SUPPLEMENTARY INFORMATION

The Enantiopreference in the Solid State Probed in Lamivudine Crystal Forms with Mandelic Acid

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On acid hydrogen position assignment and protonation pattern in the cocrystal of salt phase: The COOH hydrogen position assignment of S-mandelic acid was concluded on the basis of the fact that the residual electronic density peak in the difference Fourier map was near the carboxyl oxygen of the S-enantiomer than that of R-enantiomer which is paired with lamivudine. We have then attributed this peak to the acid hydrogen. First, its coordinates were refined freely, but short O–H bond length and short C–O–H angle were outputted. Therefore its coordinates were fixed following a riding model on the parent oxygen. At last, other proof of S-mandelic acid neutral character resides on the fact that NH_2 moiety did not receive proton in the structure: amine N–C bond length is 1.316(9) Å against 1.322(9) Å of the imine one, *i. e.*, there is a resonance structure encopassing the amine NH_2 nitrogen, C4 and the imine NH nitrogen. This precludes protonation on the NH_2 nitrogen due to engagement of its lone electron pair in the resonant double bond. Similarly, imine NH nitrogen has also a sp^2-character as observed by its trigonal planar geometry [C2–N3–C4 angle measures 123.7(6)°] and therefore it was not protonated twice. This is reinforced looking at the in-plane pairing with R-mandelate through the NH moiety. Likewise, there are not evidences of protonation of hydroxyl oxygens: there is neither residual electron density peak near to them nor hydrogen bonding compatibility with protonated OH_2 moieties. Hydroxyl oxygens of both lamivudine and mandelic acid units are saturated in terms of hydrogen bonds, as can be viewed in Figs. 2 and 4c. Carbonyl oxygen of lamivudine is also involved in intermolecular hydrogen bonding (Fig. 4c), which, together with the typical carbonyl bond length of 1.228(8) Å in lamivudine, does exclude any possibility of its protonation. In conclusion, one carboxyl moiety should be unionized in the structure to charge balance. We believe that the carboxyl bond lengths of S-mandelic acid together with these other experimental evidences tell well us its unionized COOH group and neutral character.

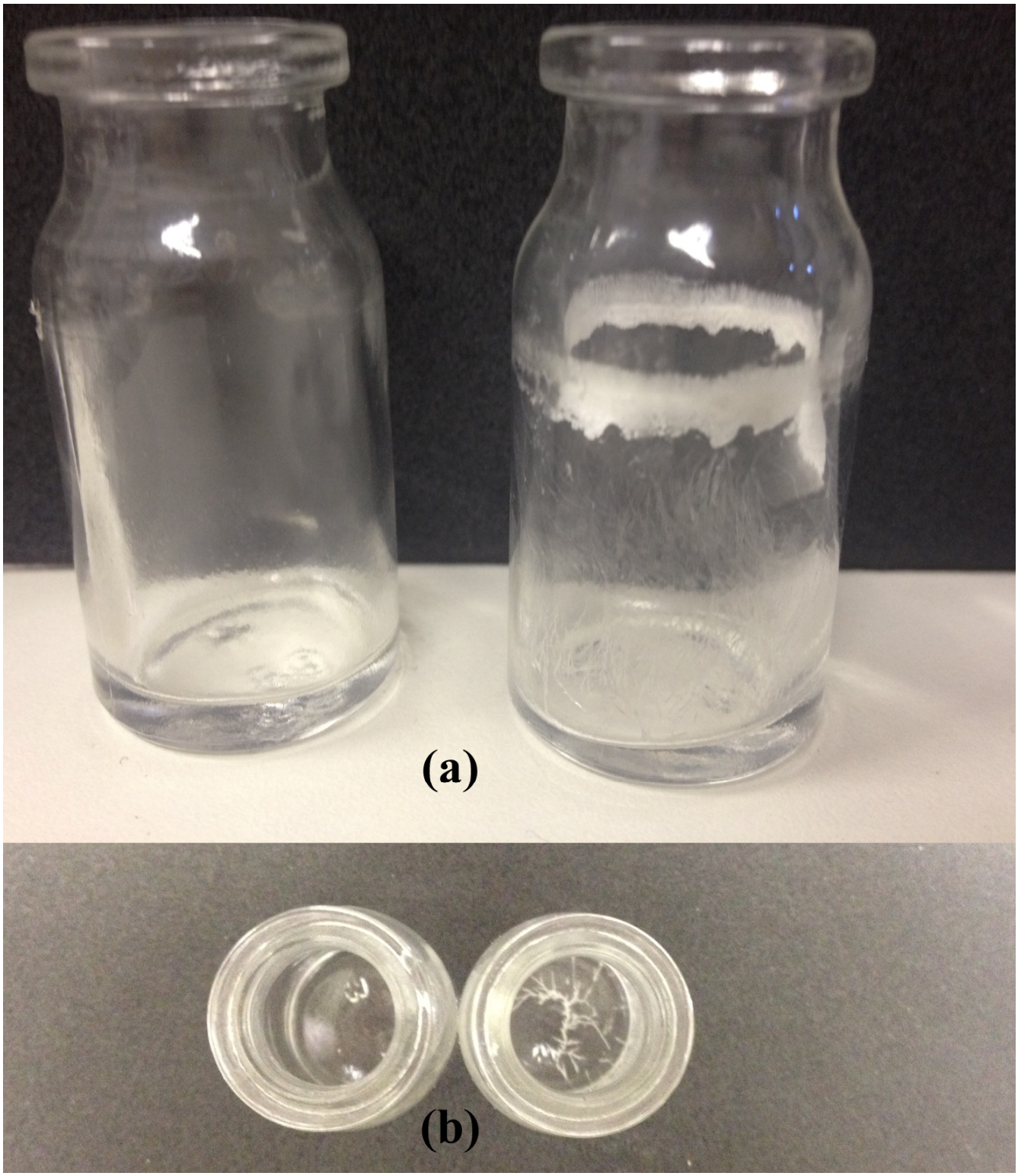

Figure S1 – a) Front and b) top views of glass crystallizers after complete solvent evaporation at 298 K from crystallization systems starting from lamivudine (10 mg, 0.04 mmol) and pure enantiomers of mandelic acid (6.5 mg, 0.04 mmol; left: S-enantiomer, right: R-enantiomer). Solvent: ethyl alcohol (2.5 mL) and water (2.5 mL).