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Characterization of the natural insecticide methylcytisine: An in silico study using classic force field

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Abstract
Insecticides play an important role in agricultural production, but misuse and resistance by pests make insecticides ineffective and harmful to the environment. Needing new substances that are less environmentally friendly but effective in fighting pests. In this context arises methylcytisine, an alkaloid that has nematicidal activity extracted in the roots of plants of genus Thermopsis. Thus, the present work aimed to characterize methylcytisine *in silico* as the initial step of molecular docking studies to test the biological potential. The molecular structure characterized using the classic force field MMFF94, obtaining the potential energy, the dipole moment, the bonding angles, the torsion, the bonding lengths and the surface representation of Van der Waals. This paper is an initial step for future studies of semi-empirical molecular modeling and molecular docking.

Keywords: MMFF94. Molecular modeling. Theoretical chemistry

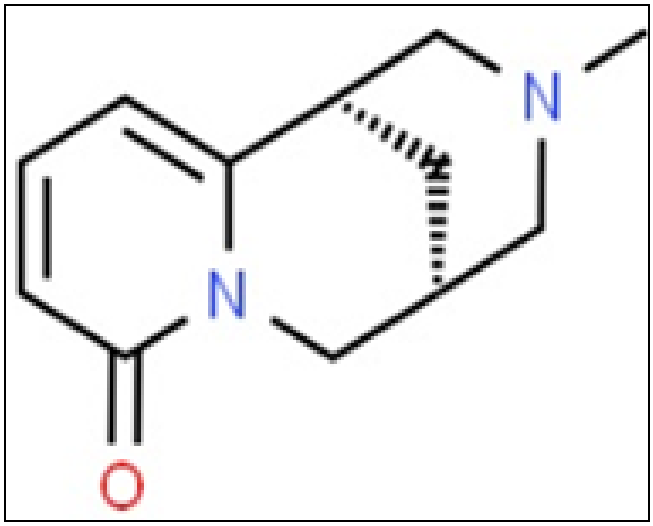
1. Introduction
Seeking to maintain economic growth, the agrarian sector looks for devices to increase production. Pests are of great concern to agricultural producers, as they attack the products causing losses in production, and consequently in the economy. To combat, farmers use tools that can kill or repel pests [1].
Insecticides are inorganic or organic substances used to attract, repel and kill insects [2]. Insecticides play an important role in agricultural production, but misuse and resistance by pests make insecticides ineffective and harmful to health and the environment. This fact generates the need for new substances that are less aggressive to human health and the environment, but effective in fighting pests.
Alkaloids are non-protein acids, classified as qualitative toxic because they act even in small quantities. They are particularly toxic to insects and often cause death [3]. In this context arises methylcytisine, an alkaloid that has nematicidal activity extracted in the roots of plants of genus *Thermopsis* [4].
Molecular modeling is understood as a grouping of tools with the functions of drawing, editing, visualizing, analyzing and storing complex molecular systems [5], offering complete electronic and structural characterization [6] enabling the cohesive planning of substances using parameters related to structure and activity [7].
Computational chemistry, using molecular modeling and theoretical calculations, performs characterizes complex compounds providing important data with high accuracy rate [8]. Force field studies, known as molecular mechanics, use classical level models to predict the energy of a molecule according to its conformation. This study allows predictions of equilibrium geometries, transitions state and relative energies between conformations or in different molecules.
Molecules in molecular mechanics are considered as a set of atoms connected differently from the quantum method that they consider containing nuclei and electrons [9]. Force field methods are important because they have parameters associated with sets of atoms remaining constant between different structures, but the hybridization of atoms must be equal [6].
The force field is a set of functions that determine energy corrections for the detachment of bonds and angulation values, seeking to minimize energy aiming at molecular stability [9]. The process of minimizing energy uses mathematical algorithms that seek to achieve the minimum energy state with attractive forces being maximized and repulsive forces reduced.
In this perspective, the present work aims the use of molecular mechanics for *in silico* characterization of methylcytisine alkaloid as an initial step for future molecular docking studies.

2. Materials and methods
The Chemspider® virtual repository [http://www.chemspider.com] was used to obtain the two-dimensional coordinates (connectivity) of the methylcytisine alkaloid, IUPAC nomenclature and physicochemical properties. For structural optimization, having as a parameter the lowest potential energy, the field strength equations at the classical level were used Merck Molecular Force Field (MMFF94) classic force field calculations [10]. The calculations were performed using Avogadro® software [11] [12], configured for cycles of 500 interactions with speed descent algorithm and convergence parameters of the order of $10e^{-7}$.
Using optimization data to obtain the geometry of the molecule, the lowest potential energy conformation, bonding characteristics and the torsion angles and dihedrals [8]. In addition to geometric optimization, an electronic optimization (following the same parameters) was performed to visualize both the dipolar moment and render

the surface map of Van der Waals.

3. Subheadings

In the Chemspider® virtual repository [http://www.chemspider.com], methylcytisine has the identification code (Chemspider ID: 204591) and nomenclature 11-Methyl-7, 11-diazatricyclo [7.3.1.02,7] trideca- 2,4-dien-6-one according to IUPAC. Also in the repository it was possible to obtain the two-dimensional structure (figure 1) of methylcytisine and physicochemical properties (table 1) important for the study of molecular modeling, for example the LogP (0.46) and LogD (-2.49) partition coefficients at pH. 5.5 Or LogD (-1.36) at pH 7.4 and polarizability (23.4 ± 0.5 10^{-24}cm3), as they are important in the study of molecular docking and molecular dynamics.



Source: Virtual Repository ChemSpider® http://www.chemspider.com/Chemical-Structure.204591.html?rid=c7c84928-3657-4550-a336-55a908af5637].

Fig 1: Two-dimensional structure of methylcystesine.

Table 1: Physico-chemical properties of compound Methylcytisine

Property	Value	Property	Value
Density	1.2 x 0.1 g/cm^3	LogP	0.49
Boiling point	400.8 ± 0.90C a 760 mmHg	LogD (pH 5.5)	-2.49
Vapors pressure	0.0 ± 0.9 mmHg a 25 °C	LogD (pH 7.4)	-1.39
Polar surface Area	24 Å ^{2}	Surface tension	49.7±5.0 dyne/cm
Vaporization enthalpy	65.2 ± 3.0 kJ/mol	Molar Refraction	58.9±0.4 cm^3

Source: Repositório virtual ChemSpider® [http://www.chemspider.com/ChemicalStructure.204591.html?rid=c7c84928-3657-4550-a336-55a908af5637].

The two-dimensional structure of methylcytisine taken from Chemspider® is in the ground state and easy to see, but has potential energy different from its native form. When a molecule is drawn or withdrawn from a virtual repository, it is not found in its most stable conformational energy and there is a need for geometric optimization in search of theoretically more stable conformation energy for more precise studies [7].

In this perspective, using the Avogadro® open license code for performing geometric optimization, configured to perform uninterrupted interaction cycles in classic level force field calculations (MMFF94 (Merck Molecular Force Field) with steepest descent algorithm parameters.

The theoretically more stable generated structure (Figure 2) carries its atoms at their lowest potential energy locations, making the overall potential energy of the molecule assume 147,348 KJ / mol without the presence of variation, reaching a steady state of the energy surface [5].

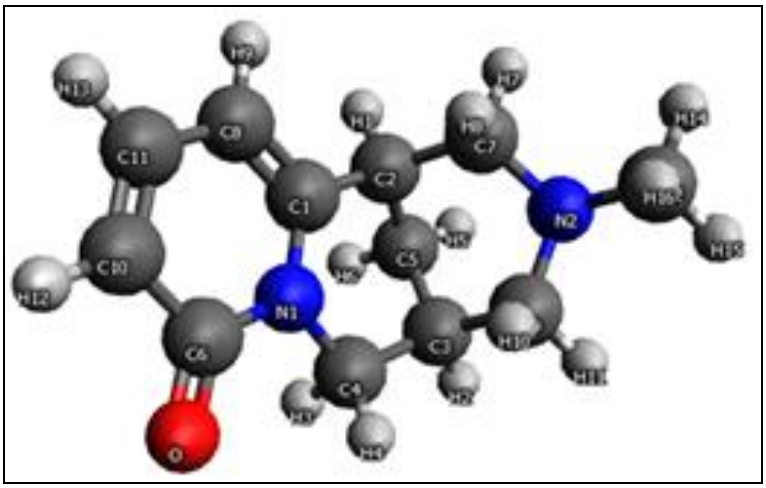


Fig 2: Optimized structure of the compound Methylcytisine using the force field MMFF94

With the energy calculations, it was possible to obtain the dipolar momentum (μ) and the surface rendering of Van der Waals (Figure 3) of methylcytisine from the electronegativity difference between the atoms, which relates how the electric charges are distributed by the molecule and to polarization (separation of the accumulation

between positive and negative charges) [13]. Structure properties such as melting and boiling points and solubility are directly linked to the dipole moment (μ) [6]. The alkaloid presented the dipolar moment of 2,193 D, proving to have a polar character.

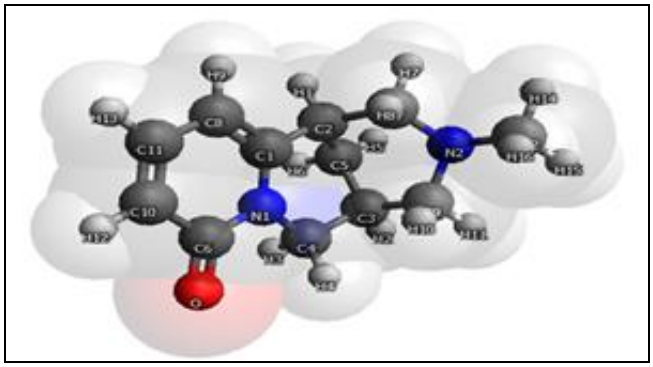


Fig 3: Van der Waals surface of the Methylcytisine.

With methylcytisine, having a theoretically more stable geometry, it is possible to calculate the valences and point charges of each atom. Although the optimized molecule is neutral, we can see from the data (table 2) that there are the presence of point charges, since they are charges from the electrons that are closer or further away from the bond atoms [13].

Table 2: Atomic properties of the compound Methylcytisine obtained after optimization using the field of force classic MMFF94 (Except H)

Element	Tipe	Valence	Partial charge
O1	O2	1	-0,268
N2	Nar	3	-0,312
N3	N3	3	-0,304
C4	Car	3	0,026
C5	C3	4	0,013
C6	C3	4	-0,01
C7	C3	4	0,03
C8	C3	4	-0,038
C9	Car	3	0,251
C10	C3	4	0,007
C11	Car	3	-0,042
C12	C3	4	0,003
C13	Car	3	0,003
C14	Car	3	-0,055
C15	C3	4	-0,013

In the final geometry of the methylcytisine alkaloid, the bonds analyzed have predominantly covalent characteristics. We can highlight the connections ((N2 - C7), (N2 - C9), (C2 - C5), (C2 - C7), (C3 - C4), (C3 - C5) and (C3 - C9) because they have rotations and the connections (O - C6) and (C1 - C8) are second order.

During conformational characterization, all bond and torsion angles could be calculated. We can highlight the largest and smallest angles between the bonds, the bonds (O - C6) and (C2 - C5) angled at 124.6180 ° and 106.1053 ° respectively. The largest and smallest torsion angles include the systems (C6 - C10 - C11 - H13) and (H9 - C8 - C11 - C10), which have angles of 179.5047 ° and -179.9590 °, respectively.

4. Conclusions

The molecular structure of the methylcytisine alkaloid was geometrically optimized by classic force field calculations MMFF94 (Merck Molecular Force Field) using the free code Avogadro® configured with Steepest Descent algorithm reaching the lowest potential energy level (147,348 KJ / mol), obtaining the theoretically more stable conformation and close to its native form.

After optimization, atomic properties were generated, such as point loads, bonding angles and torsion. Dipole moment data (2,193 D) was also generated which indicates the polarity of the compound and the surface of Van der Waals.

The data generated in this work constitute an initial step that will serve as a database for future studies of semi-empirical molecular modeling and molecular docking, aiming to optimize the alkaloid to analyze its potential.

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