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Theoretical Study of the Natural Insecticide Rotenone Clitoriacetal

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***Abstract*— Brazil, owner of a large biological diversity, is one of the largest exporters of plant inputs worldwide, and also one of the largest consumers of pesticides for pest control and increased productivity. In an attempt to combat the pests billions of dollars are being spent around the world, and this massive investment and the indiscriminate and excessive use of pesticides have caused environmental contamination and human health risks. With the interest of finding new substances with high insecticide potential and lower toxicity, attention has been focused on the natural compounds from plant extracts. The naturally occurring pesticide-effective compound Clitoriacetal has been optimized and characterized by molecular modeling methods, determining several parameters, including global reactivity descriptors. This study aimed to characterize, through quantum mechanics calculations, the Clitoriacetal rotenone, providing data for further studies to produce analogs with higher biological potential.**

***Keywords*— Molecular Modeling, Semi-Empirical PM3, Pesticides, Theoretical Chemistry.**

I. INTRODUCTION

Brazil is currently one of the largest producers of vegetables, fruits and cereals, accounting for much of the world's supply of vegetable inputs. Among the features that allow the country to stand out from the other great barns worldwide is its extreme biological, geographical and climatic diversity, making it the scene of an abundant flora and thousands of insect species. Due to the numerous biodiversity, including pests, and the fact that it occupies a prominent global position in agriculture, it is necessary for industries to use insecticides and herbicides in order to eliminate pests and promote increased productivity. Attempts to control invertebrates are very costly, totaling billions of dollars in investment [1]. The widespread, indiscriminate and excessive use of synthetic pesticides, despite the economic benefits to the industry, has led to unprecedented environmental contamination such as soil and water contamination, selective evolution of the most resistant pests or even end consumer food poisoning pesticide residues [2].

Then came the interest in investigating substances with high pesticide potential, but offering less risk to human health and the environment. Since ancient times man has been using natural insecticides from herbal extracts, being now known numerous species of plants that have insecticidal activity, and can be studied and used as an alternative form of pest control [2]. Among the most efficient naturally occurring pesticides, we can mention rotenone and rotenoids that have long been used as insecticides and pesticides [1], and in particular Rotenone Clitoriacetal, a high-strength pesticide tetracyclic compound found in the roots of the *Clitoriafairchildian* [3].

In search of an increasingly effective, stable and less polluting compound, known pesticides can be structurally characterized by molecular modeling, allowing to understand how they work and how they can be improved. This study aimed to characterize, through quantum mechanics calculations, the Clitoriacetal rotenone, providing data for further studies to produce analogs with higher biological potential.

II. METHODOLOGY

This work was developed according to the following methodology: (1) the initial molecular structure of the Clitoriacetal compound was obtained through the PubChem® virtual repository [https://pubchem.ncbi.nlm.nih.gov/] [4] and verified in in line with the literature; (2) nomenclatures and some physicochemical properties were extracted from the ChemSpider [http://www.chemspider.com] [5] and PubChem® [4] repositories; (3) the basic theoretical and topological elemental analysis of the compound was performed using the MarvinSketch and MarvinView software [6-7], used under academic license; (4) the structure was geometrically optimized using the ArgusLab® software [8], based on the methodology proposed by Stewart and Collaborators (1989) [9-10], using the semi-empirical method PM3 (Parametric Method 3); (5) HOMO and LUMO boundary orbitals, GAP, reactivity descriptors, dipole moment and Mulliken charges were characterized; (6) through the data were plotted the surfaces of HOMO and LUMO and the dipole moment vector.

III. RESULTS AND DISCUSSION

The resources used in the geometric optimization processes of a molecule or in its specific property calculations and molecular docking in the areas of theoretical chemistry and biochemistry can be reduced or minimized by using virtual simulation tools. The initial geometric structure of the compound can be downloaded for free from virtual databases containing thousands of cataloged structures, or it can be built step by step in some molecular modeling software [11]. Through the PubChem® [4] and ChemSpider [5] repositories the initial molecular structure (Figure 1) was obtained, congruent with the literature [12], and several properties and identifiers; such data as CAS identification number (64461-44-5), the official IUPAC nomenclature (6,11,12a-trihydroxy-2,3,9-trimethoxy-6,6a-dihydrochromene [3,4-b] chromen -12-one) and some physicochemical properties (Table I) are important in the study of structural characterization.

TABLE I
Physicochemical properties of Clitoriacetal structure at PubChem®.

PropertyName	**PropertyValue**
Molecular Weight	390.344 g/mol
Hydrogen Bond DonorCount	3
Hydrogen Bond AcceptorCount	9
Rotatable Bond Count	3
Complexity	600
Topological Polar Surface Area	124 A^2
Monoisotopic Mass	390.095 g/mol
Exact Mass	390.095 g/mol
XLogP3-AA	1.7

Other properties, calculated using ChemAxon's MarvinSketch [6] software, enable a basic topological analysis, measuring the total count of atoms present, bonds, rotability in certain bonds and also presents structural characteristics of the carbonic rings present in the structure. The software also allows to perform a basic analysis of the partition coefficients of the compound, calculating the LogP value (-3.13) and that the LogD value (-2.25) remained constant at pH 1.50, 5.00, 6.50 and 7.40 (where the largest amount of microspecies of the compound are present), only showing changes from pH 9.50 (LogD -2.26) decreasing as the medium becomes more alkaline. During water solubility calculations the intrinsic solubility (-1.24 LogS) of the same value as solubility at pH 7.4 (-1.24 LogS) could be calculated and the compound was categorized as highly water soluble (solubility greater than 0.06 mg / ml).

The initial molecular structure of the Clitoriacetal (Fig.1), obtained through the PubChem® repository, presents only the arrangement of atoms and their respective bonds in a planar arrangement, being a representation that allows optimal visualization, but of potential energy and different electronic characteristics. In its optimized, nativeway.

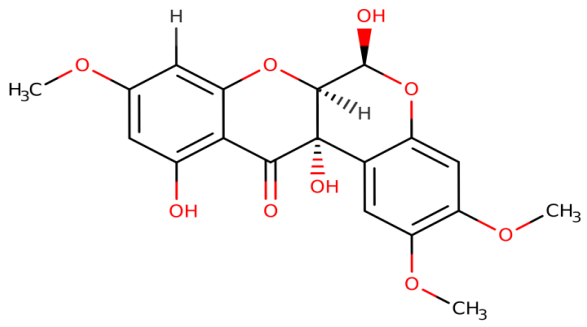

Fig. 1. The Clitoriacetal bidimensional structure

The initial elemental analysis was performed, which allows to determine which chemical elements and how much of each element make up the structure. The Clitoriacetal compound has a molar mass of 404.456, an exact mass of 404.204632610, a molecular formula (C19H18O9) and a percentage composition of 56.42% Carbon, 7.98% Hydrogen and 35.60% Oxygen. in a total of 60 atoms.

When the initial structure is obtained from an online database or built in chemical design software, it is in two-dimensional conformation, not representing the most stable and lowest potential energy conformational structure, therefore, for accurate calculations and analysis. On the structure, it must first be geometrically improved using the energy minimization process [13]. The new structure obtained (Fig. 2) includes each atom in its lowest potential energy site, making the structure theoretically as stable as possible [14]. The potential integral energy of the molecule no longer varied after reaching a stationary point on the value energy surface (-119226.5006 kcal / mol or -5170.1517 eV)

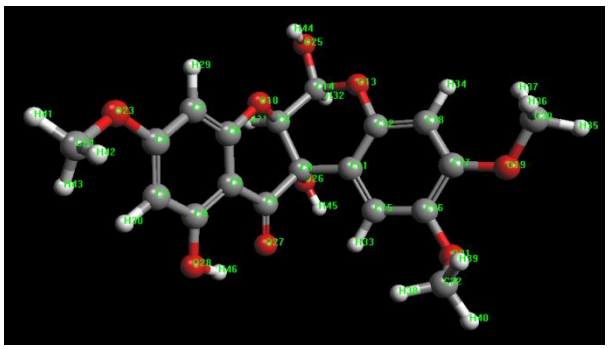

Fig. 2. The Clitoriacetal optimized structure

Atomic charges, useful for the correlational study between biological activity and molecule structure [15], can be calculated by various methods, from arbitrary charge assignment methods, using the Mulliken Population Analysis [16], which disregards electronegativity. by dividing the charge density evenly between two atoms. Using the PM3 method, the calculations show that (Table II) there was a slight variation between the atomic charges of atoms of the same element: the most charged carbon was C7 with (0.3790), while the lowest carbon was C5 with (-0.4290), varying (0.8080) charge between carbon atoms; oxygen in the same way, with the highest load being O19 with (-0.1730) and the lowest load being O27 with (-0.3744), presenting a load variation of (0.5474).

TABLE II

Mulliken charges

1	C	-0.3572	15	C	-0.1396
2	C	0.2175	16	C	-0.0134
3	C	-0.4121	17	C	-0.1348
4	C	0.2816	18	C	-0.3303
5	C	-0.4290	19	O	-0.1730
6	C	0.2399	20	C	-0.1571
7	C	0.3790	21	O	-0.1876
8	C	0.1135	22	C	-0.1448
9	C	-0.0850	23	O	-0.1905
10	O	-0.1880	24	C	-0.1542
11	C	-0.2562	25	O	-0.3102
12	C	0.1869	26	O	-0.3087
13	O	-0.2162	27	O	-0.3744
14	C	0.1389	28	O	-0.2660

The dipolar moment determines, in various molecular structures, the polar or nonpolar character of the compound, since it represents the sum vector of all polarization forces exerted by the individual atoms [13]. In the Clitoriacetal structure, the sum vector (Figure 3) was rendered using the Avogadro software based on the calculations in PM3, and presented in XYZ coordinates with values of (-1.3095 Å), (0.5166 Å) and (2.9575 Å) respectively. , with a magnitude of (3,2754 Debye).

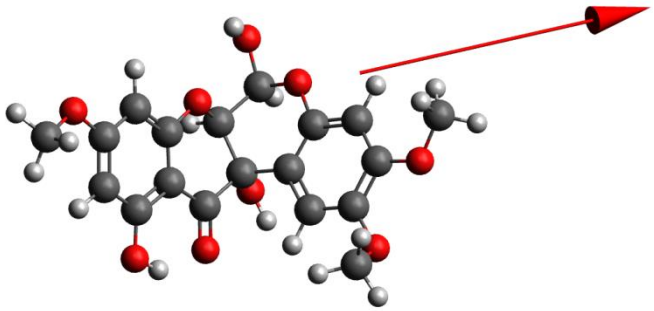

Fig. 3.*Visualization of Dipole Moment*

The boundary orbital energies were also calculated by reference to the highest occupied molecular orbital (HOMO) (Figure 4) and the least unoccupied molecular orbital (LUMO) (Figure 5). Both calculated orbitals, HOMO and LUMO, are important in molecular modeling processes, having a direct and proportional relationship to the electron donor capacity with HOMO energy and the resistive capacity of electrons to LUMO energy [16]. The calculated energy for molecular orbital 74, characterized as HOMO, was (-0,3368 au or -9,16711 eV), and for molecular orbital 75, characterized as LUMO, the energy of (-0.03189 au -0.8678 eV) was calculated.

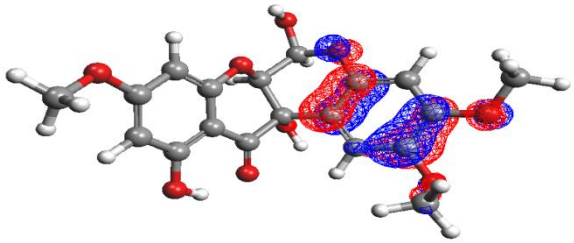

Fig. 4. HOMO – The Highest Occupied Molecular Orbital.
Source: Calculations made in PM3 method.

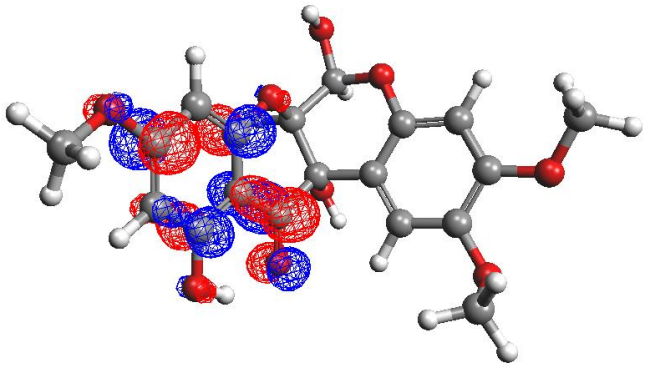

Fig.5. LUMO – The Lowest Unoccupied Molecular Orbital.
Source: Calculations made in PM3 method.

The ArgusLab® software interface, through the data generated by the PM3 method, rendered the surfaces of HOMO and LUMO, allowing to define which atoms contribute to the formation of each of these orbitals. The HOMO orbital receives a significant contribution from the benzene ring formed by the carbons C11, C12, C15, C16 and C17, with no charge being given to C18, yet receives a median contribution of oxygen O13, O19, and O21 and a reduced carbon contribution. C22. The LUMO orbital is already composed mainly of the two cyclohexanes to the right of the structure, represented by carbon atoms C2, C3, C4, C5, C6 and C7, and also receives a reasonable contribution from oxygen O23 and O27, and a negligible participation of oxygen O10 and O28.

The study of boundary orbitals (HOMO and LUMO) (Figures 4 and 5) allows to determine fundamental characteristics of the reactivity of the molecule, among which are electronegativity, electron affinity and ionization potential [17]. These data, called reactivity descriptors, define the boundaries between the overall chemical reactivity and the structural stability of the compound, as well as their correlation [18]. Reactivity descriptors are calculated from the energy values of HOMO and LUMO, starting with the value of the difference between boundary orbitals, which is an essential determinant for understanding the chemical stability of the molecule. The result of the HOMO-LUMO equation is called GAP, representing the amount of energy required for an electron to make a first transition, with the larger, more stable and non-reactive GAP molecules, and the smaller ones being more reactive [19].

TABLE III

Clitoriacetal global reactivity parameters

Parameters	Value
HOMO	-9.1671 eV
LUMO	-0.8678eV
GAP	8.2993 eV

IV. CONCLUSIONS

The natural insecticidal compound Clitoriacetal, had its molecular structure optimized geometrically through the PM3 quantum mechanical semiempirical method, performed in the ArgusLab® software, until reaching its most stable conformation theoretically and closest to its native form, reaching the minimum point of the surface. potential energy; being calculated at the end of the iterations the energy of (-5170.1517 eV) and dipole moment (μ) of magnitude (3.2754 Debye). Mulliken charge analysis was also calculated, highlighting the charge variation between atoms of the same atomic number. The boundary orbitals HOMO (-9.16711 eV) and LUMO (-0.8678 eV) were characterized and the most contributing atoms were identified for each orbital, and the GAP (8.2993 eV) was defined. The whole set of information generated with the execution of this work constitutes a basis for the steps of correlational study of structure with biological activity and obtaining new analogs aiming at improvements in the biological potential of the compound.

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