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The four stacking modes of experimental and predicted Lapachol polymorphs.

N. Di Benedetto1, Brad C. Ayers2, Mario A. Macías3, Grame P. Day2, Miguel A. Martínez-Cabrera4, L. Suescun1

Cryssmat-Lab/DETEMA, Facultad de Química, Universidad de la República, Casilla 1157, Montevideo, Uruguay,

School of Chemistry, University of Southampton, Southampton, SO17 1BJ, United Kingdom,

Departamento de Química, Facultad de Ciencias, Universidad de los Andes, Carrera 1 # 18A – 12, Bogotá, Colombia,

Facultad de Ciencias Exactas y Naturales, Universidad de Asunción, Asunción, Paraguay.

leopoldo@fq.edu.uy

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Lapachol (2-hydroxy-3-(3-methyl-2-butenyl)-1,4-naphthoquinone) is a pigment extracted from the bark of *Handroanthus heptaphyllus* (Vell.) Mattos commonly known as pink trumpet tree or lapacho. The group of 1,4-naphthoquinones and its derivatives has always attracted a lot of attention since these compounds exhibit a wide range of biological and pharmacological effects. In particular, lapachol has demonstrated properties as an antitumor, anticarcinoma, antiviral, bactericidal, fungicidal and antimalarial agent, among others. Two lapachol polymorphs were described by Larsen et al. (1992) [1] with triclinic $P\bar{1}$ (LAPA I: a=5.960(1), b=9.569(2), c=10.679(2) Å, α=96.82(2), β=98.32(2) and γ=90.32(2) ˚) and monoclinic $P2_1/c$ (LAPA II: a=6.035(1), b=9.427(2), c=20.918(5) Å and β=98.27(2) ˚) crystal structures at 105K.

During the course of an investigation of lapachol complexes we accidentally found a new polymorph, also monoclinic $P2_1/c$ (LAPA III: a= 9.5943(19), b= 6.0173(10), c= 21.566(2) Å, α= 90, β=96.815(2), γ= 90 ˚) with the unit cell closely related to that of LAPA I and LAPA II. The three structures show identical lapachol dimeric layers (formed by centrosymmetric lapachol dimers) that define the constant a~6.0, b~9.6 Å and g≈90 ˚ unit cell parameters, with exact overlap of lapachol conformations among crystal structures. These layers stack through van der Waals interactions in three different ways defining the three observed crystal structures. In LAPA I consecutive layers are just related by translation along c. In LAPA II and LAPA III consecutive layers are related by a 2_1 screw axis along a and b axes respectively.

The rigid behaviour of lapachol molecule in the three experimental crystal structures led us to examine the energy landscape of lapachol crystals, in order to test if the new lapachol polymorph could have been predicted and whether other molecular conformations are able to produce low energy crystal structures. The structure prediction algorithm [2] found the three observed crystal structures among the four lowest energy predicted structure, and additionally a fourth crystal structure with similar energy to that of LAPA III showing the same dimeric layers of lapachol with consecutive layers related by a 2_1 axis along the normal to the invariant a-b plane (LAPA IV, monoclinic $P2_1/n$: a=9.078, b=21.611, c=6.350 Å, α= 90, β=89.7, γ= 90˚).

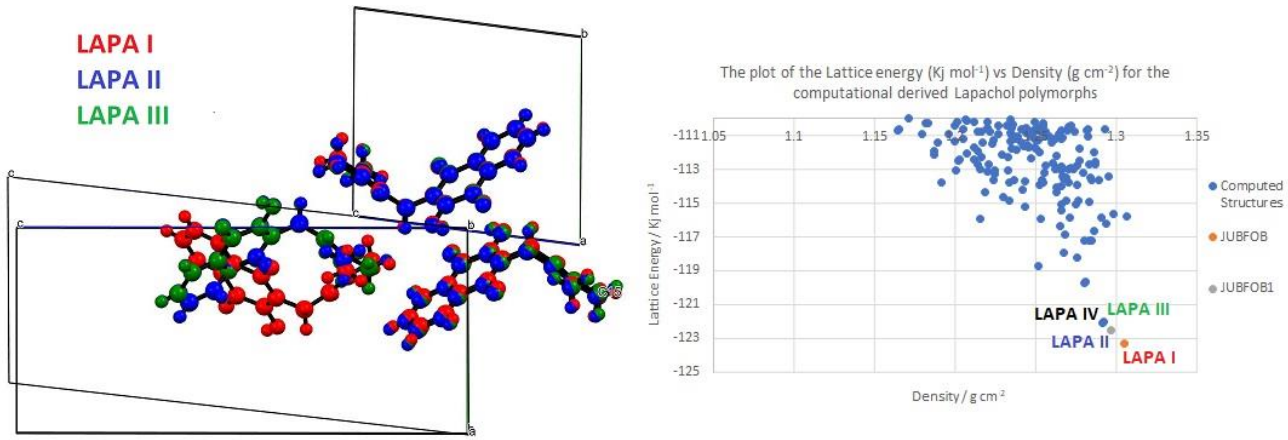

Figure 1. Left: Overlay of experimental lapachol crystal structures & unit cells. Molecules of one layer fit perfectly while the next layer shows a change in orientation in II and III. Right: Plot of lattice energy vs density for predicted crystal structures.

We will present the structural analysis of the four lapachol polymorphs emphasizing on the similarities and difference and inform of the results of the on-going search of the missing polymorph in the lab.

[1] Larsen, I.K., Andersen, L.A. & Pedersen, B.F. (1992). *Acta Cryst.* C**48**, 2009-2013.

[2] Case, D. H., Campbell, J. E., Bygrave, P. J. & Day, G.P. (2016) *J. Chem. Theory Comput.* 12(2), 910-924.