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Prediction of electronic structure, dielectric and thermodynamical properties of flurbiprofen by density functional theory calculation

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Abstract

The molecular structure of the pain killer drug Flurbiprofen has been fully optimized using Berny's optimization algorithm in Gaussian 09, using redundant internal coordinates. The dipole moments, polarizability tensors, average polarizability, anisotropy, first molecular hyperpolarizability, thermodynamics properties, dielectric constant, refractive index, dielectric susceptibility, molar refractivity, IR and Raman spectra have also been studied. A tentative assignment of the IR vibration frequencies was equally carried out. This was done by using Density functional theory calculations with three different functional B3LYB, X3LYP and BPBE by employing cc-pVDZ basis set. The calculated energy band gap (E_{gap}) of the molecule obtained by using HOMO and LUMO molecular orbitals show that the molecule has an E_{gap} value of 0.195 eV, 0.201 eV and 0.244 eV at the BPBE, B3LYP and X3LYP levels respectively. The first molecular hyperpolarizability value obtained by using the BPBE (6.79187×10^{-30} esu), B3LYP (5.07308×10^{-30} esu) and (2.74471×10^{-30} esu) methods are very large compared to that of Urea (0.1947×10^{-30} esu) reported in literature. The results also show that the molecule has a dielectric constant of 2.85×10^{-11}, 3.03×10^{-11} and 2.99×10^{-11} obtained at the PBPE, B3LYP and X3LYP levels respectively. Equally, our IR and Raman spectra were in the same range as those reported in literature.

Keywords: Electronic structure; DFT; Hyperpolarizability; Electric properties; Thermodynamical properties

1. Introduction

Flurbiprofen [(2- (2-fluoro-4-biphenyl) propionic acid, $C_{15}H_{13}FO_2$] belong to the profen class of non-steroid anti-inflammatory drug (NSAID) and is widely used in the treatment of rheumatoid arthritis [1]. This drug is a white crystalline powder that is practically insoluble in water (0.034 mg/mL [1], 0.024 mg/ml according to [2]), but soluble in alcohol [3]. It is a weak acid (pKa = 4.22) [4] that contains a biphenyl group with a fluorine atom in ortho position. Flurbiprofen is commercially available as a racemic

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mixture of S(+) and R(−) enantiomers. The S(+)-Flurbiprofen being the pharmacologically active form. So far, three crystal forms of the Flurbiprofen were detected, but only the crystal structures of form I and III were identified [5,6]. The crystal structure of form I Flurbiprofen has a triclinic symmetry. The coordinates and the structural parameters (size links, torsion angle…) have been reported in many studies [5,6]. The crystal structure of form III Flurbiprofen was identified for the first time by Grzesiak et al. in 2007 [5]. It form III crystallizes in a monoclinic network with four molecules per unit cell. The structure corresponds to the space group and of lattice dimensions a = 5.721 Å, b = 38,175 Å, c = 5.980 Å. Its crystalline structure can be obtained from crystallization from various copolymers, for example ethyl/vinyl acetate [7], the oxidized polyethylene ethyl acetate, methanol, acetonitrile [7] or again by crystallization from solutions of 2-propanol [5].

Several methods have been reported for the determination of flurbiprofen including high-performance liquid chromatography (HPLC) [8−15], liquid chromatography−mass spectrometry (LC-MS) [16,17] and gas chromatography−mass spectrometry (GC−MS) method [18]. Flurbiprofen was extracted from human urine with a solid phase extraction procedure by Hirai et al. [12]. This method is also the most comprehensive method which can extract Flurbiprofen in a single extraction procedure. Sajeev et al., 2002 [18], determined the pharmaceutical formulations of Flurbiprofen by UV spectrophotometry and liquid chromatography.

Also, Yates et al. [19] have studied the theoretical NMR spectra of Flurbiprofen using density functional theory (DFT) together with the gauge including projector augmented wave (GIPAW) method. A full geometry optimization of the crystal structure of Flurbiprofen was carried out with the DFT method with the hybrid functional B3LYP using the 6-31G(d,p) and Los Alamos National Laboratory 2-Double-Zeta (LanL2DZ) basis sets by Sagdinc and Pir in 2009 [20].

Though some studies have been carried out on Flurbiprofen, a detail knowledge of the dipole moment, average polarizability, anisotropy, polarizability, molar refractivity, dielectric constant, refractive index, dielectric susceptibility, thermodynamics properties and spectrum are beneficially to an understanding of the structure of the molecule, it interaction with other molecules. These properties are very useful in Pharmacology and drug design. In this paper we used three different DFT methods B3LYP, X3LYP and BPBE to determine the above properties.

2. Computational methodology

The molecular structure of Flurbiprofen was completely optimized by using ab-initio quantum mechanical calculations at the Restricted Hartree-Fock (RHF) level of theory without using any symmetry constraints. Initial geometry optimizations were performed using the ab-initio RHF method with 3-21G basis set. Subsequently, its results were utilized to the cc-pVDZ basis set which is a Dunning's correlation consistent basis set. The structure was refined further using DFT which is a cost effective method for inclusion of electron correlations with the three-parameter density functional generally known as Becke3LYP (B3LYP), which includes Becke's gradient exchange corrections [21], the Lee, Yang and Parr correlation functional [22] and the Vosko, Wilk and Nusair correlation functional [23]. Secondly, the 1996 gradient-corrected correlation functional of Perdew, Burke and Ernzerhof [24,25] in which the D3 version of Grimme's dispersion with the original D3 damping function [26] and the D3 version of Grimme's dispersion with Becke-Johnson damping have been added BPBE [27]. Finally, the functional of Xu and Goddard, X3LYP which is the extended density functional for accurate descriptions of nonbonding interactions, spin states, and thermo chemical properties [28] was used. The local density approximation (LDA) and the generalized gradient approximations (GGA) were used. At the first step, geometry optimization was carried out then, the IR and Raman frequencies were calculated using the Hessian which is the matrix of second derivatives of the energy with respect to geometry. The optimized molecular structure was tested by computing the second derivatives and checking that all the harmonic vibrational frequencies are real at all level of calculations. All calculations in the present work were performed using Windows version of Gaussian 09 [29] suit of ab initio quantum mechanical program. Only the results obtained with the DFT functional are reported in this work since the DFT method has proven to be one of the most accurate methods for the computation of the electronic structure of solids and most of the properties of some molecules [30−39].

3. Results and discussion

3.1. Molecular structure of flurbiprofen

The molecular structure of Flurbiprofen is shown in Fig. 1.

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