28-29 September 2023,
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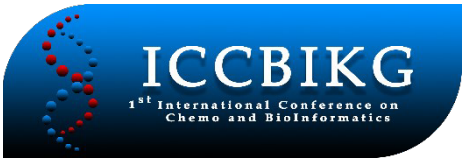

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Theoretical and experimental study of bilastine ionization

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Abstract: The protolytic equilibria of bilastine were studied experimentally and theoretically. The pK_a values were determined potentiometrically at a constant ionic strength (0.1 M NaCl) and temperature 25 °C. Energy calculation of the optimized structures of the equilibrium forms was performed at the B3LYP/6-31G (d,p) level of the Density Functional Theory (DFT). The results of the theoretical study helped to define the ionization profile of bilastine and to assign the experimentally determined pK_a values to the corresponding ionizable groups.

Keywords: bilastine, protolyitic equilibria, molecular orbital energy, quantum chemical parameters

1. Introduction

Bilastine is a second-generation oral H_1 antihistamine approved for use in symptomatic treatment of allergic rhinoconjunctivitis and urticaria with the advantage of its favourable tolerability profile and the long duration of action [1]. For the assessment of the optimal dose in the pediatric population, it is required to specifically characterize the safety and tolerability [2, 3]. To give better insight into pharmacokinetics and safety of bilastine it is important to consider its physico-chemical properties such as the ionization constant [4]. Chemical structure of bilastine (**Figure 1**) contains three ionizable centers, one acidic (carboxylic group) and two basic centers (nitrogens in benzimidazol and piperidinyl groups). To additionally clarify results obtained in experimental investigations of bilastine protolytic equilibria, the theoretical study has been performed.

2. Experimental and computational methods

The pK_a values of bilastine were determined potentiometrically using a titration system 798 MPT Titrino with a combined electrode (LL unitrode Pt1000; Metrohm). Bilastine, 2-[4-(2-{4-[1-(2-Ethoxyethyl)-1H-benzimidazol-2-yl]-1-piperidinyl}ethyl)phenyl]-2-methylpropanoic acid, was kindly donated from ALIMS. All titrations were carried out at 25°C with continuous magnetic stirring. Constant ionic strength was adjusted to 0.1 M with NaCl. The apparent ionization constants (pK_a*) were obtained in the different methanol-water mixtures (20% - 40 % wt/wt). 40 mL solutions of bilastine (5×10^{-4} M) in the methanol-water mixtures, were titrated with the 0.02 mL aliquots of standard NaOH solution (0.1017 M). On the basis of the data obtained by potentiometric titrations, the pK_a* values were calculated using a computer program Hyperquad, which enables determination of equilibrium constants in complex systems containing the overlapped acid-base equilibria.

The chemical structures of 4 equilibrium forms of bilastine that can exist in solution (**Figure 1**) were optimized at the B3LYP/6-31G (d,p) level of DFT in the gas phase using the Gaussian 03 program. The *Polarizable Continuum Model* (PCM) [5], was applied with B3LYP/6-31G (d,p)^{water} basis set to compute the energies of the *Highest Occupied Molecular Orbital Energy* (E_{HOMO}) and the *Lowest Unoccupied Molecular Orbital Energy* (E_{LUMO}), which were used to calculate quantum chemical based reactivity molecular descriptors: chemical potential (μ), electronegativity (χ), hardness (η), global softness (S), and electrophilicity index (ω) [**6**].

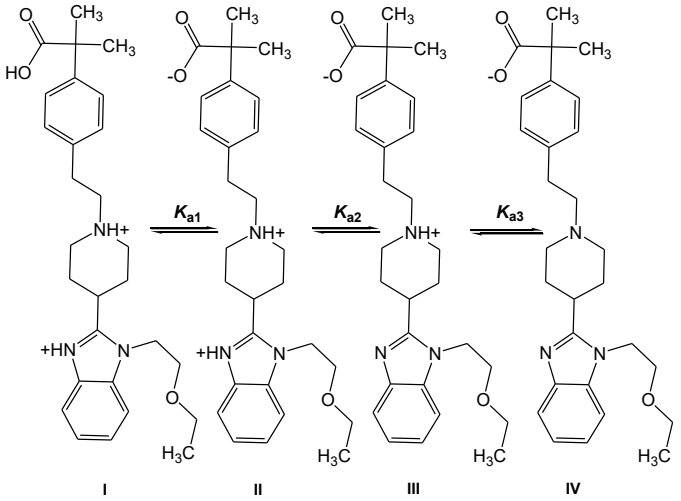

Figure 1. Equilibrium forms of bilastine: (I) dicationic, (II) cationic-zwitterionic, (III) zwitterionic, (IV) anionic.

3. Results and discussion

Due to poor water solubility of bilastine, its aqueous pK_a values (pK_{a1}=5.72 for carboxyl group; pK_{a2}=7.86 for benzimidazol nitrogen; pK_{a3}=9.68 for piperidin nitrogen) were obtained indirectly from the pK_a* values potentiometrically determined in different methanol/water mixtures (20%-40% methanol, wt/wt) by extrapolation of the pK_a*

values to 0% of methanol. To additionally clarify the order of bilastine ionization and estimate the properties of its equilibrium forms, the theoretical study was performed, and results are shown in **Table 1**. Among the calculated parameters, the electronegativity (χ) expressed the greatest importance in predicting the order of ionization [7]. It is defined as the ability of the atom in a molecule to attract electrons [7,8]. The higher values of this parameter correspond to the molecules that can be described as stronger Lewis acids, as they have a higher affinity for deprotonation [7]. Calculated χ values of bilastine equilibrium forms (**Table 1**) decrease in the order in which is assumed the ionization takes place (I > II > III > IV).

Table 1. Quantum mechanical parameters of bilastine equilibrium forms calculated at B3LYP/6-31G (d,p)PCM level.

Descriptor (eV)	I	II	III	IV
HOMO	-6.043	-3.528	-5.493	-0.693
LUMO	-1.404	-2.462	-0.488	1.199
ΔE gap	-4.639	-1.066	-5.005	-1.892
μ (chemical potential)	-3.724	-2.995	-2.990	0.253
χ (electronegativity)	3.724	2.995	2.990	-0.253
η (chemical hardness)	-2.319	-0.533	-2.502	-0.946
S (softness)	-0.216	-0.938	-0.200	-0.529
ω (electrophilicity index)	-2.989	-8.415	-1.787	-0.034

To consider the properties of the equilibrium forms in water [7] as a high dielectric solvent (ε=78.3) the PCM approach was applied and calculated E_{HOMO} and E_{LUMO} molecular orbitals are shown in **Figure 2**.

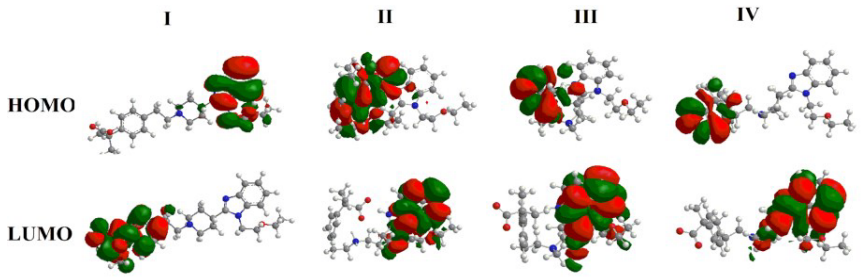

Figure 2. B3LYP/6-31G (d,p) calculated HOMO and LUMO orbitals for investigated compounds.

The lower values of the E_{LUMO} energy indicate high affinity of the compounds to accept electrons, while the high E_{HOMO} energy values indicate high affinity of the compounds to donate electrons, and vice versa [7]. Obtained distribution of the E_{HOMO} energy can confirm assumed order of ionization. In each equilibrium form the E_{HOMO} energy is localized mostly on the part of the molecule which includes carboxyl group as an acidic center (**Figure 2**). In form II, the E_{HOMO} energy is also distributed on benzimidazol nitrogen.

3. Conclusions

The ionization constants of bilastine were determined experimentally and assumed profile of the ionization were investigated in computational study. Localization of molecular orbital energy and the values of quantum mechanical parameters calculated at B3LYP/6-31G (d,p)PCM level were used to estimate the order of ionization and the properties of equilibrium forms of bilastine.

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