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Vibrational spectroscopy of lapachol, α- and β-lapachone: Theoretical and experimental elucidation of the Raman and infrared spectra

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ABSTRACT

Raman and infrared spectroscopy were applied for the vibrational characterization of lapachol and its pyran derivatives, α-lapachone and β-lapachone. Experimental spectra of solid state samples were acquired between 4000 and 100 cm^{-1} in Raman experiments, and between 4000 and 600 cm^{-1} (mid-infrared) and 600–100 cm^{-1} (far-infrared) with FTIR spectroscopy, respectively. Full structure optimization and theoretical vibrational wavenumbers were calculated at the B3LYP/6-31++G(d,p) level. Detailed assignments of vibrational modes in an experimental and theoretical spectra were based on potential energy distribution analyses, using Veda 4.1 software. Clear differentiation between the three compounds was verified in the region between 1725 and 1525 cm^{-1}, in which the ν(C=O) and ν(C=C) modes of the quinone moiety were assigned.

1. Introduction

Lapachol is a potent cytotoxic natural product extracted from the Ipe family trees (*Tabebuia* spp., Bignoniaceae), known for its anti-inflammatory, analgesic, antibiotic, and antineoplastic properties [1,2]. Under acidic condition, lapachol can undergo intramolecular cyclization and thus afford the formation of the isomers α- and β-lapachone [3,4]. The preparation of these and other pyranonaphthoquinone derivatives has been widely investigated due to their biological importance [5–14].

Besides α- and β-lapachone, the synthesis of pyranonaphthoquinones homologs, as well as the exploration of their action mechanism in biological systems, have been extensively investigated, aiming to develop new drugs with maximized biological activity. However, identification of relevant interaction modes for these molecules or reactive intermediates can be challenging due to their complexity. Nevertheless, vibrational spectroscopy has been recently used as a powerful tool in similar studies, using Raman spectroscopy for the identification of transient intermediates in mechanistic studies in solution and for the characterization of aggregation and interaction modes of these derivatives with macromolecules, such as cyclodextrins and DNA [15–19].

Refined and more robust applications of vibrational spectroscopy, as cited above, demand a clear identification and differentiation between the most important chemical groups of each compound and their correspondent wavenumbers and intensities in an experimental spectra. In this context, solid-state characterization of isolated naphthoquinones can be helpful as a first approach to determine the vibrational characterization of more complex systems containing similar pyranonaphthoquinone derivatives.

We present here the characterization and full assignment of the solid-state vibrational modes of lapachol and α- and β-lapachone using Raman and infrared spectroscopy in the region from 4000 to 100 cm^{-1}. Farfán et al. [20] have shortly reported an assignment of the vibrational modes of lapachol using infrared spectroscopy, but to the best of our knowledge, α- and β-lapachone were never fully characterized by vibrational spectroscopy. We aim to assign the most characteristic bands in the vibrational spectrum of each compound in order to help identification and/or quantification of these derivatives in more complex systems in future works. Density functional calculation at the B3LYP/6-31++G(d,p) level and potential energy distribution analyses were used for the assignment of the vibrational modes of these derivatives in the experimental spectra.

2. Experimental and computational methods

2.1. Experimental

2.1.1. Preparation of lapachol and of lapachones

Lapachol was obtained according to the literature by extraction from the heartwood of *Tabebuia* sp. (Tecoma), and it was purified by recrystallization in hexane [10]. The pyran derivatives,

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α-lapachone and β-lapachone, were obtained under acidic conditions according to the standard procedure from literature [21]. Characterizations of the three compounds by ^{1}H NMR spectra are in good agreement with the chemical shifts previously reported [4].

Lapachol (**1**): ^{1}H NMR (400MHZ) δ 1.61 (3H, s, CH_3), 1.72 (3H, s, CH_3), 3.24 (2H, d, CH_2), 5.14 (1H, m, CH), 7.60 (2H, m, CH), 8.02 (2H, m, CH).

α-lapachone (**2**): ^{1}H NMR (400MHZ) δ 1.36 (6H, s, CH_3), 1.75 (2H, t, CH_2), 2.55 (2H, t, CH_2), 7.60 (2H, m, CH), 8.01 (2H, m, CH).

β-lapachone (**3**): ^{1}H NMR (400MHZ) δ 1.40 (6H, s, CH_3), 1.78 (2H, s, CH_2), 2.50 (2H, t, CH_2), 7.43 (1H, td, CH), 7.57 43 (1H, td, CH), 7.74 43 (1H, td, CH), 7.98 43 (1H, td, CH).

2.1.2. Vibrational characterization

Solid-state FT-IR spectra of the samples were recorded in two distinct regions, i.e. mid- and far-infrared, by attenuated total reflection (ATR) using a Varian 660 and Nicolet iS50 spectrometer. The spectral resolution of the infrared spectrometers was 4 cm^{-1}. Infrared spectra were acquired with 256 scans in the mid-infrared and 128 scans in far-infrared region.

Solid-state FT-Raman spectra of the samples were recorded by a Bruker MultiRam spectrometer at room temperature with a germanium detector, maintained at liquid nitrogen temperature, using the 1064 nm Nd–YAG laser line with a resolution of 2 cm^{-1} in the region of 3600–70 cm^{-1} and 900 scans at a laser power of 100 mW. The samples were measured in the hemispheric bore of an aluminum sample holder.

2.2. Computational methods

Full geometry optimization of lapachol, α-lapachone and β-lapachone, as well as the theoretical vibrational spectra for the minimum energy geometries were obtained using Gaussian09 software [22] at B3LYP/6-31 + + G(d,p) level [23–26]. No imaginary wavenumber was obtained for any geometry employed in the simulation of the vibrational spectra, confirming that structure at minimum energy on the potential energy surface.

Both gas-phase and implicit solvation calculation using water as solvent were compared (see Figs. S1-S9). A theoretical polar environment simulated by means of the implicit solvation method IEFPCM [27,28] resulted in a better correlation with the experimental intensities of the solid-state spectra and the theoretical activities obtained for Raman spectra, especially in the region between 1800 and 1300 cm^{-1}. Furthermore, significant differences between frequencies, calculated in the gas-phase and using the implicit solvent, were not observed for the three systems. Based on this fact, we used the results from the calculations including the solvent effects for the band assignment of the experimental spectra. The vibrational modes for the optimized structures were characterized by the potential energy distribution analyses using the Veda 4.1 software [29].

3. Results and discussion

3.1. Structures

Crystallographic [30–32] and optimized geometric parameters obtained at B3LYP/6-31 + + G(d,p) level for lapachol (isomer **1a** and **1b**), α-lapachone (**2**) and β-lapachone (**3**) structures are listed in the Supplementary material (Tables S1–S4). All optimized structures are in good agreement with the crystallographic parameters.

The crystal packing of lapachol (crystallographic database code: JUBFOB) shows only one hydrogen bond, which was observed as a three-centred interaction formed by the hydrogen of the hydroxyl group (O14-H25, see insert in Table S1 and S2), the neighboring carbonyl group (C10-O11) and the analogous carbonyl group in a second molecule of lapachol, as reported by Larsen and Andersen [30]. The crystal packing of the pyran derivatives α- and β-lapachone (crystallographic database codes: 621207 and gz3007, respectively [31,32]) also presents C—H···O=C intermolecular interactions. Distinguishable units of α-lapachone in the crystallographic packing present interactions between the carbonyl group O11-C10 (see insert in Table S3) and the alicyclic or aromatic hydrogen atoms, while only alicyclic hydrogen atoms interact with the carbonyl group O12-C7. The crystallographic packing of β-lapachone also shows distinguishable units of this compound and presents interactions between O12-C9 (see insert in Table S4) and alicyclic or aromatic hydrogen atoms, but the carbonyl group O12-C10 shows interactions with both alicyclic and aromatic hydrogens. It is worth noting that the carbonyl group O11-C10 of α-lapachone and O12-C9 of β-lapachone interact differently in each unit of the crystallographic packing (with alicyclic or aromatic hydrogens) and more than one experimental band may be observed for the stretching mode of these groups, as will be commented in Subsection 3.2.2.

Due to the alicyclic moiety in lapachol, several rotamers may be optimized, from which two conformers, **1a** and **1b** (Fig. 1), present low relative energy. These two rotamers are almost isoergonic, with **1a** having a Gibbs free energy of 0.20 kcal mol^{-1} larger than for the rotamer **1b**. In both cases, the intramolecular hydrogen bond between O14-H25···O11-C10 is conserved. The first conformer (**1a**, Fig. 1) is the one directly optimized from the

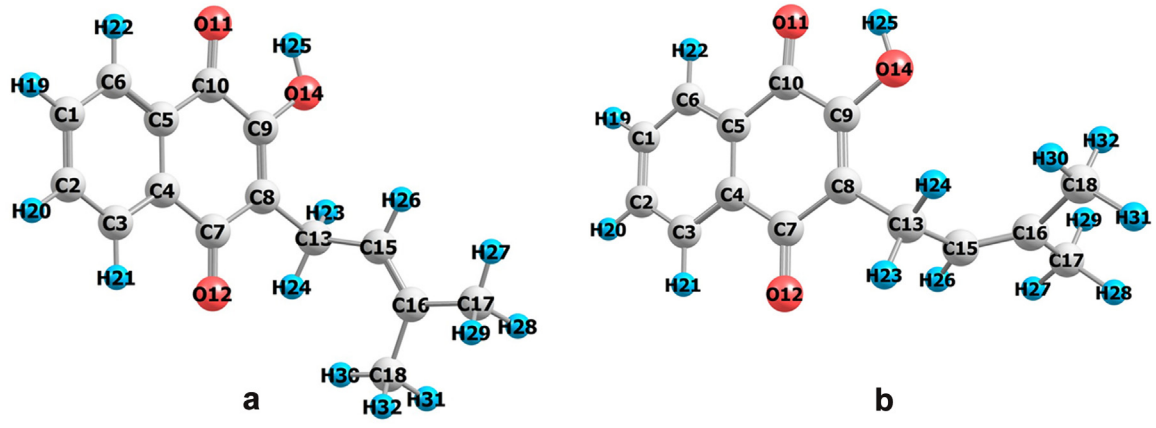

Fig. 1. Optimized structures of conformers **1a** and **1b** of lapachol.