Theoretical Characterization of Three 2,2-Diphenyl-1,3,2-oxazaborolidin-5-ones: Molecules with Fungicide Activities

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Abstract: In this study, a theoretical characterization for three 2,2-diphenyl-1,3,2-oxazaborolidin-5-ones was performed using Density Functional Theory. The analyzed molecules have antifungal activity, making them of particular interest.

Keywords: Oxazaborolidinones; DFT; B3LYP

1. Introduction

Apoptosis is an important cell death process that is commonly inhibited in cancerous cells [1]. In a different, but sometimes related health threat, fungal infections are emergent diseases with high rates of morbility and mortality in immune-compromised patients. Species of Candida and Aspergillus, as well as Cryptococcus neoformans are among the more frequent infection-causing fungi. Since they
have very low virulence factors, a reduced immune response is the main predisposing factor for acquiring these infections [2].

In the fields of both apoptosis and fungal infections, much interest is currently focused on boron-containing molecules, since many compounds with boron-nitrogen bonds have shown insecticidal, antineoplastic, herbicidal, fungicidal, and antibacterial activities [3-6]. In this class of nitrogen-boron coordinated compounds, there is a group that required special attention, the 2,2-diphenyl-1,3,2-oxazaborolidin-5-ones that are obtained from diphenyl borinic acid and an α-amino acid. Recently, we addressed a new method for the production of twelve of these 2,2-dialkyl or 2,2-diphenyl-1,3,2-oxazaborolidin-5-ones [7]. During the course of this investigation, we discovered that the compounds possess cytotoxic activity against two tumor cell lines, one from colon cancer and one from leukemia [1]. In addition, three of these compounds (1-3) have remarkable antifungal activity, Figure 1 and Table 1.

Based on our preliminary findings, and because of the lack of theoretical data for the title compounds 1-3, we conducted a theoretical characterization of the target compounds. We were also interested in pursuing computational methods for molecules of special interest [8-10].

**Figure 1.** Structure of 2,2-diphenyl-1,3,2-oxazaborolidin-5-ones

![Structure of 2,2-diphenyl-1,3,2-oxazaborolidin-5-ones](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>R= α-amino acid residue</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Gly: H</td>
</tr>
<tr>
<td>2</td>
<td>His:</td>
</tr>
<tr>
<td>3</td>
<td>Thr:</td>
</tr>
</tbody>
</table>

**Table 1.** Antifungal activity of 2,2-diphenyl-1,3,2-oxazaborolidin-5-ones, 1-3.

<table>
<thead>
<tr>
<th>Compound*</th>
<th><em>Aspergillus niger</em> 16409</th>
<th><em>Cryptococcus neoformans</em></th>
<th><em>C. albicans</em> 5609</th>
<th><em>C. parapsilosis</em> 2019</th>
<th><em>C. krusei</em> 6258</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
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<td>3</td>
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</tr>
</tbody>
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*Others α-amino acid derivatives presented no activity
Computational Methodology:

The modeling of the studied systems was done using the PC program Spartan 02 [11]. Two of the molecules (2 and 3) have a substituent that shows a sp$^3$ bond with C$_4$ of the heterocyclic moiety, while 1 is unsubstituted. First, a conformational analysis for 2 and 3 was performed in order to establish the most stable coordinates, using MMFF94s as molecular mechanics [12], implemented in the Spartan 02 program. Next, the molecules (1-3) were optimized using B3LYP/6-311++G(d,p) [13,14], as the level of density functional theory in the Gaussian 03 program [15]. Convergence criteria were set at an energy change of less than 1 x 10$^{-6}$ Hartree and a gradient of less than 3 x 10$^{-4}$ atomics units (a.u.). Vibrational frequencies were calculated on geometry-optimized structures using an analytical Hessian program, and the character of the ground states was confirmed by not imaginary frequencies calculations, performed at the same level.

2. Results and Analysis

The three molecules of interest were modeled considering a closed structure. After their optimization, however, they showed an open structure related to the coordinated H$_2$N---B, which is consistent with similar molecules. According to the geometrical parameters, it appears that the bond length between B$_2$→N$_3$ atoms is short when an amino acid residue is present in position C$_4$. Specifically, for these molecules, bond lengths were 1 (1.705 Å), 2 (1.667 Å) and 3 (1.682), distances that are consistent with values indicated in the literature (1.638-1.759 Å) [16-20]. The dihedral angles did not show significant differences around these atoms, and the bond angles (107°) around the boron atom were approximately tetrahedral. The bond angle between C$_6$-B$_2$-C$_{12}$ atoms was generally more open (117.9°) because of electronic repulsion between the two phenyl groups that causes the bond angle between O$_1$-B$_2$-N$_3$ atoms to be more closed, at 97.9°. The bond angles of C$_6$-B$_2$-C$_{12}$ and O$_1$-B$_2$-N$_3$ atoms obtained with B3LYP/6-311++G(d,p) were similar to experimental data presented in the literature by HÖpfl et al.[21], at 114.5° and 99.4°, respectively. According to HÖpfl et al.[22], the large distances observed for the C-O atoms of these systems are in agreement with covalent interactions between boron and oxygen atoms.

Our theoretical calculations, evaluated by the scheme of Natural Populations Analysis (NPA), indicated that the boron atom, B$_2$, was very polarized, with an average value of 0.873 e$^-$, whereas the oxygen atom, O$_1$, showed an average value of -0.684 e$^-$, and the nitrogen atom, N$_3$, had a value of -0.758 e$^-$. In addition, for the C$_4$ substituted compounds (2-3), the nitrogen atom, N$_3$, presented a more negative value. The boron atom became less positive, a feature assigned to an electronic gain coming from the oxygen atom O$_1$. At the same time, the carbon atoms C$_4$ and C$_5$ displayed a charge decrease. For C$_5$, the decrease in charge can be explained by the increased polarization of the O$_5$ atom. The hydrogen atom H$_3’$ of molecule 2 exhibited a greater electronic deficiency because of intramolecular interaction with the nitrogen atom of the amino acid residue ring that is located at a distance of 1.997 Å. In molecule 3, this interaction was between hydrogen atom H$_3$ and the oxygen atom of the amino acid residue, and had a distance of 1.128 Å.

According to the Lowest Unoccupied Molecular Orbital (LUMO) contour plots determined for each compound, only molecule 1 had a great electronic deficiency. In addition, for evaluated molecules 1-3, the corresponding Highest Occupied Molecular Orbitals (HOMO) contour plots were
mainly distributed around the π bonds of the phenyl groups. Additionally, mapping the electrostatic potential displayed a greater electronic deficiency for molecule 1, while in 2 and 3, because of intramolecular interactions, this effect was diminished. Finally, the thermodynamic properties of 1-3 molecules in Figure 1, were calculated at the B3LYP/6-311++G(d,p) level of theory. A recent literature search found no experimental data on these properties.

3. Conclusions

In the current study, the distance between $B_2\rightarrow N_3$ atoms of the presented 2,2-diphenyl-1,3,2-oxazaborolidin-5-ones was demonstrated to be modified by the amino acid residue on $C_4$. This residue also modifies the charges of the heterocyclic atoms. The intramolecular interactions changed several molecular properties, including the charge of hydrogen atoms, $H_3/H_3'$, and the LUMO contours.

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References and Notes


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