Research Article

iMedPub Journals
http://www.imedpub.com

Chemical informatics
ISSN 2470-6973

2015
Vol. 1 No. 1:6

DOI: 10.21767/2470-6973.100006

Structural Features on Polymorphism of Diclofenac Acid

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Abstract

A structural study of diclofenac acid was carried out by density functional theory (DFT) calculations. Five different structures were found to corresponding its minimum energy conformations. Among several interconvertible rotations, the five most stable structures were studied and the intramolecular interactions governing the corresponding conformational preferences were considered and energy values were related to each other. Some theoretical structures are in agreement with the conformations experimentally detected in polymorphic structure of diclofenac acid. Evidence for intermolecular hydrogen bonds formation, as among amine, carboxylic groups and adjacent chloro moiety leading to most stable structures in single molecule.

Keywords: Diclofenac acid; DFT; Hydrogen bond; Structure; Conformation; Polymorphism

Received: June 30, 2015; **Accepted:** September 08, 2015; **Published:** September 11, 2015

Citation: Borges RS, Carvalho ES, Gabriel S Cabral, et al. Structural Features on Polymorphism of Diclofenac Acid. Chem Inform. 2015, 1:1.

Introduction

Diclofenac acid or 2-[(2,6-dichloro-phenyl)-amino]-phenylacetic acid is an excellent nonsteroidal anti-inflammatory drug (NSAID) [1] used in the treatment of pain disorders. It has numerous solid forms, including various diclofenac salts. Among them, an exemplary of diclofenac acid crystal forms including one monoclinic form which is recrystallized from methanol by slow evaporation, and another which is recrystallized from acetone [2]. Diclofenac acid also exists in an orthorhombic form, which is recrystallized from hot methanol by slow evaporation [3]. Several forms of diclofenac salts include potassium diclofenac dihydrate [4], sodium diclofenac tetrahydrate [5], and sodium diclofenac pentahydrate [6]. Thus, the polymorphism of diclofenac depends on the recrystallization conditions [7,8].

In fact, the study of polymorphism in pharmaceutical substances is important because of possible changes in their solubility, dissolution and shelf life [9]. Therefore, it is important to characterize both pharmaceutical and theoretical properties in their solid state and formulations, especially those substances dispersed or embedded in a polymer matrix and different solvent, to establish that they still preserve the required pharmacological properties, including their chemical and physical properties and biological activities.

Actually, the use of computational methods is an indispensable tool for the understanding of the physical and chemical properties of molecules, mainly related to its use in pharmaceutical systems. In this work, a theoretical study of diclofenac acid is performed to understand the intramolecular or intermolecular interactions, providing information about the variation of the most stable polymorphic structures of diclofenac acid.

Methodology

All calculations were performed with the Gaussian 03 molecular package [10]. Prior to any DFT calculations, the structure of diclofenac acid was submitted to PM3 [11] geometry conformational search. Afterwards, the PM3 geometry was fully optimized with the B3LYP hybrid density functional theory [12,13] using the 6-31G(d,p) basis sets [14,15]. Only the most stable conformation for a given structure was used and all of them are free from negative frequencies. The energy barrier (ΔE) was calculated as the energy difference between the structures of lower energies (2-5) and the respective the structure of higher energy (1) (Eq. 1).

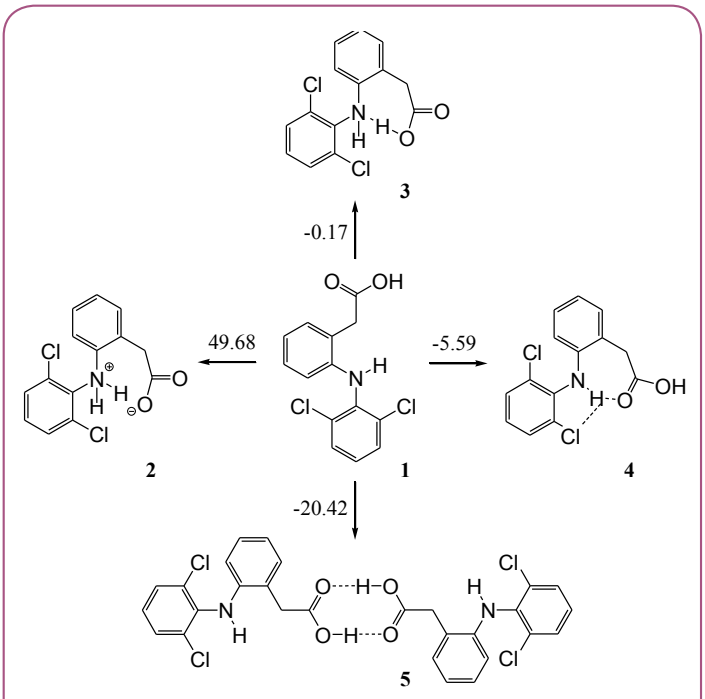

Figure 1 Synthetic route for chalcone based 1,2,3-triazole (CT series) compounds.

$\Delta E = E_f - E_i$ (Eq. 1)

Results and Discussion

The present study on diclofenac acid polymorphism using energy barriers (DE) among each possible conformational structures, seeking to understand which conformational structure are most found and compared to experimental studies. **Figure 1** summarizes the ΔE and their corresponding conformational structures obtained by using the hybrid Density Functional Theory B3LYP and 6-31G(d,p) basis set. We have found five main structures named gas phase **(1)** zwitterion **(2)**, acid-base interaction **(3)**, orthorhombic structure **(4)**, and dimer **(5)** due to their energy or conformational structures.

In drug development different forms of a pharmaceutical substance may display different physical and chemical properties. Thus, the pharmaceutical substances may change to different polymorphs, solvates or pseudo-polymorphs, de-solvates or amorphous materials after standard pharmaceutical processes such as crystallization, milling, freeze drying, spray drying and solid dispersion, which may change their pharmaceutical activities [9]. In fact, every structure has different energies among their diverse physical forms. Therefore, the pharmaceutical industry requires a strategy to characterize polymorphic drugs and produce drugs of consistent quality and the theoretical methods can be used for a better understanding.

Concerning energy barriers (ΔE) **(Figure 1)**, the B3LYP/6-31G(d,p) basis set two groups were separated using interactions mainly hydrogen bond: intermolecular and intramolecular. The zwitterion **(2)** formation, where the ΔE values of 49.68 kcal/mol can be unfavorable. The high values are due to a low basicity on nitrogen biphenyl. In addition, two chloro on *ortho* position of phenyl ring decrease the nitrogen basicity. In fact, the hydrogen bond interaction on acid-base structure **(3)** had shown a low ΔE values of -0.17 kcal/mol when compared with gas phase structure **(1)**.

Nevertheless, the increase of hydrogen bonding gives structure more stable. Therefore, the orthorhombic structure **(4)** and dimer **(5)** have shown the lower ΔE values of -5.59 and -20.42 kcal/mol, respectively, where the N-H works like an acid group and carbonyl acting as an electron donating group.

However, the orthorhombic structure **(4)** has more functional groups involved with molecular interaction, forming a more rigid structure than dimer **(5)**. This behavior restricts other possible conformations. Further, dimer **(5)** could have a difficult solvation mainly due to its high molecular weight. Hence, the high molecular structure may be related with an increase of intermolecular repulsion and because of its different free dihedral groups, other conformations should be possible. Therefore the dimer structure **(5)** can be more flexible. In **Figure 2**, all intramolecular and intermolecular interactions can be observed.

Furthermore, there have been reports that the physical and chemical properties of diclofenac depends on the acidity of the conditions to which it is exposed. The solubility of diclofenac is substantially governed by the pH of the surrounding solution [16,17]. It can undergo an intramolecular cyclization under the acidic conditions found in gastric juices [18]. Herein, our theoretical results mainly for the orthorhombic structure (4) are in agreement to its crystallographic structure obtained by using of X-ray powder diffraction.

Conclusion

The theoretical study shows that the most stable conformational structure exhibited the lowest energy barriers. This property can be attributed to increase of intermolecular when compared to intramolecular interactions. The increase of hydrogen bonding gives more stable structures. Orthorhombic structure has more functional groups involved with molecular interaction than dimer structure. These results explain the probable more involvement of oxygen, halogen and nitrogen groups on intramolecular interaction of stable conformation.

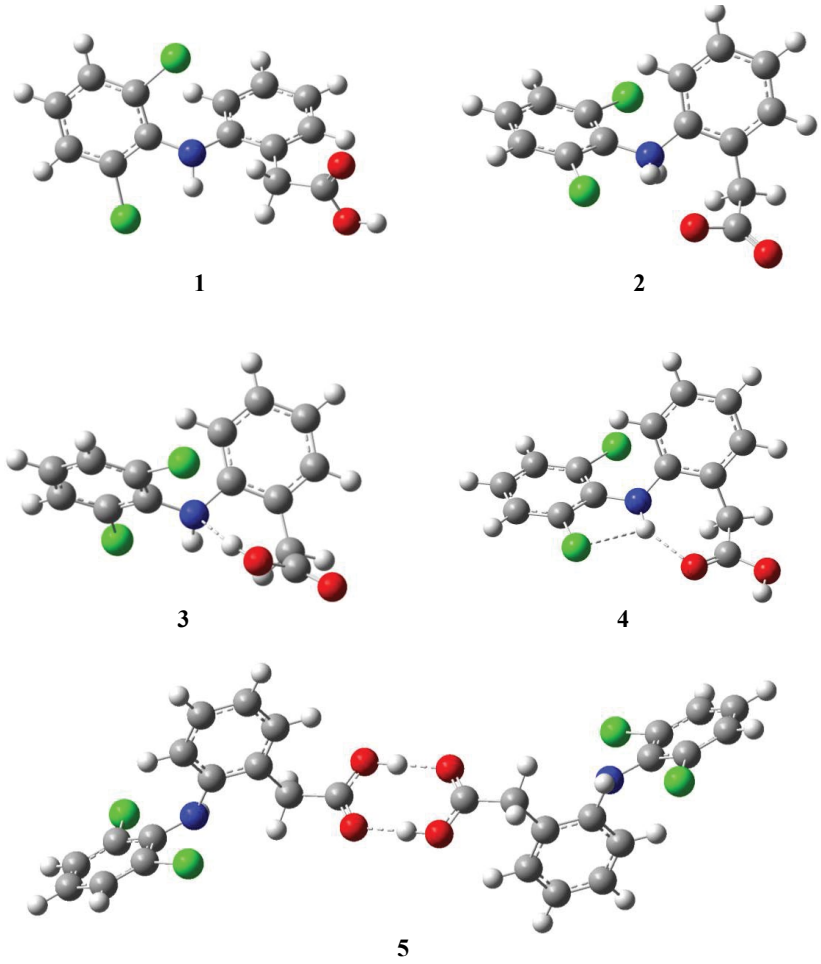

Figure 2 Conformational structures of diclofenac acid by DFT/B3LYP/6-31G(d,p).

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