

# Fascinating Polymorphism in Lapachol Powders

N. Méndez, L. Suescun

<sup>1</sup>*Cryssmat-Lab/DETEMA, Facultad de Química, Universidad de la República. Av. Gral. Flores 2124, Montevideo 11400, Uruguay*

*leopoldo@fq.edu.uy*

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 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,  $\alpha=96.82(2)$ ,  $\beta=98.32(2)$ ,  $\gamma=90.32(2)$  °) and monoclinic  $P2_1/c$  (LAPA II:  $a=6.035(1)$ ,  $b=9.427(2)$ ,  $c=20.918(5)$  Å,  $\alpha=90$ ,  $\beta=98.27(2)$ ,  $\gamma=90$ °) crystal structures at 105K obtained by slow evaporation in different solvents.

During the course of an investigation of lapachol complexes with transition metals 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,  $\alpha=90$ ,  $\beta=96.815(2)$ ,  $\gamma=90$ °) [2] with the unit cell closely related to that of LAPA I and LAPA II. This new polymorph would form in a third solvent. The three structures show identical lapachol dimeric layers (formed by H-bonded centrosymmetric lapachol dimers) that define the constant  $a\approx 6.0$ ,  $b\approx 9.6$  Å and  $\gamma\approx 90$ ° 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 doubling the  $c$  axis.

Lapachol crystals show plate morphology due to the layered nature of the crystal structures. Grinding the crystals to obtain powders for conventional X-ray powder diffraction analysis using Bragg-Brentano geometry always yield highly oriented samples and resulting powder diffraction patterns were impossible to fit through the Rietveld method. In an attempt to obtain the different polymorphs of lapachol from the respective solvents directly in powder form by fast-cooling of hot saturated solutions, a still strongly lamellar powder is obtained that forms paper-like sheets of crystalline material when filtered in vacuum and dried. The impossibility to characterize these and the rest of the powders through conventional diffraction led us to collect transmission X-ray powder diffraction data at the ESRF (using the Momentum Transfer service) on the as-obtained powders and silica-gel-particle-added ground crystals of some of the polymorphs.

Surprisingly, the fast-crystallized powder of lapachol obtained from all the solvents (those used to obtain LAPA I, II and III and others) does not show the expected powder diffraction pattern, but a completely different one common to all of them, suggesting the fast-crystallization method provides a fourth polymorph for which the structure will be shown.

[1] Larsen, I.K., Andersen, L.A. & Pedersen, B.F. (1992). *Acta Cryst.* **C48**, 2009-2013.

[2] Di Benedetto, N.; Ayers, B. C., Macías, M. A., Day, G. P. Martínez-Cabrera, M. A., Suescun, L. (2024) To be submitted to *Acta Cryst.* **B**.

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