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Electronic structure analysis of isomeric preferences of canonical and zwitterionic forms of lornoxicam

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ABSTRACT

Lornoxicam, is a non-steroidal anti-inflammatory drug (NSAID) and has analgesic, anti-inflammatory and antipyretic activity. Various polymorphic forms of drugs belonging to oxicam class are known in the literature and study of their polymorphic behavior has become a research interest over the past few years. Due to the differences in the conformational arrangement of the molecules in the crystal lattice, polymorphic forms of a drug substance can exhibit different physicochemical properties–solubility, density, dissolution, pK_a, etc. Density functional (DFT) study has been carried out on various canonical and zwitterionic forms of lornoxicam. The electronic level details revealed that, the existence of polymorphism in lornoxicam can be traced to the prototropic exchange which helps in the interconversion of one polymorph to the other. Electronic structures of all the probable isomers of lornoxicam at HF, B3LYP and M06L levels using 6-31 + G(d) basis set have been analyzed. The comparative analysis of their relative Gibbs free energies in the gas, solution and explicit water phase revealed that the form of global minimum structure differs with respect to the varied conditions. Microsolvation calculations show that three water (3W) molecules are sufficient to stabilize the zwitterion **ZO**. Therefore, transition of canonical to zwitterionic form can happen under the influence of explicit water molecules. Further, transition state studies point out easy conversion between the two zwitterionic states (**ZN** ↔ **ZO**). This phenomenon can be attributed to the observed polymorphism in lornoxicam.

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1. Introduction

Lornoxicam is a new non-steroidal anti-inflammatory drug (NSAID) from the oxicam class. It exhibits anti-inflammatory activity and is a potent analgesic agent in post-operative pain, rheumatoid arthritis, osteoarthritis and acute lumbar-sciatica conditions [1]. These effects are as a result of non-selective inhibition of cyclo-oxygenase-1 and -2. Additionally, it plays an important role as chemo-preventive and chemo-suppressive agent [2]. It has an improved safety profile owing to its shorter half-life [3]. The crystal structure of two polymorphic forms (I and II) of lornoxicam was established by Zhang et al. using various characterization techniques such as; FTIR spectroscopy, DSC experiments, X-ray powder diffractometry (XPRD), and thermogravimetric analysis [4]. Form I is found to have a triclinic space group while form II belongs to orthorhombic lattice system dominated by intermolecular and intramolecular hydrogen bonds, respectively. In addition to this, lornoxicam also known to exist as a zwitterion in acidic media owing to keto-enol tautomerism [5]. Fig. 1 shows the three important structures of lornoxicam in canonical and zwitterionic forms (**ZO** and **ZN**).

Zwitterions of amino acid are extensilvely studied using experimental and theoretical methods [6–14], but the same in drugs are rarely exposed: (i) Relative energies of canonical form and zwitterions (ii) the number of water molecules required to make canonical and zwitterionic form isoenergetic (iii) the charge solvated state (canonical) vs. the salt bridged (zwitterionic) states of amino acids are being extensilvely studied using quantum chemical studies. Drug molecules which are known to act in their zwitterionic state are governed by their electric field which is believed to be the driving force for their drug action [15,16]. Acknowledging the importance of such concepts and the fact that such studies on therapeutic drug molecules hitherto remained unexplored, we intended to implement similar studies for the identification of electronic structure of the anti-inflammatory drug, lornoxicam.

Many of the drugs belonging to oxicam class are known to exist in different polymorphic forms [17–21]. Several studies explaining the details of various polymorphic states of piroxicam are reported in the literature [18,20]. Among them a few reports highlight the importance of proton transfer during the interconversion of polymorphic forms, which mostly involves tautomeric conversion [21,22]. Distinctive molecular interactions are shown by canonical

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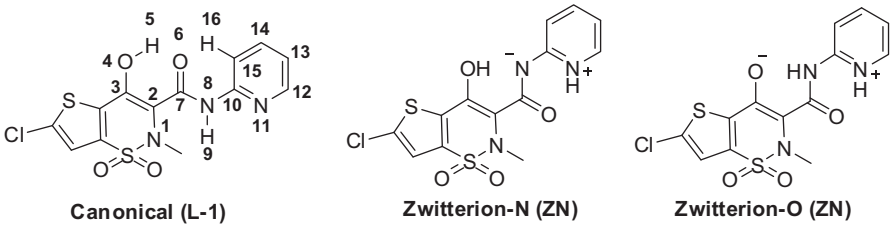

Fig. 1. 2-D structures of canonical (**L-1**), zwitterion O (**ZO**) and zwitterion N (**ZN**) in place of isomers write forms of lornoxicam.

and zwitterionic states underlying the differences in their hydrogen bonding pattern. Quantum chemical studies in the context of understanding acid–base behavior of oxicams is studied by Ho et al. [5]. They have introduced a proton-exchange scheme to predict the microscopic pK_a values corresponding to the possible deprotonation pathways. They combined these microscopic pK_a values to predict the macroscopic pK_a values of oxicam compounds. Similarly, Franco-Pérez et al. studied several microspecies involved in the prototropic equilibria of oxicams using time-dependent density functional theory (TD-DFT) [23].

Lornoxicam has not received much exploration in the context of physical and quantum chemical studies. There are no reports displaying the energetics of canonical and zwitterionic forms of lornoxicam and relating the thermodynamic stabilities and the prototropic exchanges associated with this drug molecule. Considering the fact that polymorphism effect the physiochemical behavior of drug molecules which ultimately effect their bioavailability, we decided to carry out DFT [24] study to analyze the most stable form among several canonical and zwitterionic forms of lornoxicam under the gas and solvent phase conditions. QM/MM studies carried out by Tahan et al. states that, the varied dielectric constant effect the energy profiles of canonical and zwitterionic species [25]. Hence, it is worth exploring the stabilities of different forms of lornoxicm under the conditions of varied polarity. We have also envisaged the thermodynamical outcome of different forms of lornoxicam under the microsolvation conditions by considering the explicit water molecules. Further, the proton transfer pathway for the interconversion of canonical to the zwitterionic form of lornoxicam has also been explored under different operating conditions to examine their effect on the energetics of this interconversion.

2. Methods and computational details

Complete geometry optimizations were performed on various canonical and zwitterioinc forms of lornoxicam using Hartree–Fock (HF) [26], Becke-Lee–Yang-Parr (B3LYP) [27,28] and M06L [29] method with 6-31 + G(d) basis set in both the gas and solution phases (IEFPCM model [30]) respectively using Gaussian 09 [31] suite of programs. Crystal structure of lornoxicam (CCSD code: EHIGUX [32]) which was used in a study on metal-oxicam coordination compounds by Tamasi et al. [2] has been taken for this study as a reference structure for generating 11 possible canonical forms along with the zwitterionic states (**ZN** and **ZO**) of lornoxicam. Intramolecular H-bonding for the most significant (**L-1**, **ZN**, **ZO**) forms were confirmed by AIM (atom in molecule) calculations using the AIM2000 software [33–36]. Different solvents (ethanol, acetone, dichloroethane, dichloromethane and tetrahydrofuran) were used in order to study the effect of their polarity on the relative energy trends of canonical and zwitterionic forms of lornoxicam. Their choice was in accordance to their respective dielectric constants (K = 80.00, 24.55, 21.00, 10.50, 9.10 and 7.50) with the values in the decreasing order. The pathway for the conversion of canonical into zwitterionic forms was also explored by taking explicit water molecules (n = 1, 2) in consideration. Frequencies were computed analytically to characterize each point as a minimum or a transition state, and also to estimate the zero point vibrational energies (ZPE)-corrected to Gibbs free energy. The calculated ZPE [37] values (at 298.15 K) were scaled by a factor of 0.9806, 0.9153 and 0.9780 for B3LYP, HF and M06L levels respectively [38–40].

3. Results and discussion

3.1. Isomeric and zwitterionic preferences

Lornoxicam is a monoprotic weak acid [3] and it exists in canonical and zwiterionic states (Fig. 1). In the canonical state 11 different isomers are in principle possible for this drug candidate. DFT calculations [24,41] were carried out to scan the potential energy surface (PES) [42] of lornoxicam by taking into consideration all the possible isomeric and zwitterionic forms. Geometrically optimized structures with their respective relative energies (Fig. 2, Table 1 and Fig. S1, Supporting Information) in the gas and solution phases were analyzed. The results have indicated that the isomeric form **L-1** is the most stable form in the gas phase condition, at three different levels of theory namely B3LYP, HF and M06L. It is characterized by three intramolecular H-bonds, however the other isomeric forms are >5 kcal/mol less favorable than this global minimum energy structure. **ZN** and **ZO** are two important zwitterionic forms of lornoxicam which are characterized by the presence of two intramolecular hydrogen bonds at their negative and positive centers. These are about ~7 kcal/mol less stable on the potential energy surface compared to the most stable canonical form (**L-1**). However, under the solvent phase conditions **ZO** gains thermodynamic stability and turns out to be a predominant form. In comparison, **ZN** form comes out to be relatively less stable by 5.03 kcal/mol in the solvent phase condition. Its lower stability in the solvent phase is attributed to its buried negative nitrogen center as compared to openly accessed oxygen (negative center) of **ZO**. The isomeric form **L-1** can interconvert to **ZO** form via rotation across C2–C7 with exchange of hydrogen from the amide nitrogen to the pyridine ring followed by a transfer of hydrogen from enolic oxygen to amide nitrogen. The relative stability of N or O zwitterionic forms in an oxicam class of drugs is governed by the nature of substituents. The stability of **ZO** can be rationalized due to the presence of electron withdrawing 2-chlorothieno ring which markedly enhances the acidity of enolic proton. This is because of low gas phase deprotonation energies of lornoxicam (3.5–5.25 kcal/mol) as compared to other drug candidates (0.07 to 3.48 kcal/mol) belonging to the oxicam class [5]. To further analyze the correlation between the geometrical and topological parameters of intramolecular H-bonds in three important forms of lornoxicam (**L-1**, **ZO** and **ZN**), the theory of atoms in molecules (AIMs) was used. The correlation between the properties of bond critical points (BCPs) and H-bond energies both in the conventional and unconventional H-bonds were found in the literature [43–46]. The results are mentioned in Table 2 and the corresponding molecular graphs are provided in Fig. S2 (Supporting Information). All

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