Poster

The search for the 4th stable polymorph of Lapachol

N. Méndez[1], M.A. Martínez-Cabrera[2, 3], L. Suescun[1]

[1]Cryssmat-Lab/DETEMA, Facultad de Química, Universidad de la República, Montevideo 11800, Uruguay, [2]Facultad de Ingeniería, Universidad Nacional de Asunción, Ayolas, Paraguay, [3]Centro de Investigaciones de Productos Naturales y de Síntesis Mariano Roque Alonso, Paraguay

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, α=96.82(2), β=98.32(2), γ=90.32(2) °) and monoclinic $P2_1/c$ (LAPA II: a=6.035(1), b=9.427(2), c=20.918(5) Å, α=90, β=98.27(2), γ=90°) 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 °) [2] with the unit cell closely related to that of LAPA I and LAPA II. The three structures show identical lapachol dimeric layers (formed by H-bonded centrosymmetric lapachol dimers) that define the constant a≈6.0, b≈9.6 Å and ≈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.

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 [3] 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 $P112_1/n$: a=6.350, b=9.079, c=21.611 Å, α=90, β=90, γ=89.7° given with unique axis c).

Since the three observed polymorphs of lapachol were obtained simply by using different solvents, an extensive search for different crystallization conditions is being developed, both looking for LAPA IV single crystals and powders using different solvents and conditions. The layered nature of the compounds is a very strong limitation towards the characterization of powder samples of lapachol. The possible existence of mixed stacking in powders obtained from different solvents at different precipitation speeds and temperatures is also being studied and the results will be discussed.

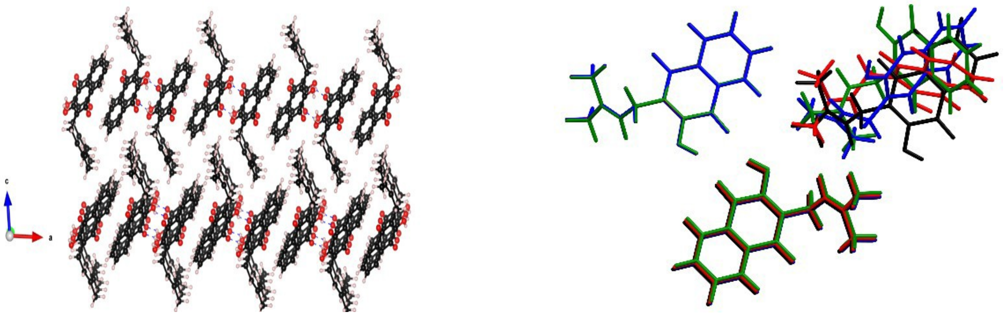

Figure 1. (left) Two layers of lapachol dimers in LAPA III. (right) Overlay between three nearby molecules of the four predicted lapachol polymorphs (fit of one molecule in the left for the four structures). LAPA I (black), II (green), III (blue) and IV (red).

[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**.

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

L.S. acknowledges PEDECIBA-Química (Uruguay) for its continuous support to perform fundamental crystal structure studies.