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A theoretical quantum study of the intramolecular interactions and chemical reactivity of polymorphs A and B of famotidine in the gas, DMSO, and aqueous phases

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ABSTRACT

In the present work, we have studied the intramolecular interactions and chemical reactivity of famotidine polymorphs A and B in the gas, DMSO, and aqueous phases at the X/def2TZVP level of theory (where *X* = wB97, wB97X, and wB97XD) and using the SDM solvation model. Also, the plane-wave density functional theory through the PSPW formulation was used to analyze the global reactivity parameters of famotidine. The geometry optimization of polymorphs A and B indicated extended and folded configurations, respectively. The results indicate that polymorph B exhibits a greater number of intramolecular interactions than polymorph A. Also, polymorph B is slightly more nucleophilic than polymorph A, which suggests better antiulcer activity by famotidine in a folded configuration.

1. Introduction

Famotidine, (3-[[2-(diaminomethylideneamino)-1,3-thiazol-4-yl]methylsulfanyl]-N′-sulfamoylpropanimidamide), is a histamine-H2 receptor antagonist that can inhibit the secretion induced by acetylcholine and gastrin [1]. It is used in the treatment of gastrointestinal disorders such as aspiration syndrome, gastroesophageal reflux disease, dyspepsia, peptic ulcer, and Zollinger–Ellison syndrome [2,3]. It has also been used in the treatment of Parkinson's [4] and Alzheimer's diseases [5]. Famotidine is considered to be safe and is generally well tolerated, causing very few adverse reactions [6]. However, it has recently been reported that this antiulcer drug may induce immunoglobulin E-mediated anaphylaxis and have cross-reactivity with nizatidine and ranitidine [7]. Additionally, famotidine might induce an anaphylactic reaction via a nonallergic mechanism such as a direct mediator release from mast cells or basophils [7]. Although any allergic effects caused by famotidine have been clearly identified, there is still no consensus on the mechanism related to such allergenic processes [8]. Moreover, due to its extensive use to prevent gastric ulcer, traces of famotidine and their metabolites have been found in water, causing environmental troubles [9].

In the solid state, famotidine may exist in crystal forms A, B, and C, [10]. However, only the polymorphs A (FamA) and B (FamB) exhibit monotropic behavior [10–14]. The metastable polymorph B may undergo heat-induced or solvent-induced transformation to produce the stable polymorph A [15–18]. Ferenczy et al. [19] indicated that this behavior is because of the excess internal energy of FamA with respect to FamB, which is largely counterbalanced by the increased intermolecular interactions energy in FamA. From last information, it is clear that famotidine polymorph geometries are strongly influenced by the presence of intramolecular interactions. Also, FamA is the thermodynamically more stable form, but FamB is the kinetically favored form with more pharmacological activity than FamA [18]. However, the reasons by which FamB is more reactive than FamA are unknown. Thus, a detailed study of the chemical reactivity exhibited by FamA and FamB may be fundamental to understanding their chemical behavior. In this sense, the accepted theories of quantum chemistry can provide valuable information to reach such objective. Sagdinc and Bayari studied the FTIR spectrum of FamB through molecular mechanics and semiempirical methods [20]. They reported that the calculated geometric parameters of famotidine at the AM1 semiempirical level compare favorably with the corresponding X-ray structure of famotidine [20]. On the other hand, Muthu et al. calculated some electronic properties of famotidine using

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the Density Functional Theory (DFT) at the B3LYP/6-311G(d,p) level of theory [21]. They obtained an extended structure of famotidine where the more electrophilic active sites are located on guanidine and thiazol groups [21]. Baranska et al. analyzed famotidine's structure from experimental and theoretical points of views and indicated that famotidine geometries in the dimethyl sulfoxide (DMSO) and gas phase are equivalent to those observed in the solid state [22,23]. However, Marosi et al. [24] found through NMR and quantum calculations that in DMSO, famotidine must exhibit an extended conformation instead a folded conformation, as predicted by Baranska et al [22,23]. Additionally, Marosi et al. indicate that in DMSO, the hydrogen bond involving one of the sulfonamide NH_2 protons and the thiazole nitrogen does not exist [24].

These controversial reports indicate that more studies at the molecular level are necessary to clarify the structures and chemical behavior of FamA and FamB. Moreover, a good prediction of these molecular structures would allow for adequate evaluation of the chemical reactivity of this important drug to explain its pharmacological activity. To the best of our knowledge, a quantum mechanical study of intramolecular interactions in FamA and FamB in the gas, DMSO, and aqueous phases has not been done. Moreover, an analysis of the chemical reactivity of these polymorphs has not been reported yet. Therefore, in the present work, we analyze the importance of the intramolecular interactions in the conformation of FamA and FamB in these conditions. We also evaluate the global and local reactivity descriptors of these polymorphs to get a better understanding of the chemical behavior of this important antiulcer drug.

2. Theoretical background

2.1. Intramolecular interactions analysis

To analyze the intramolecular interactions in FamA and FamB, we used the non-covalent interactions (NCI) index reported by Johnson et al. [28,29]. This index is based on the reduced density gradient, s, and the electron density, ρ:

$$s = \frac{1}{2(3\pi^2)^{1/3}} \frac{|\nabla\rho|}{\rho^{4/3}} \tag{1}$$

s can be plotted against $sign(\lambda_2)$, where $sign(\lambda_2)$ is the second curvature of ρ [28,29]. In this plot, a spike with a negative sign of λ_2 indicates bonding interactions [28,29], while a depletion in the density is characterized by a positive sign of λ_2, indicating non-bonded interactions [28,29]. Also, Van der Waals interactions may be related to a negligible density overlap that gives $\lambda_2 \approx 0$. Thus, an analysis of the sign of λ_2 allows us to identify different types of weak interactions, while the magnitude of the electron density can be associated with the strength of the interaction [28,29]. A spike localized in the negative zone indicates a stabilizing interaction, while a spike in the positive region is indicative of destabilizing interactions [28,29].

2.2. Chemical reactivity analysis

The chemical reactivity of FamA and FamB is analyzed through conceptual reactivity parameters derived from DFT. These parameters can give information about the general chemical behavior of a molecular system [30]. The global parameters are the electronic chemical potential (μ), the electronegativity (χ), and hardness (η) [31–33]:

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{v(r)} = -\frac{1}{2}(I - A) \tag{2}$$

$$\chi = -\mu \tag{3}$$

$$\eta = \left(\frac{\partial \mu}{\partial N}\right)_{v(r)} = \left(\frac{\partial^2 E}{\partial N^2}\right)_{v(r)} = (I - A) \tag{4}$$

where E, N, and $v(r)$ are the energy, number of electrons, and the external potential of the system, respectively. The vertical electronic affinity (A) is calculated as $A = E(N) - E(N+1)$, where $E(N)$ and $E(N+1)$ are the total ground-state energies in the neutral N and singly charged $(N+1)$ configurations. The ionization potential (I) is calculated as $I = E(N-1) - E(N)$. Some reports suggest that the Koopmans' theorem may become valid for calculations of the global reactivity parameters at the DFT level [34–36]. Under this approximation, A is related to the LUMO energy (ε_L), while I is associated with the HOMO energy (ε_H) [34–36]. Thus, $\eta = (\varepsilon_L - \varepsilon_H)$ and $\mu = \frac{1}{2}(\varepsilon_L + \varepsilon_H)$. Another reactivity descriptor is the global electrophilicity index (ω) [37]:

$$\omega = \frac{\mu^2}{2\eta} = \frac{(I+A)}{2(I+A)} \tag{5}$$

which may be rewritten in terms of the Koopmans' theorem as $\omega = (\varepsilon_L + \varepsilon_H)^2/(2(\varepsilon_L - \varepsilon_H))$. In addition to the global reactivity parameters, it is possible to define local reactivity descriptors that can be used to study the reactivity on different sites within a molecule [30]. This local reactivity can be evaluated through the Fukui function ($f(\vec{r})$) [38,39], which is defined as [38]:

$$f(\vec{r}) = \left(\frac{\partial \rho(\vec{r})}{\partial N}\right)_{v(r)} = \left(\frac{\partial \mu(\vec{r})}{\partial v(r)}\right) \tag{6}$$

where $\rho(\vec{r})$ is the electronic density. The Fukui Function (FF), Eq. (6), can be evaluated using a finite difference approximation. However, the discontinuity of the electron density with respect to the number of electrons (N) leads to three types of FF for a system, namely $f^+(\vec{r}), f^-(\vec{r})$, and $f^0(\vec{r})$ for nucleophilic, electrophilic, and free radical attacks, respectively [30]:

$$f^+(\vec{r}) = \rho_{N+1}(\vec{r}) - \rho_N(\vec{r}) \tag{7}$$

$$f^-(\vec{r}) = \rho_N(\vec{r}) - \rho_{N-1}(\vec{r}) \tag{8}$$

$$f^0(\vec{r}) = \frac{1}{2}\left[\rho_{N+1}(\vec{r}) - \rho_{N-1}(\vec{r})\right] \tag{9}$$

3. Methodology

The initial geometries of FamA and FamB were the experimental structures reported by Overgaard and Hibbs [14]. These geometries were optimized using the dispersion-corrected density functionals wB97, wB97X, and wB97XD [40,41] in the gas, DMSO, and aqueous conditions. These functionals were chosen because they have proved to be an excellent method to study the dispersion interaction forces present in intramolecular interactions [40,41]. Moreover, it has been reported that the interaction energies evaluated through wB97XD are comparable to the results obtained at the CCSD(T) level of theory [42]. Also, we use the def2TZVP basis set [43,44]. The solvent was modeled through the SMD solvation model reported by Truhlar et al. [45]. Also, a correction energy correlation, was performed employing the second order Moller Plesset's theory (MP2) [46]. All these calculations were carried out through the packages Gaussian 09 [47] and NCIplot [28] and they were visualized with the Gausview [48], Arguslab [49], and GNUplot packages [50]. Additionally, the Pseudopotential Plane-Wave Density Functional Theory through the PSPW formulation as implemented in NWchem was used to compare the results obtained with localized