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Theoretical calculation and structural studies for a new nitrogen derivative from nor-lapachol

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HIGHLIGHTS

- Synthesis of a new derivative of nor-lapachol.
- X-ray crystallography of N-methyl-amine-nor-lapachol.
- Theoretical calculations about the orbitals through DFT method.
- Analysis of molecular electrostatic potential maps front the Hirschfeld surfaces.

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ABSTRACT

Nor-lapachol is a semi-synthetic naphthoquinone obtained by oxidative degradation from natural lapachol. This compound and its derivatives have been investigated for its interesting biological properties. Several naphthoquinone derivatives have been synthesized and characterized using different physicochemical and computational techniques, as such DFT, MM, spectroscopy and X-ray crystallography. Here, the structure of 2-methylamine-3-(2-methyl-1-propenyl-1-yl)-1,4-naphthoquinone was determined by X-ray crystallography and the geometry was optimized using B3LYP functional along with the 6-31G(d) basis set, which was also used in all calculations. The obtained results were compared with the structure determined experimentally, and both structures showed high similarity. Besides, some molecular properties of this compound were also calculated by using DFT as well as Hirschfeld surface.

1. Introduction

Nor-lapachol **1** [4-Hydroxy-3-(3-methylprop-2-enyl)naphthalene-1,2-dione] is a semi-synthetic naphthoquinone obtained from lapachol **2** by oxidative Hooker degradation [1] and the naphthoquinones have been found in fungi, bacteria and animals [2]. This group of compounds exhibits a wide range of biological activities such as antitumor, antibiotic, antimalarial, trypanocidal and leishmanicidal, belong others [3]. Lapachol is isolated from heartwood of the tropical tree *Tabenia* sp (Bignoniaceae), a plant widely distributed across the Brazilian Amazon, typically co-existing within a given region or forest a plant found [4]. Many of the biological activities of lapachol and its analogues are related with production of reactive oxygen species by redox cycling or intercalation between DNA base pairs and their electronic and redox properties [5,6]. The plant from where lapachol was originally found shows ancient ethnopharmacological uses by indigenous from Brazil, Argentina, Bolivia, Colombia, among others. They are used against diseases like malaria, fevers, syphilis, cancer, malaria, trypanosomiasis, microbial infections and disorders of stomach disorders [7].

A major focus of the pharmacological use of lapachol **2** and its derivatives is related to the control of tropical diseases [1,8–10]. Among these derivatives is nor-lapachol that is a semi-synthetic derivative of natural lapachol **2** obtained by the Hooker oxidative degradation (Scheme 1) [11]. In the search for molluscicides with potential in the focal control of parasitary diseases in endemic countries, especially schistosomiasis (a disease caused by *Schistosoma mansoni*) new nitrogen derivatives from nor-lapachol **1** were

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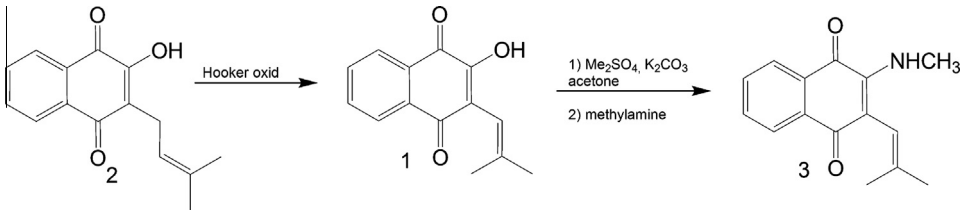

Scheme 1. Synthesis of 2-methylamine-nor-lapachol derivative **3.**

synthesized by Barbosa and collaborators, which are the lowest homologues of the lapachol **2** derivatives reported previously and showed to exhibit molluscicidal activity against *Biomphalaria glabrata* [1,9]. These derivatives showed low to medium LC_{50} values, similar to those reported previously for the homologous series of nitrogen derivatives of lapachol. Heterocyclic quinones containing nitrogen atoms are also known to exhibit excellent antitumor and other biological activities [12]. Many derivates from lapachol have been synthesized and characterized by X-ray [5,13–15]. In general, these structures share a planar naphthoquinonic ring which some modifications are directly related to their biological activity [13,16].

There are many studies in the literature aiming to elucidate and understand the structural and electronic properties of quinones. For example, Vessecchiet et al. have performed an experimental and computational study with the aim to understand the influence of alkyl side chains on the gas-phase reactivity of 1,4-naphthoquinone derivatives. In this work, the authors employed electrospray ionization tandem mass spectrometry and quantum chemical calculations (B3LYP/6-31+G(d,p)). One of the main results obtained in this work indicated that the effect related to the intramolecular hydrogen bond on the stability of each conformer can be explained based on the AIM (quantum theory of atoms-in-molecules) and NBO (natural bond orbital) analyses [17]. An interesting article presented by Sala et al. has shown an overview on different structural modifications of natural and synthetic quinones that have been subjected to trypanocidal studies. In this review, the authors have presented the mechanism of action and structure–activity relationships of the quinone derivatives, as well as theoretical calculations that discuss the relationship between stereo-electronic properties and the trypanocidal activity [18]. Another study has performed the preparation of 2-(4-X-phenylene)amine-1,4-naphthoquinones using $MgCl_2$ and p-toluenesulfonic acid as catalysts. The authors studied the effect of H^+ and Mg^{2+} as catalysts from DFT calculations (B3LYP/6-31G(d) level). The main results indicated that the ferrocenyl and methoxy groups have similar electron donor properties in a 2-(4-methoxy)amine-1,4-naphthoquinone [19].

In the present work, we synthesized the 2-methylamine derivative of nor-lapachol as a new entity from nor-lapachol. The geometric parameters of the compound were determined by X-ray diffraction and compared to theoretical calculations, which were carried out using the density functional theory (DFT), with the B3LYP functional and 6-31G(d) basis set. Finally, for a detailed understanding of the intermolecular interactions, an analysis of the molecular crystal structure was performed from Hirshfeld surface.

2. Experimental

2.1. Synthesis of the compound

Alkylation of nor-lapachol **1** with dimethyl sulphate in acetone and potassium carbonate, yielded the corresponding methoxy derivative, and immediately submitted to nucleophilic displacement with methylamine to furnish the novel compound **3** (Scheme 1). The crystallization process happened from the evaporation of the dichloromethane after having purified for column.

2.2. Crystal structure determination

A single crystal of red colour measuring 0.10 × 0.14 × 0.10 mm of **3** was selected for X-ray diffraction. Intensity data were collected at room temperature (T = 298 K) using a Kappa-CCD diffractometer monochromated by graphite of Enraf Nonius with Mo Kα radiation (λ = 0.71073 Å) and the Collect software as well as Scalepack for cell refinement [20]. A total of 19732 reflections were measured to a maximum 2θ of 27.88°. No significant absorption effect (μ = 0.083 mm^{-1}) was revealed, so no absorption correction was applied. The crystal structure was solved by direct methods and it was anisotropically refined with full matrix least square on F^2 using SHELX-97 program. H atoms attached to C atoms were located on stereochemical grounds and refined with fixed bond lengths and angles, each riding on a carrier atom, with an isotropic displacement parameter amounting 1.2 times the value of the equivalent isotropic displacement parameter of atoms to which they are bonded. The H atoms linked to nitrogen were located by Fourier synthesis difference and were set as isotropic. The final model showed a disagreement of 0.0537 [Rall = 0.0937] and GOF = 1.027. For data collection, it was used COLLECT, cell refinement HKL SCALEPACK, data reduction HKL DENZO and SCALEPACK [20]. The structure was solved using SHELXS-97 and refined using SHELXL-97 [21]. The structure representation was prepared using ORTEP-3 and the WinGX software was used to prepare material for publication [22].

2.3. Theoretical methods and computational techniques

The DFT method developed by Hohenberg and Kohn has proved to be a good tool for theoretical rationalization of structural and electronic properties of atoms, molecules and solids [23–25]. So, in this study, the B3LYP functional along with the 6-31G(d) basis set was used in all calculations, which are implemented in the Gaussian03 program [26–28]. Some electronic properties were also calculated for both structures (crystallographic and optimized ones), as well as the graphical representations of HOMO (the highest occupied molecular orbital) and LUMO (the lowest unoccupied molecular orbital), which are obtained from Gaussian03 program. The molecular Hirshfeld surface in the crystal structure was deduced through the theory of crystal partition into regions, with the objective of integrating the atomic electron density. The surface mapping was used to describe the intermolecular contacts, considering the region of the donor and receptor, depending on the radius of van der Waals (VdW) [10,29,30]. The molecular Hirshfeld surface was constructed on both *de*, *di* and the VdW radii of the atom, enables identification based on the electron distribution calculated as the sum of spherical atomic electron densities. The normalized contact distance (*dnorm*) is based on the regions of particular importance to intermolecular interactions. The combination of *de* and *di* in 2D fingerprint plot format [31–34] provided the intermolecular contacts in the crystal. The Hirshfeld