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Neo-Chlorogenic Acid: Conformational and Molecular Analysis by Semi-Empirical Methods

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***Abstract* – This paper shows results regarding semi-empiric results for neochlorogenic acid, from geometrical results to molecular descriptors. The gap energy of neochlorogenic acid is considerably higher, having great potential to biochemical applications.**
***Keywords* – chlorogenic acid, HOMO/LUMO, Pearson theory.**

I. INTRODUCTION

Viral diseases are a global concern since remote times, and medical science constantly brings new resources and researches to stop (or, at least, minimize) the virotic action over human health. Being very small infectious agents, viruses are a non-living association of a nucleic acid (either DNA or RNA) with a protein encapsulation[1]. Being an obligatory intracellular parasite, virus has its effectiveness inside the cell when inoculates its nucleic acid, taking control of the metabolic paths of the cell. Therefore, viruses can infect both vegetal and animal cells, including human cells[1]. The HBV, Bhepatits virus, is a chronic disease that attack liver cells and still has no cure[2]. Use of antiviral for HBV treatment is widely applied, such as entecavir, tenofovir and many others. Since its effectiveness are considered very high, the side effects are also pronunciated, and those odds can bring new solutions for HBV treatment, such as using natural products, such as neo-chlorogenic acid (NCA). This molecule is naturally syntethized by a equimolar esterification caffeic acid and quinic acid to produce chlorogenic acid[3], Fig. 1.

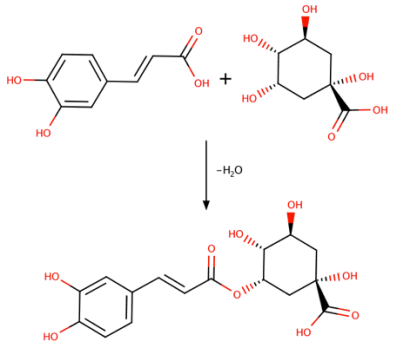


Fig. 1. Scheme of NCA synthesis by direct esterification.

Once hydroxyls from quinic acid has different sterical configuration, this esterification produces other isomers, such as NCA and crypto-chlorogenic acids[3]. The therapeutical effects of chlorogenic acid class is known in literature, and neo-chlorogenic acid has potential use for HBV antiviral uses. Once clinical and laboratorial results showed the efficacy of NCA over diminishing the HBV virulence[4], the molecular properties of NCA over HBV is still unknown. This hollow can be filled by computational chemistry, such as semi-empiric methods.

The semi-empiric along quantum methods brings fundamental information regarding microscopic properties of the molecules, such as HOMO/LUMO orbital energies, molecular electrostatic potential, conformational energy and so on[5]. Those properties reflects on reactivity over many systems, such as chemical and biological, and those properties takes effect over chemical (or biochemical) reactions[1], [6]. In this context, this paper describes an initial

semi-empirical behavior of NCA for further *in silico*applications.

II. METODOLOGY

The applied methodology was based on previous work of Marinho and coworkers [6-8]. Molecular structure of NCA was acquired in PubChem® repository (CID 5280633). Marvin was used for drawing, displaying and characterizing chemical structures, substructures and reactions, Marvin 19.8, 2019, (http://www.chemaxon.com). Also, Calculator Plugins were used for structure property prediction and calculation in the same Marvin versionrunning an academic license[9]. Molecular geometric optimization were conducted in ArgusLab® software, version 4.0.1 running an open software license. Quantum calculations used Hamiltonian PM3 as functional[10]. to calculate the HOMO (highest orbital molecular orbital) and LUMO (lowest unoccupied molecular orbital) energies, molecular electrostatic surface map (MESP), lowest energy of NCA molecule, Mulliken charges, formation enthalpy and dipolar moment. Other properties, such as partition and distribution coefficient and pKa, were calculated in Marvin software package.

III. RESULTS AND DISCUSSIONS

The molecular structure of NCA was acquired in PubChem® and inserted in Marvin software, following several calculations. Table I shows calculated properties of NCA molecule.

Table I
Solubility properties of NCA calculated by Marvin software.

Property	Value
pKa	3.33
Water solubility	High (more than 0.06 mg mL^{-1})
log P	0.07

NCA molecule presented solubility in water (higher than 0.06 mg mL^{-1}), and presented acidic properties as expected. The protonation goes on carboxylate in quinic part of NCA. The charge that follows deprotonation isn't distributed over the molecule, once the quinic region of NCA do not present any sp^2 bond and the charge do not spread[11]. Once the molecule presents high solubility, the partition coefficient tends to be in polar region in an octane/water interface. Therefore, the polar surface area is quite high, once the molecular surface is high.
In order to compute the NCA composition and a theoretical mass spectrometry, Fig.2 and Table II shows those results calculated from Marvin.

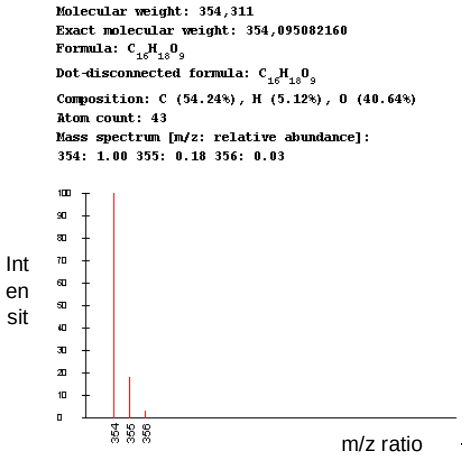


Fig. 2Calculated molecular descriptors for NCA and theoretical mass spectrum.

Fig.2 shows the calculated molecular weight for NCA, and the mass spectrum shows the relative abundance of NCA in function of m/z ratio. Having different isotopes, carbon in NCA has three relative abundances. Being NCA calculated with 354 g mol^{-1}, NCA+1 (355 g mol^{-1}) and NCA+2 (356 g mol^{-1}) reflects the isotopic carbon abundance, once the hydrogen isotopes distribution is smaller than carbon. Therefore, the m/z ratio shows the distribution of carbon isotopes of NCA in Marvin.

The geometrized molecule of NCA optimized by PM3 is showed in Fig.3 .

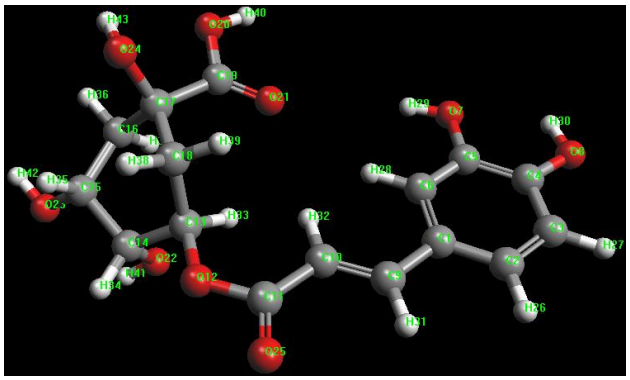


Fig. 3. Low energy conformation of NCA calculated by PM3 method.

The geometrization of NCA molecule is important to assess the lowest energy of conformation, once Lennard-Jones principle is followed[11]. The geometry that follows a lower energy in all molecules is considered the lowest global conformation, once the chemical bond and atoms are placed in a low potential energy configuration. Also, thermodynamic and molecular properties were calculated and shown in Table II .

Table II
Calculated parameters from PM3 calculation for NCA

Parameter	Value
Entalpy of formation	-353.103 kcal mol^{-1}
Geometrization energy	-111.077,380 kcal mol^{-1}

Once esterification is a spontaneous reaction in general, the enthalpy of formation goes exothermically, as seen in Table 2 . Also, the high molecular size of NCA brings a very low potential energy, and the higher polarity of NCA brings a higher dipole moment, a result that is congruent with positive log P values.

In order to quantify the charge from molecules, individual Mulliken charges were calculated and shown in Table 3. The electronegativity drives the Mulliken charge in all molecules in absence of external electrical field. In general, negative values bring two situations: the electron density is placed upon the atom, or the electron density is placed upon the atom due to resonance hybrids in sp^2 bonding orbitals[12], [13]. The reciprocal is true: positive values means electron density displacement due to another electronegative atom or resonance charge displacement. For NCA, the negative charge is placed in oxygen atoms, and charge distribution is shown in Fig.4. Red grids means higher electron density, and white grids means lower electron density.

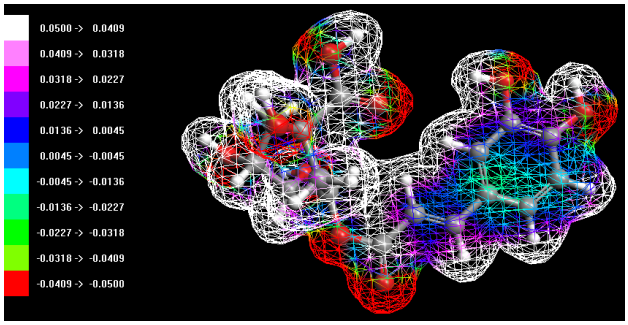
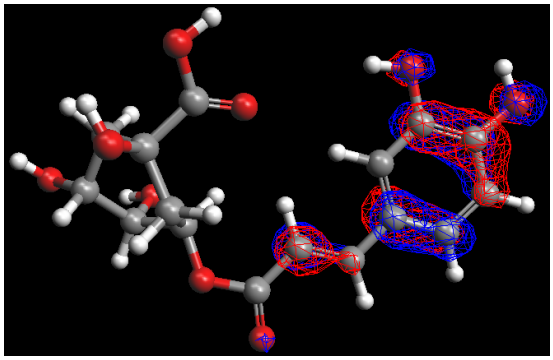
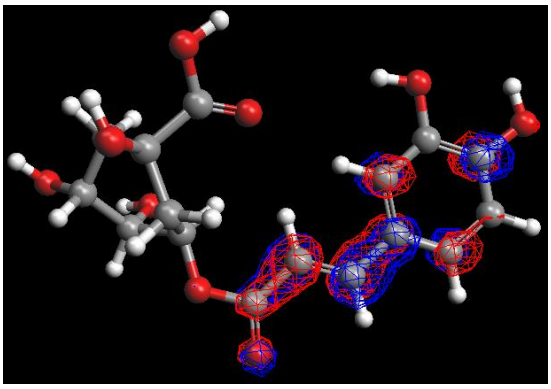


Fig. 4. Calculated electrostatic map for NCA.

In order to study the NCA reactivity, frontier orbitals (HOMO and LUMO) were calculated from geometrized molecule, and Figs.5A e 5B show the lobes from each calculation.



(A)



(B)

Fig. 5. HOMO (A) and LUMO (B) orbitals for NCA. The blue lobe refers to positive wavefunction, and blue lobe refers to negative wavefunction.

Table III

Atom	Charge	Atom	Charge
01 C	-0.1002	**24 O**	-0.3045
02 C	-0.1494	**25 O**	-0.3606
03 C	-0.2248	**26 H**	0.1994
04 C	0.0801	**27 H**	0.2193
05 C	-0.0030	**28 H**	0.2198
06 C	-0.2199	**29 H**	0.2420
07 O	-0.2604	**30H**	0.2383
08 O	-0.2342	**31 H**	0.2080
09 C	-0.0436	**32H**	0.2242
10 C	-0.3632	**33H**	0.1609
11 C	0.4397	**34H**	0.1513
12 O	-0.2449	**35 H**	0.1324
13 C	-0.0196	**36 H**	0.1336
14 C	-0.0143	**37 H**	0.1674
15 C	-0.0312	**38 H**	0.1711
16 C	-0.3297	**39 H**	0.1583
17 C	0.1330	**40 H**	0.2613
18 C	-0.2980	**41 H**	0.2342
19 C	0.3668	**42 H**	0.2235
20 O	-0.3329	**43 H**	0.2315
21 O	-0.4189		
22 O	-0.3224		
23 O	-0.3203		

Figs.5A and 5B shows the HOMO and LUMO orbitals for NCA is distributed over sp^2bondings (phenolic ring and C=C bond), once pi bonding has a lateral lobe, which increases the HOMO energy[7], [13]. LUMO orbitals is also distributed over sp^2bondings due to an empty pi orbital from C=C bonding. In order to acquire important molecular descriptors from HOMO and LUMO calculations, Table IV.

Table IV
Molecular descriptor for NCA molecule.

Parameter	Value
HOMO energy	0.326 eV
LUMO energy	-0.027 eV
Gap energy	0.299 eV
Chemical hardness	0.149 eV
Chemical softness	3.351 eV

Table 4 shows the calculated molecular descriptors from NCA. The gap energy is the negative difference between LUMO and HOMO energies[14]:

$$E_{gap} = -(E_{LUMO} - E_{HOMO}) \quad \text{Eq. 1}$$

Once the energy difference dictates the reactivity of the molecule, higher E_{gap} values means more reactivity of the molecule. Also, the HSAB theory interfers on reactivity, once the charge/radius ratio influences on molecular polarizability. So, considering $-E_{LUMO}$ = I (ionization energy) and $-E_{HOMO}$ = A (electron affinity), the molecular hardness and softness,

$$\eta = \frac{(I-A)}{2} \quad \text{Eq. 2}$$

$$\chi = \frac{(I+A)}{2} \quad \text{Eq. 3}$$

where η stands for molecular hardness and χ for molecular softness. The calculated values of NCA shows a great softness and lower hardness, meaning that the molecule has tendency to donate electrons rather to receive electrons. Therefore, the reactivity stands for higher HOMO (or electron affinity)

energies, menaing a potential for chemical (or biochemical) reactions.

IV. CONCLUSIONS

The molecular descriptors of NCA was calculated by semi-empiric calculation. Being a polar molecule, the dipole moment had its intensity calculated, along other properties, such as HOMO and LUMO energies. The results showed that the NCA molecule has potential for chemical and biochemical reactions due to higher HOMO energies.

V. ACKNOWLEDGMENTS

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