

Solid-State Supramolecular Assembly of Salicylic Acid and 2-Pyridone, 3-Hydroxypyridine or 4-Pyridone

Stipe Lukin,¹ Tomislav Stolar,¹ Martina Tireli,¹ Dajana Barišić,¹ Marco di Michiel,² Krunoslav Užarević,¹ Ivan Halasz^{1,*}

¹ Division of Physical Chemistry, Ruđer Bošković Institute, Bijenička c. 54, HR-10000 Zagreb, Croatia

² ESRF - the European Synchrotron, 71 Avenue des Martyrs, 38000 Grenoble, France

* Corresponding author's e-mail address: ivan.halasz@irb.hr

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Abstract: Mechanochemical milling of equimolar mixtures of salicylic acid with three hydroxy derivatives of pyridine provided three new phases. With 2-hydroxypyridine, which is in fact present as 2-pyridone, a discrete cocrystal supramolecular assembly is formed. 3-hydroxypyridine and salicylic acid formed a salt and an extended network of hydrogen bonds while the product of the reaction of 4-hydroxypyridine (present as 4-pyridone) and salicylic acid remained structurally uncharacterized. All three hydroxypyridines retain the tautomeric form as in their respective pure phases upon cocrystal formation. Where possible, reaction profiles have been extracted from *in situ* monitoring via Rietveld refinement to show direct product formation which could be well described using the first-order reaction rate law.

Keywords: cocrystal, mechanochemistry, *in situ* monitoring, salicylic acid, hydroxypyridine.

INTRODUCTION

SUPRAMOLECULAR assembly in the solid state has been widely recognised for its benefits in comparison to equivalent solution procedures which are reflected in more efficient and selective reactions, stoichiometry control as well as in better atom- and energy-economy.^[1–6] Here, we have focused on the mechanochemical formation of supramolecular multicomponent solids, *i.e.* cocrystals,^[7–9] of salicylic acid (sal) and three hydroxypyridine derivatives: 2-pyridone (2hyp), 3-hydroxypyridine (3hyp) and 4-pyridone (4hyp). While solid 3-hydroxypyridine exists as such,^[10] 2-hydroxypyridine^[11–14] and 4-hydroxypyridine^[15] assume rather a pyridone tautomeric form in the solid state (Figure 1). Next or our interest in fundamental aspects of mechanochemical reactions where we have studied these reactions by *in situ* reaction monitoring using synchrotron powder X-ray diffraction.^[16–18] We were also interested if a change of

the tautomeric form of each of the hydroxypyridines would occur upon cocrystal (or salt) formation.

Milling of equimolar mixtures of sal with each of the hydroxypyridine derivatives provided new compounds. In the case of 2-pyridone, a cocrystal of sal and 2hyp (sal2hyp) is formed as confirmed by crystal structure determination

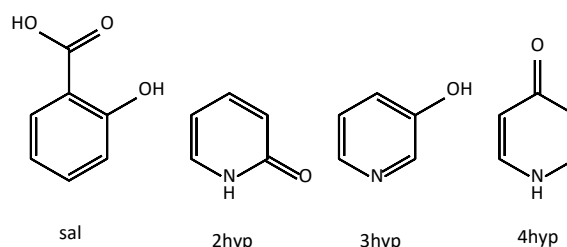


Figure 1. Molecular structures of salicylic acid and three hydroxypyridines. Preferred tautomeric forms are displayed.

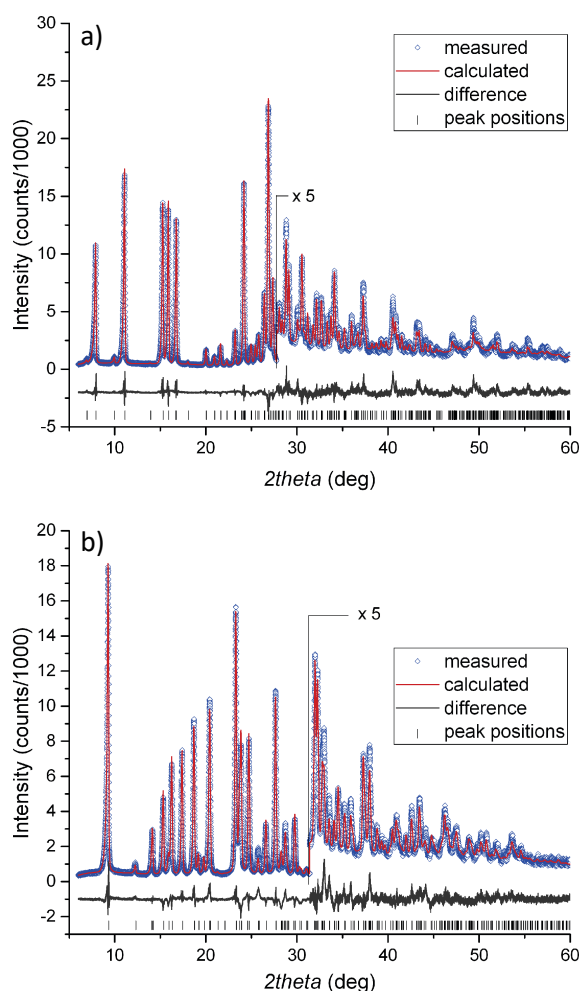


Figure 2. Rietveld plots for the structures of (a) sal2hyp and (b) sal3hyp solved from powder X-ray diffraction data ($\text{CuK}\alpha$, $\lambda = 1.54 \text{ \AA}$). The high-angle regions are enlarged to reveal more detail.

from laboratory powder X-ray diffraction data (Figure 2). The cocrystal is composed of discrete supramolecular assemblies of the dimer of 2hyp molecules, which retain the pyridone tautomeric form, with two sal molecules residing on each side of the 2hyp dimer forming hydrogen bonds towards the keto O atoms of 2hyp (Figure 3a).

Two polymorphs are known for the starting 2hyp. The orthorhombic polymorph forms an extended network of hydrogen bonds^[11–13] while in the monoclinic polymorph molecules of 2hyp form dimers.^[14] Our starting 2hyp belonged to the orthorhombic polymorph. Formation of sal2hyp, where 2hyp molecules form dimers, indicates a thorough rearrangement of crystal structures of both 2hyp and sal during mechanochemical milling. Having crystal structures of all the participating phases enabled Rietveld refinement of time-resolved powder diffraction patterns and extraction of reaction profiles.

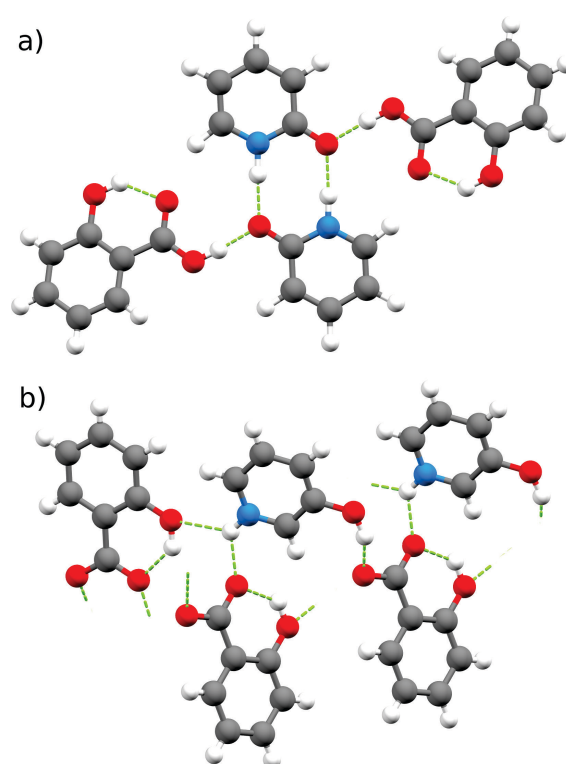


Figure 3. Supramolecular assembly of (a) sal and 2hyp into discrete hydrogen-bonded units and (b) sal and 3hyp into an extended network of hydrogen bonds. sal2hyp is a cocrystal while sal3hyp is a salt.

Reaction profile derived from *in situ* PXRD monitoring shows a direct formation of the sal2hyp product with kinetics conforming to a first-order reaction rate. However, a "break" in kinetic curve derived from PXRD data can be observed at *ca.* 12 min. The kinetic curve is thus better described by two separate first order reactions, one up to and one after 12 min milling (Figure S1). This disruption in kinetics needs not have an origin in the chemical behaviour of the reaction but may also be due to physical characteristics of the reaction mixture such as uneven mixing due to sticking of the reaction mixture to the walls of the milling jar. Also, sal is apparently consumed slightly faster than 2hyp which, if not caused by deviations from a uniform and homogeneous reaction mixture, indicates partial amorphisation of sal during milling.

Mechanochemical reaction of equimolar amounts of sal and 3hyp resulted in proton transfer from sal carboxylic group to the 3hyp nitrogen and thus yielded a salt, rather than a cocrystal. The crystal structure of sal3hyp was also solved from laboratory powder diffraction data revealing an extended three-dimensional network of hydrogen bonds (Figure 3b). *In situ* reaction monitoring revealed direct formation of sal3hyp, the kinetic profile of which adheres well to the first-order reaction rate (Figure S2).

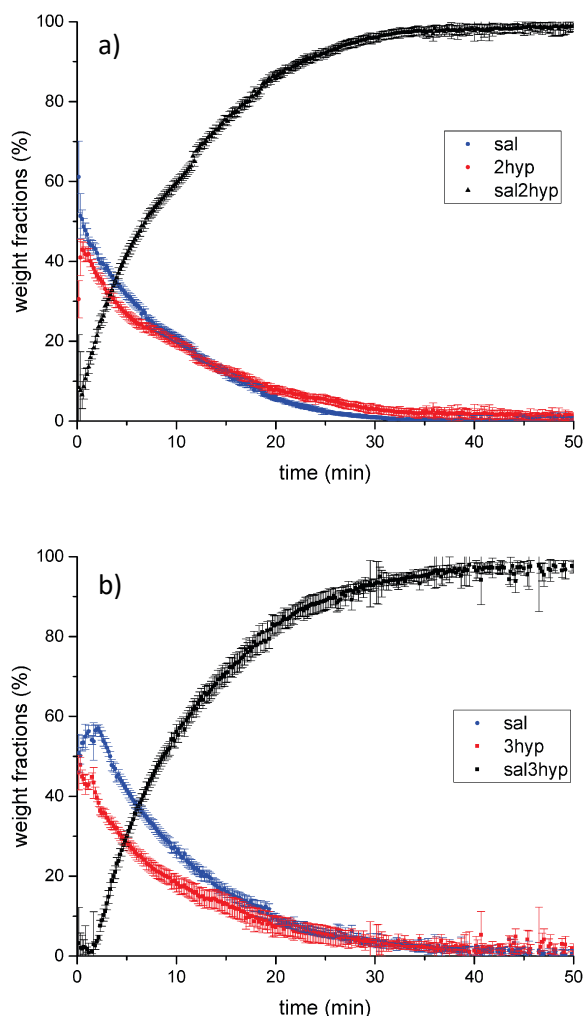


Figure 4. Reaction profiles as derived from PXRD monitoring of (a) sal2hyp formation and (b) sal3hyp formation. In (b) the reaction mixture is undergoing homogenisation in the first 2 min milling causing unexpected variations in weight fractions.

Reaction rate constants for both the consumption of reactants sal and 3hyp as well as the formation of the product sal3hyp are the same, within estimated standard deviations. The same reaction rates for all reaction participants indicates a highly crystalline reaction mixture throughout milling.

Reaction of sal and 4hyp resulted in the formation of a new phase after *ca.* 50 min milling, but here, PXRD showed an intermediate phase that formed soon into milling and persisted for *ca.* 20 min (Figure 5). As with sal2hyp and sal3hyp, we have attempted to solve the crystal structure of the final product, but were not successful. Additionally, despite the known crystal structures of two polymorphs of 4hyp,^[15] our starting 4hyp did not correspond to any of them and apparently, belongs

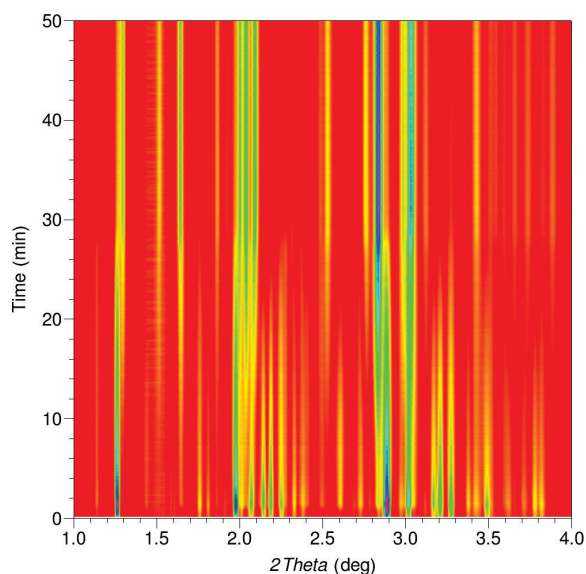


Figure 5. Time-resolved powder diffraction for milling of equimolar mixture of sal and 4hyp. Color code: red - low, violet - high. The intensities have been taken to the power of 1 / 1.4 to accentuate weaker reflections.

to a third polymorph. We have attempted to solve its crystal structure as well, but were also not successful. Similarly, the intermediate phase also remained structurally uncharacterised hindering Rietveld refinement of *in situ* collected PXRD patterns.

Infrared spectra of starting compounds and the product indicate that sal4hyp is a cocrystal and that 4hyp retained its pyridone tautomeric form in the cocrystal (Figures S5–S7). Also, while acid-base properties in solution can hardly be expected to be directly transferable to proton transfer reactions in the solid state,^[19] we note that the difference in solution-determined pK_a values between salicylic ($pK_a = 3.0$) acid and pK_a values for the conjugated acid of 4hyp ($pK_a = 3.1$) is only 0.1 which strongly suggests cocrystal formation. The difference in pK_a values for conjugated acids of the other two hydroxypyridines^[20] ($pK_a = 5.2$ for 2hyp and $pK_a = 4.8$ for 3hyp) and salicylic acid is around 2 and is not indicative for either cocrystal or salt formation.^[21]

CONCLUSION

We have described supramolecular assembly of salicylic acid and three derivatives of hydroxypyridine in the solid state under mechanochemical processing and studied the formation of the corresponding cocrystals or salts by using *in situ* reaction monitoring by powder X-ray diffraction. 2hyp and 4-hyp, which are in their pure phases present in the pyridone tautomeric form cocrystals with sal while 3-hyp and sal form a salt. Crystal structures of sal2hyp and

sal3hyp have been determined from powder diffraction data to reveal a discrete supramolecular assembly in the sal2hyp cocrystal and an extended network of hydrogen bonds in the sal3hyp salt. sal4hyp remained structurally uncharacterised but appears to be a cocrystal according to its infrared spectrum. Formation of sal2hyp and sal3hyp proceeds directly from reactants, is well described by the first-order reaction rate law, and the reactions are, on the 250 mg scale, complete within 50 minutes milling at 30 Hz. We are currently pursuing structural characterisation of 4hyp and its cocrystal with sal.

EXPERIMENTAL

Milling reactions were performed in polymethylmetacrylate (PMMA) vessels using an IST500 (InSolido Technologies) mixer mill operating at 30 Hz. Two stainless steel balls (each weighing 1.42 g) were used as the milling media. In each reaction, 1 mmol of sal and 1 mmol of the corresponding pyridone or hydroxypyridine were weighed in separate halves of the reaction vessel. In situ monitoring was performed at the new ESRF beamline ID15A at the European Synchrotron Radiation Facility (ESRF) in Grenoble, France analogously as was previously described for experiments at the old ID15B^[22] or the new ID31.^[23] Experimental hutch of ID15A was air-conditioned to 22 °C. X-ray radiation wavelength of 0.177 Å was selected using a multilayer monochromator, diffraction data were recorded on a Dectris Pilatus CdTe 2M detector positioned 1057 mm from the sample, radial integration of the raw diffraction images was performed using an inhouse script in MATLAB, exposure time for each pattern was 9.0 s and time separation between consecutive diffraction patterns was *ca.* 10 s.

Crystal structures of sal2hyp and sal3hyp were solved from laboratory powder diffraction data collected in the Bragg-Brentano geometry on a theta-theta Aeris Panalytical powder diffractometer. Indexing, Pawley refinement, structure solution by simulated annealing in direct space and rigid-body Rietveld refinement have been performed using the program Topas. The cif files, containing also the measured and calculated diffraction patterns, have been deposited with the Cambridge Crystallographic Data Center (CCDC) under the deposition numbers 1834809-1834810. These data can be obtained from the CCDC upon request.

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Supplementary Information. Supporting information to the paper is attached to the electronic version of the article at: <https://doi.org/10.5562/cca3339>.

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