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FULL PAPER

Computational Studies of Fullerene Derivatives as Pesticide Captors

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Abstract:

The use of pesticides in tropical countries such as Brazil has grown resulting in alarming health damage statistics, deaths and environmental pollution. Considering its potential risk and the difficulty on detecting their residues instantaneously in field, six fullerene derivatives were planned using semiempirical calculations and molecular docking to understand its potential as adsorbents and captors of agricultural organophosphate (Ops) pesticides. As Ops were selected acephate, cadusafos, chlorpyrifos, dimethoate, fenitrothion, phenthoate, malaoxon, malathion, methyl-parathion and terbufos. The proposal 4 had the best results and between the Ops, fenitrothion presented the best results, followed by malathion, malaoxon, phentoate and methyl-parathion.

Keywords: captors; fullerene derivatives; molecular docking; molecular modeling; organophosphates; pesticides

1. Introduction

Brazil is among the ten largest economies in the world, being a major producer and exporter of commodities. However, coupled with high productivity, the agrochemicals consumption made this country one of the leaders of agricultural market [1].

There are several pesticide groups one of them is the organophosphates (Ops) [2] which generate serious impacts on human health, specially on the acetylcholinesterase (AChE) enzyme inhibition leading to an acetylcholine (Ach) accumulation in the synapses processes, resulting in loss of muscle command, irregular heartbeat, respiratory depression followed by death [1].

It is estimated there are more than three million cases of organophosphate poisoning and more than 250,000 deaths per year from intentional autointoxications, representing 30% of the world's suicides. Most exposures occur in agrarian societies, where pesticides are readily available [1]. Considering the problems that arise from the pesticides use and its potential risk even as the difficulty on detecting Ops residues instantly in field, it led to the development of sustainable pesticides detectors and captors. Nowadays, with computational tools and technological advances available it has become possible to simulate molecules behavior, in computer, more realistically [3]. Three-dimensional molecule editing techniques and structural optimization using semiempirical PM7 Hamiltonian [4], and molecular docking were used to predict *in silico* the interaction energy between Ops pesticides and fullerene derivatives, designed based on AChE active site, as target to the organophosphates compounds, to describe in molecular level the interaction of Ops with proposed molecules.

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2. Results and Discussion

After semi-empiric calculations using the PM7 Hamiltonian and MOPAC software it was possible to extract the electronic and structural properties presented in Table 1.

Table 1. Structural electronic properties of organophosphates.

Pesticide Op	ΔH_f/ kcal.mol^{-1}	Total energy / e.V	Dipole / D	ε_{Homo}/ e.V	ε_{Lumo}/ e.V	E_{bg}/ e.V	μ/ e.V	η/ e.V
Acephate	-186.51	-2053.66	1.80	-8.78	-0.11	8.67	-4.45	4.34
Cadusafos	-177.18	-2661.93	0.83	-8.77	-0.45	8.32	-4.61	4.16
Chlorpyrifos	-199.08	-3482.22	1.71	-9.14	-0.84	8.30	-4.99	4.15
Dimethoate	-180.62	-2380.12	3.11	-9.07	-0.84	8.24	-4.96	4.12
Fenitrothion	-170.99	-3282.02	7.51	-9.24	-1.05	8.19	-5.14	4.10
Phentoate	-201.01	-3416.09	4.40	-8.94	-0.86	8,08	-4.90	4.04
Malathion	-119.86	-3780.05	4.55	-7.23	-0.96	6.27	-4.09	3.13
Malaoxon	-285.89	-3903.74	2.64	-8.44	-0.44	8.00	-4.44	4.00
Methyl-parathion	-170.45	-3132.27	6.35	-9.40	-1.14	8.27	-5.27	4.13
Terbufos	-170.18	-2688.83	4.93	-8.38	-0.57	7.81	-4.47	3.90

The heat of formation (ΔHf) of most pesticides are energetically favorable. The total energy fluctued between -3904 eV and -2054 eV, values related to malaoxon and acephate respectively. The dipole had a significant increase from 0.82818 D of cadusafos to 7.50611 D, relative to fenitrothion.

HOMO energies ranged between -7.225 eV and -9.404 eV and LUMO between -0.110 eV and 1,137 eV. The highest values for both were relative to methyl-parathion. The bandgap energy of the majority varied around 8 eV, except for the malation and terbufos, with values below. As for the conversion of malathion to malaoxon, it was observed that the low E_{bg} of malation is explained by the instability of the molecule at environmental conditions. This hypothesis was confirmed by literature data [5].

Fenitrothion and methyl-parathion had higher values of μ and, in general, an insignificant difference between μ and η (bandgap), which indicates little stability variation. Among Ops, methyl-parathion and fenitrothion presented the most satisfactory results of reactivity.

Regarding the fullerene derivatives, the Table 2 summarizes the results of electronic structural properties obtained in the calculations.

Table 2. Structural electronic properties of fullerene derivatives.

Fullerene derivatives	ΔH_f / kcal.mol^{-1}	Total energy/ e.V	Dipole / D	ε_{HOMO}/ e.V	ε_{LUMO}/ e.V	ε_{bg}/ e.V	μ/ e.V	η/ e.V
Derivative 0	816.33	-7847.42	1.43	-9.00	-3.00	6.00	-6.00	3.00
Derivative 1	768.97	-8292.64	2.14	-8.99	-2.99	6.00	-5.99	3.00
Derivative 2	802.27	-9209.83	5.73	-8.95	-2.94	6.01	-5.94	3.00
Derivative 3	637.44	-9294,47	30.32	-4.86	-1.25	3.61	-3.06	1.81
Derivative 4	671.74	-10211.45	27.83	-4.99	-1.04	3.94	-3.02	1.97
Derivative 5	661.61	-10212.01	20.25	-5.22	-1.00	4.22	-3.11	2.11
Derivative 6	664.01	-10211.86	27.15	-5.37	-1.33	4.05	-3.35	2.03

The results for all properties had significant difference between proposals 0 to 2 to proposals 3 to 6. As for the formation heat, there was a reduction of about 150 kcal per mol in average from the 0-2 proposals to the others and the total energy became even more negative. It was verified that all proposed molecules are polar, but those of number 3 to 6 are expressively more. For pesticides, cadusafos, chlorpyrifos and acephate are the least polar, and should be closely linked to proposals 3 to 6.

For the prediction of a viable interaction, the connection between $\text{HOMO}_{\text{fullerene}}$ and LUMO_{Ops} should be calculated. The proposals with the highest HOMO value were number 1 and 2, followed by 4, 5 and 6. The LUMO values of methyl-parathion and fenitrothion were markedly higher than the other pesticides studied. Considering that proposals 1 and 2 do not have the complete catalytic triad, it is suggested that the link between proposals 4 to 6 to these two Ops would be feasible for the capture of the pesticide. The docking energies obtained follow on figure 1.

Concerning bandgap energy, it has been observed that proposals 0, 1 and 2 were more stable, it means more difficulty to bind to Ops. Otherwise, the molecules 3 to 6 had lower values, it is inferred that they are more reactive.

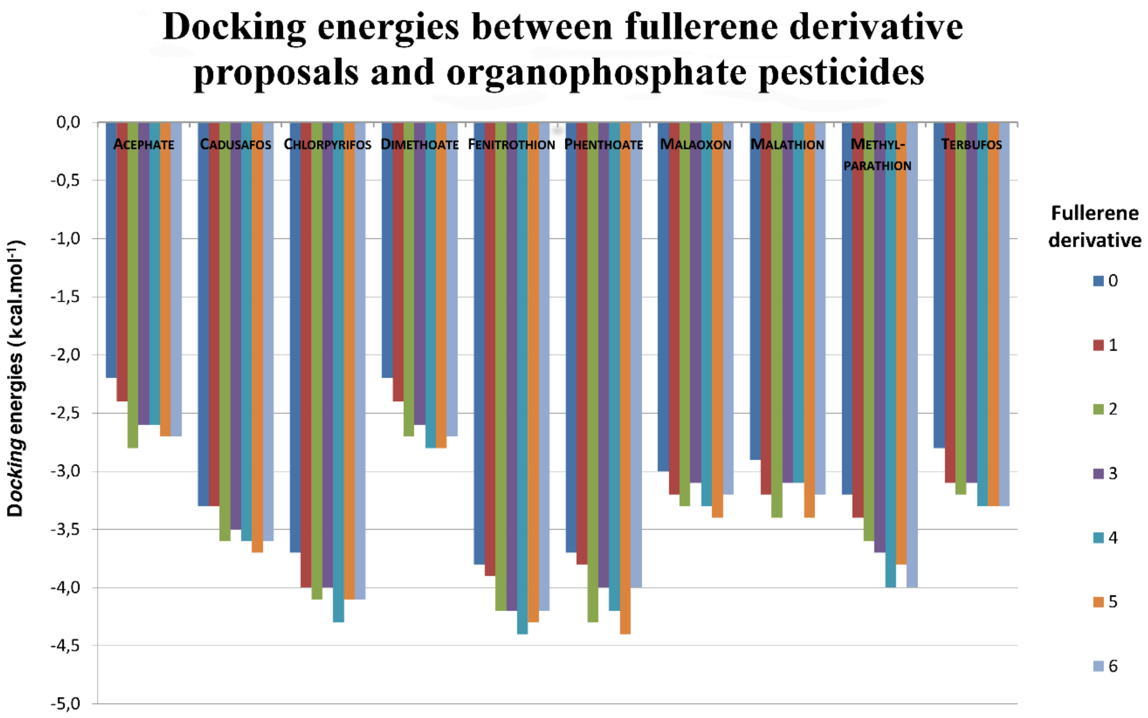

Figure 1. Docking energies between fullerene derivative proposals and organophosphates.

The lowest values of docking energy were for proposals 2, 4 and 5. It was adopted -4.0 kcal.mol^{-1} as a reference limit for favorable dockings. Among the Ops the chlorpyrifos, fenitrothion, phenthoate and methyl-parathion had the best results. Images of the docking interactions were generated and are available attached.

It was observed that semiempirical methods failed to describe the double bond between sulfur and phosphorous from malathion and the resonance at the end of the methyl-parathion chain, due to a potential barrier in both cases.

The electronic structural properties data of the complexes 'proposal-pesticides Ops' were obtained using the semiempirical PM7 method, as well as done for the individual molecules. A table with the values is available attached.

Some properties had abrupt behavior change from proposal 0-2 to 3-6, such as heat of formation, dipole moment, HOMO energy and chemical potential. Others had a gradual transition, such as total energy, LUMO energy and chemical hardness.

The heat of formation (ΔH_f) was positive for all complexes and it was observed that proposals 3 to 6 had a reduction in the average values , indicating a lower energy demand for complex formation. Regarding pesticides, malathion and malaoxon had the lowest overall mean values.

On the total energy or energy of Gibbs (G), the values ranged from -9901 eV (acephate-proposal0) to -14120 eV (malaoxon-proposals 5 and 6), with emphasis on malathion and malaoxon values, especially for that with full triad proposals.

There was a considerable change in the value of complexes dipole, especially for proposal 4 (0.94247 D to 16.41164 D), compared to the dipole value of the fullerene derivative sole (27.82601 D). It means that the derivative 4 may function as a precipitating agent of pesticides in water.

The bandgap parameter presented lower values for proposal 3, followed by proposals 5 and 6, which suggests more reactivity. On Ops the results were well distributed, with lower values for terbufos, malation and chlorpyrifos, followed by cadusafos and malaoxon.

Regarding the chemical hardness (η), proposals 3 and 4 were highlighted with the lowest values. It suggests they are the most reactive or polarizable proposals among those tested.

To describe the reactivity parameters, the Koopmans theorem was used, which describes the ionization potential (IP) and the electronic affinity (EA) as εHOMO and εLUMO, respectively, with negative signal [6]. The increase of IP for the fullerene derivatives was: proposal 0>1>2>4>3>6>5. Considering that the complete catalytic triad occurs from proposal 4 onwards, then the order of molecules with reactivity predicted as the biological would be 4>6>5. High values of IP and EA indicate characteristic of electron acceptor (electrophilic), so they can be efficient in adsorption and/or dissociation of pollutant molecules, such as Ops.

The best docking result was between fenitrothion and proposal 4 with an energy of -4.4 kcal/mol and an inter atomic distance between phosphorous of pesticide and oxygen of hydroxyl group of fullerene derivative of 3.4 Å. The docking process have, as one of the parameters of good fit analysis, the distance between the oxygen of the fullerene serine and the phosphorus atom of the pesticide, since this is the central interaction in the biological systems reactions. The O_{Ser}-P_{Ops} distances were estimated with PyMOL software and the best one is shown on figure 2.

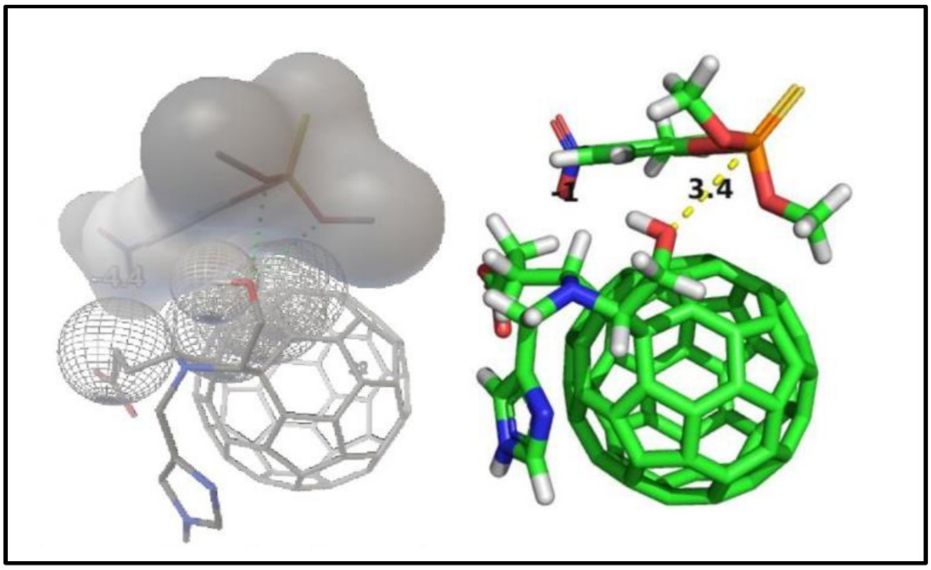

Figure 2. Docking between proposal 4 and fenitrothion.

The obtained distance oscillations varied between a favorable fit, which was assumed as 3.0 Å to 4.0 Å on average, or the connection with the opposite side of the Op. Intermediate values were not obtained. Considering the number of values above 4.0 Å, proposals 1, 2 and 4 had the best overall average of O_{Ser}-P_{OP} distances and the general order in this parameter was: proposals 1>2=4>5>0>3=6.

Ki

Docking energy and Ki are directly proportional. As a way of correlate the theoretical to experimental data, for validation of the investigation method, the theoretical Ki was estimated from the docking values and the results were grouped and changed into a graph, Figure 3.

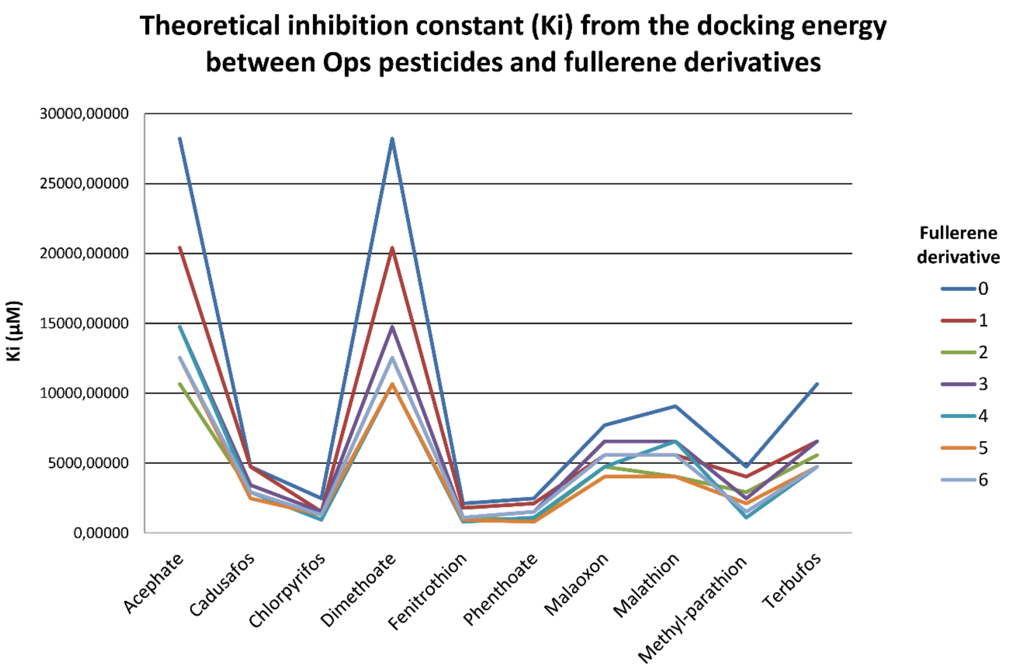

Figure 3. Theoretical inhibition constant (Ki) from the docking energy between Ops pesticides and fullerene derivatives.

Considering Ki as a toxicity indicator, according to the results the most dangerous among Ops studied were fenitrothion, chlorpyrifos, phenthoate and methyl-parathion. The behavior of derivatives proposals followed a general pattern for each Op, as figure 3 shows.

3. Material and Methods

The research was done in steps to obtain structural and electronic properties of Ops, fullerene derivatives proposals and its complexes, as well as docking energies and inhibition constant (Ki) estimation.

The choice of fullerenes (C_{60}), discovered by Kroto [7], as nanocomposite support was the starting point of the experimental design. The next step was obtain the properties that allow Ops adsorption hence fullerenes with aromatic valences substitutes by groups based on the side chain of AChE's catalytic triad composed by serine (Ser), glutamate (Glu) and histidine (His). The proposals were designed according to figure 4.

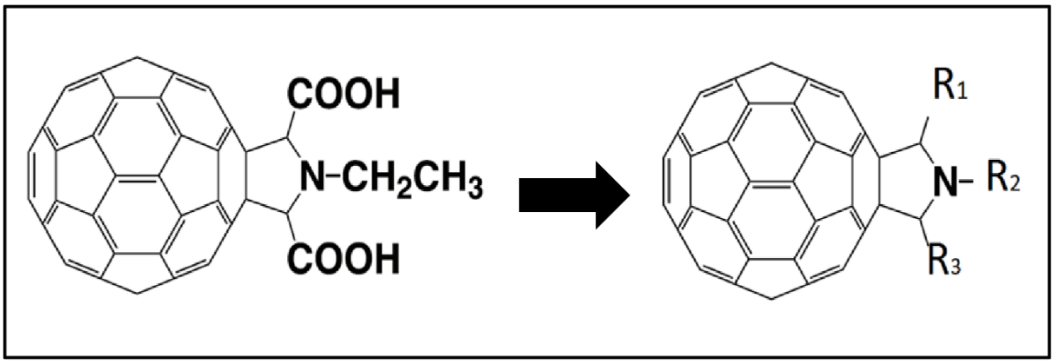

Figure 4. Structure of the fullerene derivatives developed in this research.

The structure proposed by Shoji *et. al*. [8], on the left side, had the side chains changed into R_1, R_2 and R_3, that were replaced by said amino acids side chains analogue structures, in different positions following the organization:

Proposal 0: R_1=R_2= R_3=H (control)

Proposal 1: R_1=R_2=H; R_3=Ser

Proposal 2: R_1= His; R_2=Ser; R_3=H

Proposal 3: R_1= Glu; R_2=Ser; R_3=H

Proposal 4: R_1=Ser; R_2=His; R_3=Glu

Proposal 5: R_1=His; R_2=Ser; R_3=Glu

Proposal 6: R_1=Ser; R_2=Glu; R_3=His

All amino acids were used in the L-form (levorotatory). The final images of molecules were generated by the PyMOL software and they are available on figure 5.

It is yet important to cite and justify that this type of modification at fullerene derivatives is also reported in literature by our research group in a recent work [9] as a proposal to favoring the interaction between these derivatives and pesticides since are based on amino acids of acetylcholinesterase's active site.

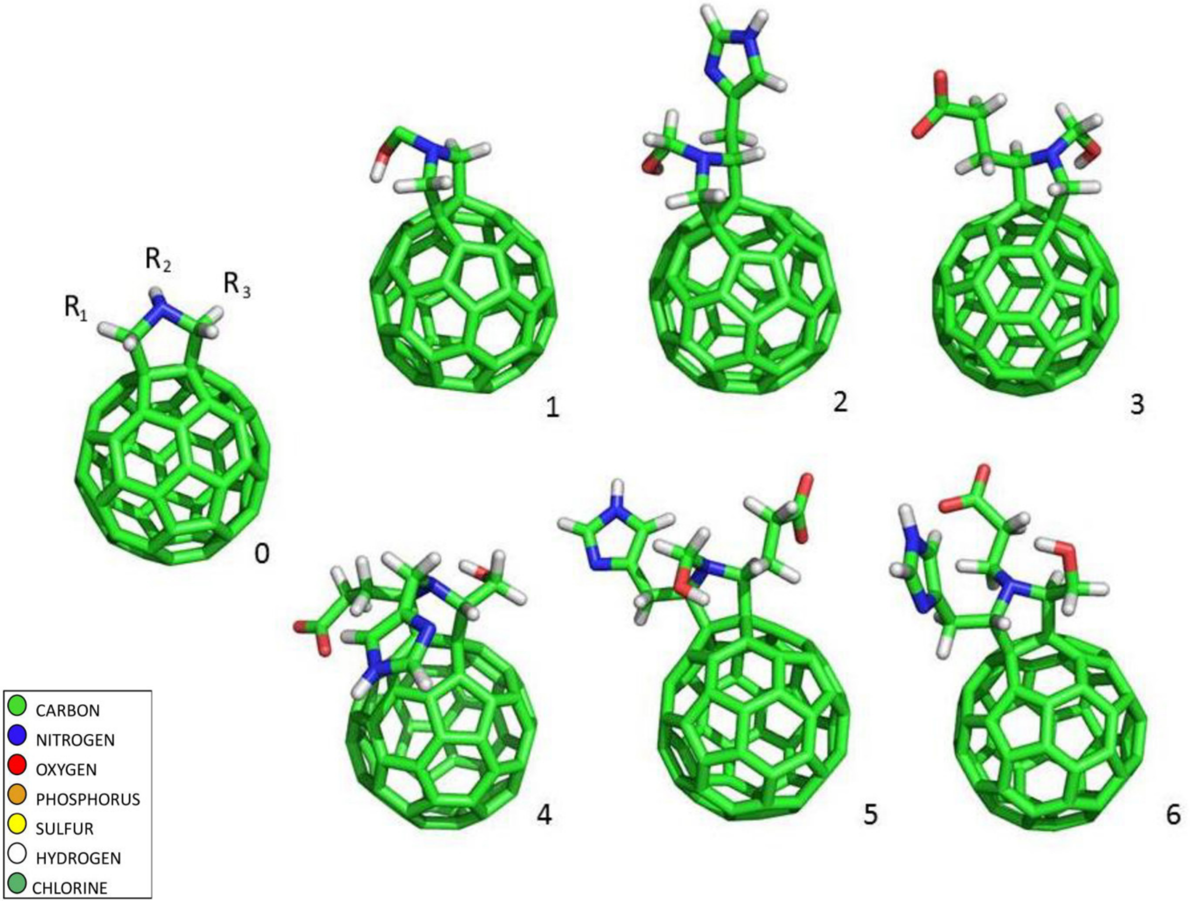

Figure 5. Fullerene derivatives proposals.

As a target, pesticides were chosen due to high consumption in Brazil and the difficulty of detecting poisonings in the field. They are shown on figure 6.

The drawings of proposals and Ops were made with GHEMICAL [10] software. The files were optimized with the force field TRIPOS 5.2 [11] and were made conformational random analyzes. Proposals containing the amino acid glutamate were calculated as deprotonated. Then the structures were optimized using the semiempirical PM7 Hamiltonian, as implemented in the MOPAC package [12], and the calculations were performed considering the vacuum. It was estimated pH 7.0 because many of the pesticides are used diluted in water.

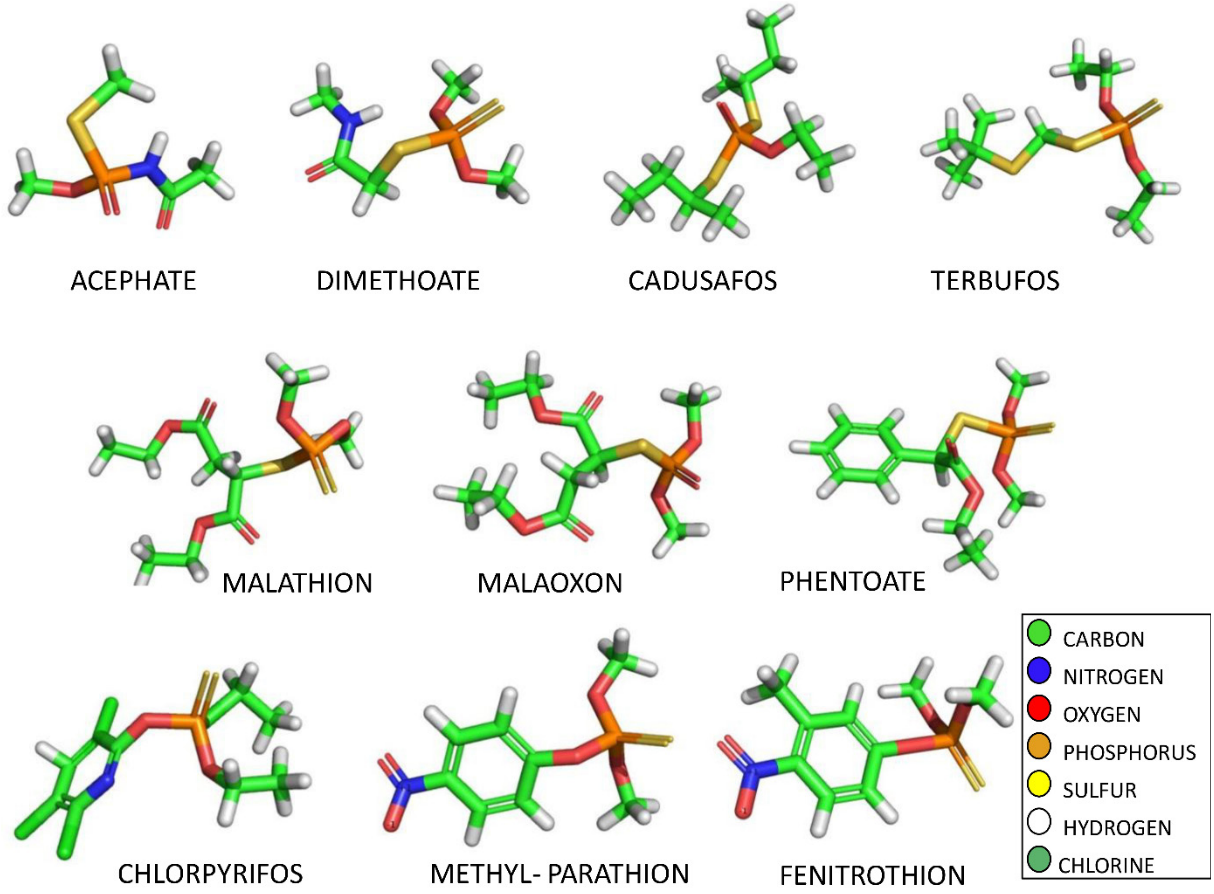

Figure 6. Organophosphate pesticides selected.

The conversion of files was made by Babel program [13], to enable the calculation by MOPAC. Both the proposed molecules and Ops, individually, underwent semiempirical optimizations using the PM7 method. The electronic structural properties of proposals and organophosphates were calculated. The heat of formation, total energy, dipole, ƐHOMO and ƐLUMO were extracted. The data of bandgap (E_{bg}), chemical potential (μ) and chemical hardness (η) were calculated from the data obtained.

Then the charges were checked using ACPYPE software [14], by the AM1-BCC method. The subsequent calculations were molecular dockings. In order to perform it was necessary to convert file to '.pdb' format with Gmolden program [15] and check the charges again, then convert by the AutoDock Tools program [16], as well as check the degrees of freedom of binders.

The grids were designed considering a whole molecular area of receptor and ligand. The parameters and dimensions were: receptor= (name_OP).pdbqt; 3D coordinates of the grid center: center_x=0,902; center_y= 3.352; center_z=0.634; Grid size: x_ size=18; size_y=18; size_z=18; Spacing=1,000; CPU=4; num_modes=10.

To analyze the complexe structures generated by the docking were used VMD [17], PyMOL [18] and AutoDock Tools softwares. After the design and optimization steps, the three-dimensional coordinates of proposals and Ops were simultaneously opened with the AutoDock Vina program, to calculate the interaction energy between them. After the dockings runs the lowest energy was verified through Vinascrengettop software [19]. The files were converted by Babel to obtain the electronic structural properties of the complexes.

From the docking energy values, experimental LD_{50} of pesticides were estimated. The values were compared with theoretical data, from Hamadache *et al*.'s article [20].

4. Conclusions

In the present work, we have used semiempirical methods to study 6 fullerene derivative proposals and 10 Ops pesticides, to search the best derivative proposal to adsorb and capture the Ops. Based on the docking energies, the most favorable connection were to fenitrothion and fentoato and, among the proposals, to number 4. The adsorption energy was favorable or exothermic for the majority. The proposal 4 had the best results and among Ops, malation followed by malaoxon were highlighted. Due to theoretical Ki, chlorpyrifos, fenitrothion, phentoate and methyl-parathion had results that indicate higher toxicity, and precisely these Ops had the best docking fits. Then, the results indicate that the proposal of fullerene derivative number 4 was the best for the Ops capture and the fenitrothion had the best performance among the pesticides studied, followed by malation, malaoxon, fentoato and methyl-parathion. The present results show that molecular modeling, including conformational analysis, calculation of properties as stereo-electronic parameters and molecular docking studies, is a promising tool in the sustainable alternatives development of environmental nanotechnology.

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