymorphic modifications (i.e., anhydrous and hydrated form of Lamivudine). It is in clinical use for HIV positive and hepatitis B positive patients (UK Patent Application 1991, 9111902.4). Lamivudine is a synthetic nucleoside analog that is being increasingly used as the core of an antiretroviral regimen for the treatment of HIV infection [1,2]. Lamivudine is rapidly absorbed after oral administration with an absolute bioavailability of 86 ± 16%, peak serum concentration of Lamivudine (C_{max}) of 1.5 ± 0.5 mcg/mL and mean elimination half-life of 5–7 h, thus necessitating frequent administration to maintain constant therapeutic drug levels [3]. Vibrational spectroscopy has significant contributions towards the studies of structure and physico-chemical properties of molecular systems. Density functional theory (DFT) and ab initio quantum chemistry are cost-effective general procedures for studying the physical properties of the molecules. Chu et al. [4] used a synthesis based on D-mannose, whilst Jeong et al. developed [5] an alternative synthesis using D-galactose, which was employed to evaluate biological aspects of Lamivudine [6]. The ^{13}C chemical shifts of Lamivudine in deuteriomethanol solution was measured and listed by Jin et al. [7]. However, infrared spectroscopic measurements and detailed theoretical studies based on DFT methods for Lamivudine have not been reported so far. This work deals with spectroscopic characterization and DFT studies of hydrate and anhydrous Lamivudine.

Experimental

Lamivudine was obtained from Sigma–Aldrich Laboratories (>99%) and used as received. The solid state FTIR spectrum was recorded in the region 4000–400 cm^{-1} in evacuation mode on Nexus 670 DTGS using KBr pellet technique with 4.0 cm^{-1} resolution. Thermogravimetric (TGA) studies were carried out on SDT Q600 V8.3 Build 101 instrument. The mass losses and heat response of the changes in sample were measured from 0 to 1100° C. The heating rate was 20 degree Kelvin per minute in air atmosphere.

Computational details

All the theoretical computations were performed at restricted Hartree Fock (RHF) and B3LYP levels on a Pentium IV/1.6 GHz personal computer using the Gaussian 03W program package [8]. The geometry optimization was carried out using the initial geometry generated from standard geometrical parameters at restricted Hartree Fock level and DFT methods adopting 6-31G(d,p) basis set to characterize all stationary points as minima. In DFT methods, Becke's three parameters exchange–functional (B3) [9,10] combined with gradient-corrected correlation functional of Lee, Yang and Parr(LYP) [11] by implementing the split-valance polarized 6-31G(d,p) basis set [12,13] have been utilized for the computation of molecular structure optimization and vibrational frequencies. The optimized geometry was used in the vibrational frequency calculations at the RHF and DFT levels to characterize all stationary points as minima. Finally, calculated normal mode vibrational wave numbers provide thermodynamic properties by way of statistical mechanics. The vibrational frequency assignments were made with a high degree of accuracy with the help of Chemcraft software program [14]. The ^{13}C chemical shifts were calculated with GIAO method using corresponding TMS shielding. The absolute shielding and ^{13}C NMR chemical shifts were predicted by the NMR calculations on the stationary points obtained after optimizations.

Results and discussion

Molecular geometry

The optimized geometry of anhydrous and hydrated Lamivudine, obtained at the RHF and B3LYP levels of calculation, is provided in Table 1 in accordance with the atom numbering scheme given in Fig. 1. Table 1 compares the bond length and bond angles of anhydrous and hydrated Lamivudine. From the calculated values, we can find that most of the optimized bond length and bond angles are slightly larger than the experimental values of structurally related molecules [15], due to this the theoretical calculation belongs to the isolated molecules in the gaseous phase whereas the experimental results belong to the molecules in the solid phase. Table 1 also gives the geometry difference between hydrated and anhydrous form of Lamivudine obtained from RHF and B3LYP methods. It is to be noticed that there is an appreciable bond angle difference and insignificant bond length difference is observed in both RHF and B3LYP methods.

Bond order and TGA analysis

Table 2 presents the bond order of anhydrous and hydrated Lamivudine. Bond order is related to bond strength. The weakest bonds, which are assumed to be cleaved preferentially and relatively low pi bond character. Knowledge of thermal behavior is not essentially for proper processing and fabrication, but also for complete characterization of the chosen drug especially thermal stability and for selection of appropriate end users. The sample weight and its rate of weight loss were continuously measured as a function of temperature and hence the thermal stability was studied from TGA curve. The anhydrated Lamivudine sample weighing 5 mg was heated from 0 °C temperature to 1100 °C in air atmosphere at a heating rate of 20 °C/min and thermogram is depicted in Fig. 2. The major weight loss occurs in the region from 229 to 366 °C. About 8% weight losses occur at 229 °C was attributed to the elimination of water molecule present in the sample due to moisture content of water molecule. At temperature 366 °C, the major weight losses about 50% is observed due to the fact that N6-C12 bond breakage. From Table 2, it is noted that bond between N6–C12 possess relatively low pi bond character with low bond order value of 0.84 and 0.9 obtained from RHF and B3LYP method respectively. Hence, N6–C12 has the smallest bond order and refers to the possible cleavage site in Lamivudine. The bond distance of N6–C12 is somehow longer than the other N–C bond distance in the title molecule, it once again confirms the weakest bond and it is the preferential site for cleavage to occur. The very strongest bond is C1–O7 with the bond order value of 1.65 predicted from both RHF and B3LYP methods confirms the double bond character. So, the theoretical bond order analysis was applied to declare TGA observation. Also from Table 2, it is evident that anhydrous and hydrated forms of Lamivudine do not show any significant changes in bond order values obtained from the two methods (RHF and B3LYP).

Atomic charges and ^{13}C NMR chemical shift

Total atomic charges on the various atoms of molecule were obtained by Mulliken population analysis are given in Table 3. It may be noted that the nitrogen atoms N2, N6 and N15 have large net negative charge was observed in the two methods. Also the electronegative oxygen atoms O7 and O8 possess large net negative charge. In the hydrated Lamivudine molecule, it was found that the charges on O7 and O8 have appreciably increases by 0.03 esu in RHF and B3LYP methods. The carbon atoms C1, C3, C5 and C12