Computational and Theoretical Chemistry 1115 (2017) 229–238

Contents lists available at ScienceDirect

Computational and Theoretical Chemistry

journal homepage: www.elsevier.com/locate/comptc

Elucidation of the complex deprotonation routes of Changrolin, the antihypertensives LQM-303 and LQM-303b, and their derivatives

Manuel Alejandro Hernández-Olivares, Agustin Ibarra-Escutia, Gabriela Mendoza-Sarmiento, Alberto Rojas-Hernández *, Annia Galano *

Departamento de Química, División de Ciencias Básicas e Ingeniería, Universidad Autónoma Metropolitana-Iztapalapa, Av San Rafael Atlixco No. 186, Col. Vicentina C.P. 09340, México D.F., Mexico

ARTICLE INFO

Article history:
Received 6 May 2017
Received in revised form 23 June 2017
Accepted 26 June 2017
Available online 27 June 2017

Keywords:
Phenolic compounds
Acid-base equilibrium
Site acidity
Hydrogen bonding
Atoms in molecules

ABSTRACT

Elucidating the most likely deprotonation routes for polyprotic molecules is crucial in order to know the structures of the species prevailing under specific pH conditions. This is particularly important for molecules with potential applications as medical drugs, since different acid-base species, with the same deprotonation degree, may not interact in the same way with biological targets. The 19 polyprotic molecules investigated here are particularly challenging because they present phenolic and tertiary amino groups, which have similar ease of deprotonation, and also a high conformational complexity. Deprotonation energies in aqueous solution were estimated using the Density Functional Theory, and used as a quantitative criterion to identify the most likely deprotonation routes for the target molecules, which are proposed here for the first time. In addition, the LUMO and LUMO+1 distributions were also analyzed, and used as a qualitative criterion to support the proposed deprotonation routes. It is suggested that using both molecular orbitals combined for systems with small (LUMO+1) - LUMO energy gaps may provide a more useful picture in this context.

1. Introduction

Chemical compounds susceptible to be involved in acid-base equilibria are widely distributed in nature and frequently present in daily human life. They can be found not only within our body, but also in our diet and in many pharmacological drugs. The tendency of these compounds to deprotonate is quantified by their acid dissociation constants (K_a), which are frequently expressed as pK_a. However, knowing their pK_a values is not the only relevant physicochemical data regarding the speciation of chemical compounds at different pHs. In the particular case of polyprotic molecules, it is also important to know the chemical structure of the different acid-base species. For example, using the hypothetical molecule H_3A to illustrate this point, the following acid-base equilibria can be postulated:

$$H_3A \overset{pKa1}{\rightleftharpoons} H_2A^- \overset{pKa2}{\rightleftharpoons} HA^{2-} \overset{pKa3}{\rightleftharpoons} A^{3-}$$

While the H_3A and A^{3-} species are unambiguous, different structures might be associated to the H_2A^- and HA^{2-} species, due to the presence of various chemical groups susceptible to deprotonation. Accordingly, identifying the most likely deprotonation route is crucial to properly characterize this kind of chemical systems and all the species involved. Moreover, it has been demonstrated that deprotonation can alter the chemical reactivity and physiological behavior of chemical compounds [1–9].

Albeit deprotonation processes can be investigated using various experimental techniques [10–14], computational protocols have also been demonstrated to be very useful for that purpose [10,15–21]. In the present work the Density Functional Theory (DFT) has been used to explore the acid-base equilibria of 2,6-bis(pyrrolidin-1-ylmethyl)-4-(quinazolin-4-ylamino)phenol (changrolin), 4-terbutyl-2,6-bis(thiomorpholin-1-ilmetil)phenol (LQM-303), and 4-terbutyl-2,6-bis(morpholin-4-ilmethyl)phenol (LQM-303b), which are polyprotic molecules (Scheme 1). The most likely deprotonation routes were identified for these compounds and also for some of their derivatives (Scheme 2).

Our interest on these compounds arises from their pharmacological properties. Changrolin, and its structural analogs are known for their anti-arrhythmic properties [22,23]. In addition, some decades ago its anti-hypertensives effects were established, and

* Corresponding authors.
E-mail addresses: suemi918@xanum.uam.mx (A. Rojas-Hernández), agal@xanum.uam.mx (A. Galano).

http://dx.doi.org/10.1016/j.comptc.2017.06.023
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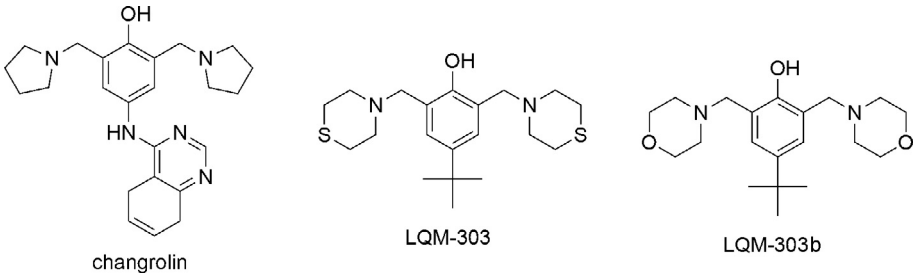
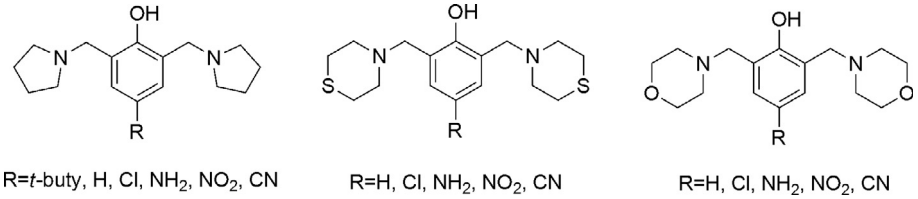


Scheme 1. Structures of changrolin, LQM-303, LQM-303B and their studied derivatives.



Scheme 2. Structures of the studied derivatives of changrolin, LQM-303 and LQM-303b.

attributed to the presence of phenol and pyrrolidine rings [24–26]. More recently, some compounds (known as the LQM family) were synthesized and proven to present also anti-hypertensives properties [27–29]. These compounds retain the phenol moiety, but differ from changrolin in that they have morpholin and thiomorpholin rings instead of pyrrolidine. LQM-303 and LQM-303b are two of these anti-hypertensives. In the particular case of LQM-303, its anti-hypertensive effects were found to be similar to those of the commercial drug losartan [29]. Due to its potential use as pharmaceutical drugs, and their polyprotic nature, it is important to elucidate their deprotonation routes. This would allow identifying the most likely species at each deprotonation degree, i.e. the most abundant species at each particular pH. Hopefully, the presented study would contribute to a better characterization of the investigated compounds under physiological conditions, and provide useful physicochemical insights that might facilitate interpreting their experimental behavior.

2. Computational details

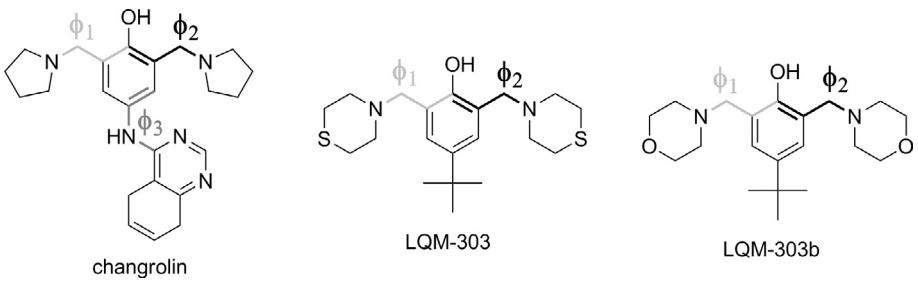
All the electronic calculations were carried out with the package of programs Gaussian 09 [30]. Full geometry optimizations, without imposing any symmetry constrains, and frequency calculations were performed at the M05-2X/6-31+G(d,p) level of theory, in conjunction with the solvation model based on density (SMD), [31] using water as solvent. Geometry optimizations were performed in solution since, particularly for phenolic compounds, optimized geometries can be significantly different from those obtained in gas phase. The Cartesian coordinates of all optimized structures are provided as Supplementary Material. The M05-2X functional has been chosen because it is recommended (together with M06-2X and M06) for systems where main-group thermochemistry, kinetics, and non-covalent interactions are all important [32]. Local minima were identified by the absence of imaginary frequencies. Thermodynamic corrections at 298.15 K were included in the calculation of relative energies. Topological analyses were computed with the AIM2000 program [33].

3. Results and discussion

3.1. Structural complexity

The first step of this investigation was to perform conformational analyses of changrolin, LQM-303 and LQM-303b. The two dihedral angles involved in the arrangement of the thiomorpholine and morpholine moieties were explored for LQM-303 and LQM-303b, respectively. For changrolin, in addition to the angles related to the pyrrolidine rings, that ruling the position of the quinazolin-4-ylamino moiety was also explored (Scheme 3). This search was carried out to identify the most likely conformers involved in the deprotonation processes.

Considering the phenol and the pyrrolidine –thiomorpholine or morpholine, depending on the compound– groups, three possible deprotonation steps are anticipated ($H_3A^{2+} \leftrightarrows H_2A^{+} \leftrightarrows HA \leftrightarrows A^{-}$), with H_3A^{2+}, H_2A^{+}, HA and A^{-} representing the investigated compounds in their maximum protonation degree, after the first,



Scheme 3. Dihedral angles considered in the conformational searches.