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# The role of a liquid in “dry” co-grinding: a case study of the effect of water on mechanochemical synthesis in “L-serine — oxalic acid” system

Evgeniy A. Losev<sup>a,b</sup> and Elena V. Boldyreva<sup>a,b</sup>

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The results of the synthesis in “L-serine – oxalic acid – water” system were compared for co-grinding of powder samples with water added in four different ways: as crystal water to either or both of the reactants or as a drop of a liquid phase. The products formed on co-grinding were compared with each other, and with those that crystallise from solutions on slow evaporation at ambient conditions, on spray drying and on antisolvent crystallisation. Co-grinding of dry anhydrous reagents gave only trace amounts of the product phase (anhydrous 1:1 serinium oxalate), apparently due to the interaction with the trace amounts of water in the air. In the presence of crystal water or water added as a liquid phase the polymorphs of [L-serH]<sub>2</sub>[ox]•2H<sub>2</sub>O (as pure forms or in a mixture) were formed. Neat co-grinding of anhydrous oxalic acid with L-serine monohydrate or of anhydrous L-serine with oxalic acid dihydrate gave polymorph II (kinetic form). Co-grinding of L-serine monohydrate with oxalic acid dihydrate as well as liquid-assisted grinding with sufficient amount of liquid water added gave polymorph I (thermodynamic form) and polymorph 2 (with a very low transformation degree) if too little water was added. Seemingly, solid-state reaction proceeded in fact in the liquid phase at a contact between the solid particles, and did not depend on the crystal structures of initial components. The role of mechanical treatment in inducing the synthesis is merely bringing the reacting species into contact, improving their mixing, and facilitating the dehydration of crystal hydrates. The reaction could be observed also on storage of mixtures, *via* the intermediate aqueous solution formed at the contacts between particles, to give the same intermediate product as obtained by spray drying, whereas antisolvent crystallisation and slow evaporation gave the same polymorph as was eventually observed on LAG or on prolonged storage of a solid mixture.

## Introduction

Co-grinding of solid components is becoming increasingly popular as a method of organic synthesis alternative to the traditional synthesis in solution.<sup>1-3</sup> This technique does not require large amounts of solvents what is environmentally friendly, and is cheaper as compared with multi-stage solution synthesis. An extra advantage is that co-grinding often gives higher yields of desirable products<sup>4</sup> or the phases that cannot be obtained by any other techniques.<sup>5,6</sup> This approach is used, in particular, to prepare molecular co-crystals that find applications as pharmaceuticals, novel NLO materials, ferromagnetics, membranes, catalysts and absorbents.<sup>7-14</sup> Mechanical treatment of molecular solids is applied also to solve the enantiomeric resolution problem.<sup>15-19</sup>

A common approach to predict the outcome of the reaction in a solid mixture on grinding is to consider the complementarity of supramolecular synthones (functional groups). This concept dominates in modern crystal engineering of organic solids.<sup>20</sup> For example, the analysis of numerous molecular compounds showed that such functional groups as carboxyl, amide and hydroxyl groups typically interact with each another in co-crystals.<sup>21</sup> In addition to hydrogen bonds, typical intermolecular interactions important for the molecular crystals are halogen bonds, van der Waals

interactions and  $\pi$ - $\pi$  interactions.<sup>22,23</sup> Potentially, there exist many ways to connect molecular species *via* these interactions thus generating a rich variety of compounds.

Model calculations are also widespread for “virtual” screening of molecular co-crystals to predict the probability of co-crystal formation. Common approaches are to analyse and to compare the lattice energies of adducts and reactants<sup>24</sup>, to analyse inter- and intramolecular geometry<sup>25</sup>, to calculate the hydrogen bond propensity combined with a statistical analysis of the occurrence of hydrogen bonds in the relevant structures present in CSD<sup>26</sup>, to calculate the interaction site pairing energies<sup>27</sup>.

At the same time, to obtain a solid compound in a real experiment, it is not sufficient to select correctly the starting reactants. For the same reactants, the outcome of a crystallisation in solution depends strongly on the relative concentrations of reactants, on the order of adding them to solution, and on other details of the crystallisation procedure.<sup>28</sup> The outcome of a mechanochemical synthesis may strongly depend on grinding conditions such as the type of mechanical activator, mode of treatment, substance load, *etc.*<sup>29-32</sup>

One of the variable parameters that can have a pronounced effect on the outcome of co-grinding of solid powders is the presence of liquid in the system.<sup>33</sup> Adding even a drop of

Table 1. Numeration of mixtures depending on the choice of starting components for co-grinding experiments

Mixture №	Starting components*	Starting components (formulae)
1	L-serine (anhydrous) + oxalic acid (anhydrous)	$\text{NH}_3^+-\text{CH}_2(\text{OH})-\text{COO}^- + \text{H}_2\text{C}_2\text{O}_4 (\alpha\text{-form})$
2	L-serine monohydrate + oxalic acid (anhydrous)	$\text{NH}_3^+-\text{CH}_2(\text{OH})-\text{COO}^- \cdot \text{H}_2\text{O} + \text{H}_2\text{C}_2\text{O}_4 (\alpha\text{-form})$
3	L-serine (anhydrous) + oxalic acid dihydrate	$\text{NH}_3^+-\text{CH}_2(\text{OH})-\text{COO}^- + \text{H}_2\text{C}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$
4	L-serine monohydrate + oxalic acid dihydrate	$\text{NH}_3^+-\text{CH}_2(\text{OH})-\text{COO}^- \cdot \text{H}_2\text{O} + \text{H}_2\text{C}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$
5	L-serine (anhydrous) + oxalic acid (anhydrous) + water (drop)	$\text{NH}_3^+-\text{CH}_2(\text{OH})-\text{COO}^- + \text{H}_2\text{C}_2\text{O}_4 (\alpha\text{-form}) + \text{H}_2\text{O}$

\* For all experiments a molar ratio L-serine:oxalic acid was 2:1 in accordance with a stoichiometry of the final products<sup>35</sup>.

liquid to the solid mixture (liquid-assisted grinding) can have a drastic effect both on the products formed and on the very possibility of the chemical interaction.<sup>34-36</sup> The amount of liquid and its chemical composition were shown to be equally important.<sup>37</sup> The mechanism how a very small amount of liquid can influence a reaction in a bulky mixture remains unclear, though several models taking into account the solubility of components and relative rates of their dissolution, as well as the effect of added liquid on the rheology of mixtures, on the polarisation of components and on the possibility of creating hydrothermal conditions as a result of mechanical treatment have been proposed.<sup>32,38-40</sup> Attempts to understand the mechanism of some LAG processes were performed recently using *in situ* X-ray powder diffraction monitoring.<sup>41-43</sup>

A solvent can be not only added drop-wise as the liquid phase, but be present in molecular form, if the starting reactants are used as solvates. An interesting question is if the state in which the same solvent is introduced into the system has a significant effect on the outcome of the mechanochemical reactions. For example, it is well-documented that many reactions that proceed on grinding solid mixtures of crystal hydrates, cannot be induced on similar treatment of anhydrous forms, though mechanical treatment of hydrates alone does not result in dehydration. There seem to be only sporadic comparative studies of the result of grinding of solid mixtures with water added a) as a liquid phase, or b) as crystal water, all other chemical components, as well as the conditions of mechanical treatment being the same. For example, neat grinding of anhydrous citric acid and theophylline was shown to give an anhydrous co-crystal, whereas neat co-grinding of crystal hydrates or liquid-assisted co-grinding of anhydrous components with water added as a liquid phase was shown to give a co-crystal hydrate.<sup>9</sup> For caffeine the results were somewhat different. Neat grinding of anhydrous caffeine with either anhydrous citric acid or citric acid monohydrate did not result in any reaction at all. Liquid-assisted grinding of anhydrous caffeine with anhydrous citric acid, as well as neat grinding of caffeine hydrate with citric acid, citric acid monohydrate, or liquid assisted grinding of caffeine hydrate with anhydrous citric acid gave the same product, an anhydrous co-crystal.<sup>9</sup> Thus, in the two cases a hydrated reactant could either enable the formation of an anhydrous co-crystal (as in the case of caffeine), or steer the reaction towards the formation of a co-

crystal hydrate (as in case of theophylline). In another study<sup>44</sup> the outcomes of the neat and liquid-assisted co-grinding of different polymorphs and a dihydrate of carbamazepine with nicotinamide were compared. Though the presence of water and the crystal structure of the starting polymorph did influence the kinetics of the reaction, the product was essentially the same in all the cases, namely the anhydrous 1:1 co-crystal, form I.<sup>44</sup> Obviously, much more examples should be studied, to make any generalisations.

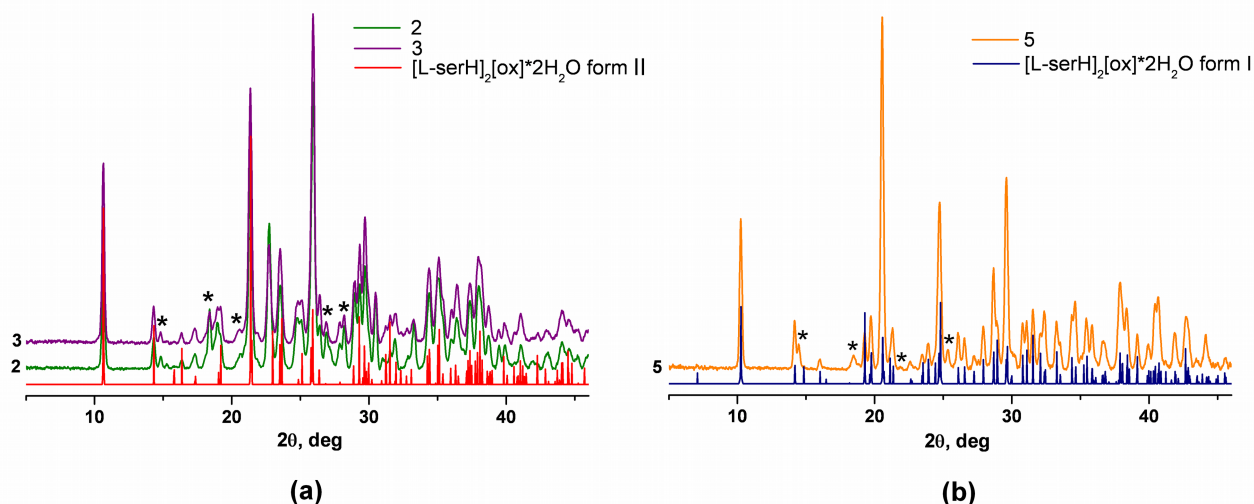
The aim of the present study was to carry out a systematic comparison of the result of co-grinding of the same chemical species with water added in different forms for one more system that could allow one to compare all possible combinations of solid hydrated, solid anhydrous and liquid phases, namely “L-serine - oxalic acid - water” (Table 1).

Previous research conducted in our group by N. Shikina and S. Arkhipov<sup>45-48</sup> has shown that several salts and salt hydrates of different stoichiometry, or of the same stoichiometry, but different crystal structure (polymorphs) can be formed in this system on slow crystallisation from solutions under different conditions and on co-grinding. Independently, another group has obtained various salts and salt hydrates in the “L-serine - oxalic acid - water” system by different techniques, including dry grinding, slurry and kneading techniques, and has followed their stability under different relative humidity conditions.<sup>35</sup> The list of L-serinium salts obtained in the research by the two groups included two forms of bis-L-serinium oxalate dihydrate ( $[\text{L-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$ ), L-serinium oxalate ( $[\text{L-serH}][\text{Hox}]$ ) and one unknown phase. Single crystal X-ray diffraction, XRPD and DSC were used to characterise the obtained products.<sup>35,45-48</sup>

## Experimental

### Materials

L-serine (Sigma-Aldrich, 99%) and oxalic acid dihydrate (Reachim, commercial grade) were used without preliminary purification. L-serinium monohydrate was obtained by recrystallisation of L-serine from water solution. Anhydrous oxalic acid ( $\alpha$ -form) was obtained from dihydrate either by crystallisation from 70 % (volume percent) solution of sulfuric acid or by heating up to 100 °C under vacuum. All substances were examined by means of X-ray powder



**Fig. 1** The powder diffraction patterns for the reaction products in the systems 2 and 3 (a) and 5 (for  $\eta=1$ ) (b).  $[\text{L-serH}]_2[\text{ox}]\cdot 2\text{H}_2\text{O}$  form II (a) and  $[\text{L-serH}]_2[\text{ox}]\cdot 2\text{H}_2\text{O}$  form I (b) were obtained as the main products (the calculated XRPD patterns shown red and blue respectively<sup>35</sup>). Small admixtures of initial reactants (or by products) are indicated by stars

diffraction.

### Mechanical treatment

Mechanical grinding was carried out in a vibrational ball mill Retsch Cryomill: total substance mass — 0.5–0.6 g; amount of balls — 2; mass of ball ~ 0.6 g; vibration frequency — 24 Hz. The treatment was performed in cyclic mode (3 cycles in 20 minutes with pauses for manual breaking of conglomerated particles). Cryogrinding was also performed in 3 cycles (20 minutes each with 2 periods of intermediate cooling for 5 minutes in between, during intermediate cooling the vibration frequency slows down to 5 Hz).

### Spray drying

Spray drying of stoichiometric aqueous solution of L-serine with oxalic acid (molar ratio 2:1 respectively) was carried out using a Mini Spray Dryer, B-290 (BÜCHI Labortechnik, Switzerland): aspirator rate  $35 \text{ m}^3 \text{ h}^{-1}$ , feed flow  $0.9 \text{ mL min}^{-1}$ , spray gas flow  $601 \text{ l h}^{-1}$ , inlet temperature was selected as 65, 80 and  $100^\circ\text{C}$  (in accordance with thermal stability of two forms of  $[\text{L-serH}]_2[\text{ox}]\cdot 2\text{H}_2\text{O}$ ), outlet temperature was 50, 58 and  $70^\circ\text{C}$ , respectively. An accuracy of heating control was  $\pm 2^\circ\text{C}$ . The volume of solution was about 12 mL, and the total amount of substance about 2.5 g.

### Antisolvent crystallisation

Acetone and ethanol (both chemically pure) were used to induce crystallisation of stoichiometric solutions of L-serine and oxalic acid (molar ratio 2:1). The volume of an antisolvent was about 2 times larger than that of the solution.

### X-ray powder diffraction

All samples were characterised by powder XRD analysis: Bruker GADDS diffractometer, Cu K $\alpha$  radiation ( $\lambda = 1.5418 \text{ \AA}$ ),  $2\theta$  ranging from  $5^\circ$  to  $46^\circ$  with operating potential of 40 kV and current of 40 mA. All data were obtained in reflection mode with a scanning time of 480 s per sample.

### IR-spectroscopy

The FTIR ATR spectra were recorded by using a DigiLab Excalibur 3100, Varian spectrometer equipped with a MIRacle ATR accessory in the range  $600\text{--}4000 \text{ cm}^{-1}$  with resolution  $2 \text{ cm}^{-1}$ .

### Sieving

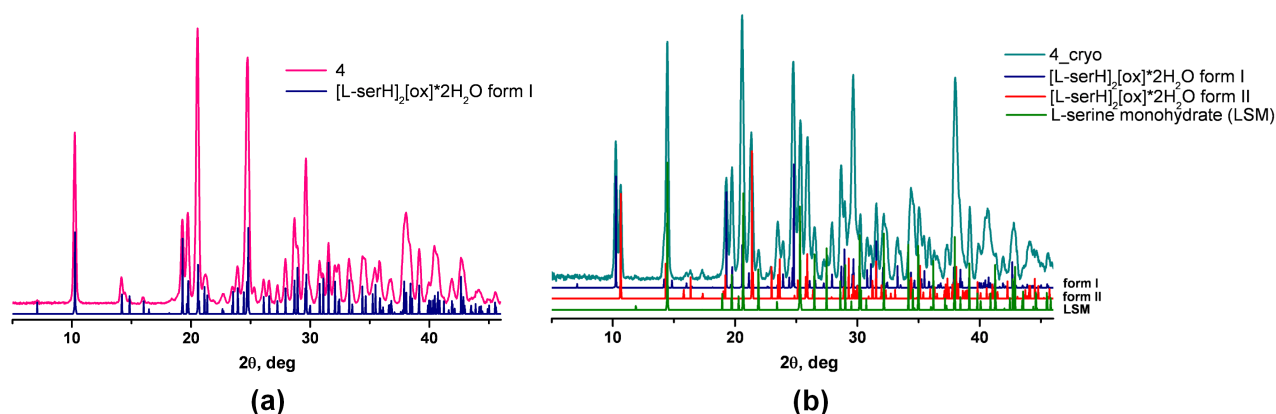
Powders for mechanical treatment were sieved by Retsch sieves with aperture size 200 and  $100 \mu\text{m}$ .

## Results and discussion

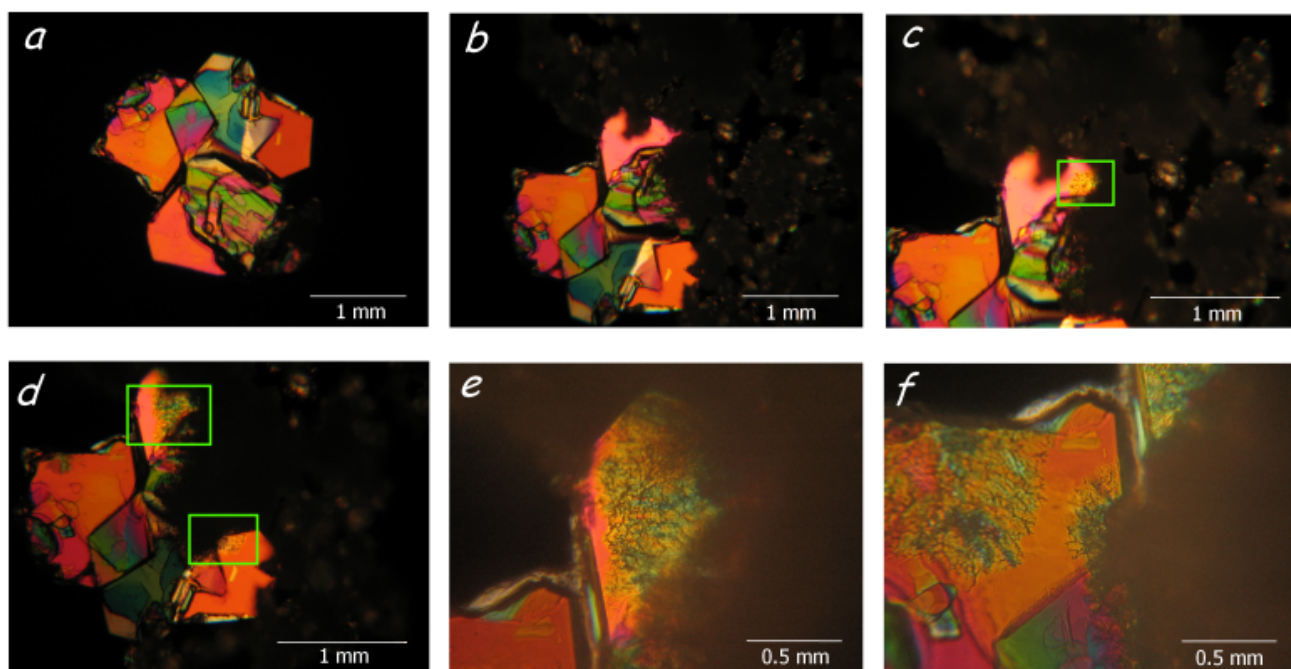
Five variants of combining oxalic acid, L-serine and water (either as molecules in crystal hydrates, or in a separate liquid phase) were studied (see their numeration in Table 1). The products formed on co-grinding were compared with each other, and with those that crystallise from solutions on slow evaporation at ambient conditions, on spray drying and on antisolvent crystallisation.

Practically no reaction occurred on co-grinding of the two anhydrous forms (system 1), only the traces of anhydrous 1:1 salt  $[\text{L-serH}][\text{Hox}]$  could be observed, apparently due to the interaction with the traces of water in the air. The 1:1 ratio in the product salt was observed both when the starting reactants were taken in 2:1 and 1:1 ratio. This is slightly different from the system “glycine - oxalic acid” in which no reaction at all could be observed on co-grinding of anhydrous components,





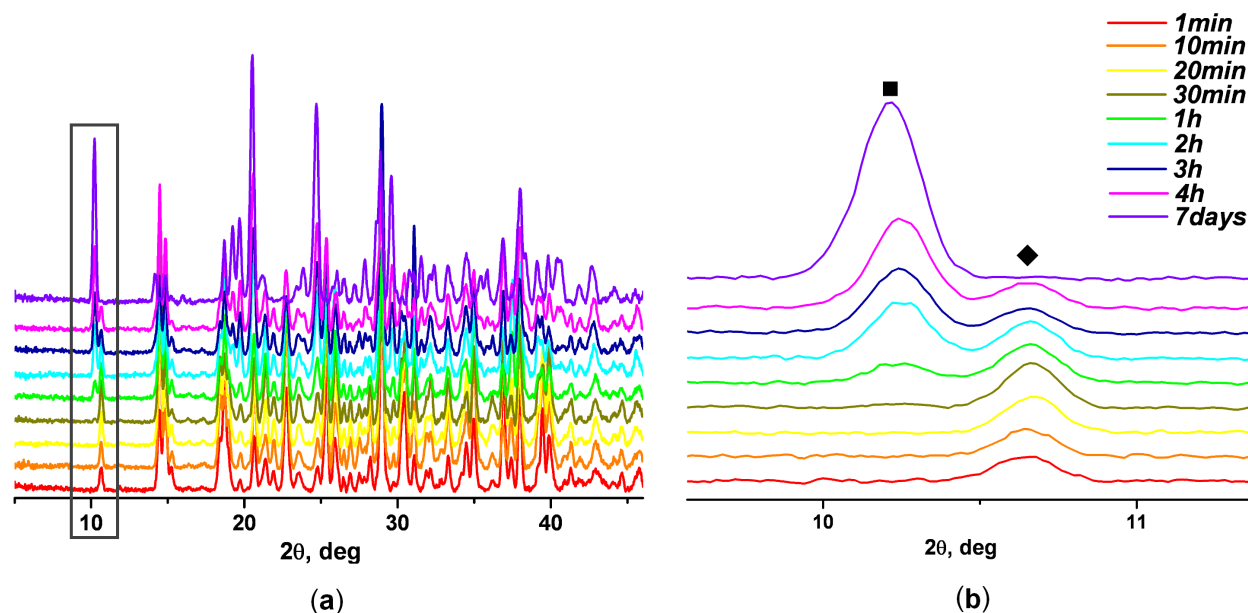
**Fig. 2** Comparison of two XRPD patterns after co-grinding in the same system (L-serine monohydrate + oxalic acid dihydrate (2:1)) at room temperature (a) and liquid nitrogen temperature (b). Quantitative yield of  $[L\text{-serH}]_2[\text{ox}]\cdot 2\text{H}_2\text{O}$  form I at RT experiment versus the mixture of  $[L\text{-serH}]_2[\text{ox}]\cdot 2\text{H}_2\text{O}$  form I and form II in the case of cryo-grinding



**Fig. 3** Dehydration of the crystals of L-serine monohydrate (LSM) brought into contact with the powder of oxalic acid dihydrate (OAD) at a selected site. a – Several intergrown crystals of LSM before contact with OAD; b – the powder of OAD brought in the contact with LSM (initial time moment); c – start of the dehydration (location highlighted by the frame); d – dehydration at two sites (the interface propagating through the crystal of LSM); e – end of the process; f – a view of another part of the crystal of LSM that had no contact with OAD and dehydrated later (to compare the dehydration patterns). The experiment was performed using a polarising microscope POLAM L-213M

probably because it was possible to provide slightly different conditions and exclude the presence of atmospheric water better.<sup>45,49</sup> A dihydrated 2:1 salt  $[L\text{-serH}]_2[\text{ox}]\cdot 2\text{H}_2\text{O}$ , form II, was obtained as a result of the mechanical treatment of systems 2 and 3. The powder diffraction patterns of the products in the systems 2 and 3 were identical, the outcome not depending on the choice of which component be taken as a crystal hydrate (Fig. 1a). For the system 4 almost complete transformation into the salt I ( $[L\text{-serH}]_2[\text{ox}]\cdot 2\text{H}_2\text{O}$ ) was observed with a slight admixture of L-serine monohydrate. (Fig. 2a). The amount of liquid phase injected into the system

5 was varied according to  $\eta$ -criterion:  $\eta=0.05$ , 0.1, 0.25 and 1 that corresponds to a LAG mode (the criterion was introduced by T. Friscic and takes into account amount of added liquid and total mass of solids:  $\eta=V(\text{liquid}, \mu\text{L})/m(\text{sample}, \text{mg})$ ).<sup>50</sup> Liquid-assisted grinding experiments with various amounts of injected water gave either form II of  $[L\text{-serH}]_2[\text{ox}]\cdot 2\text{H}_2\text{O}$ , or form I, depending on the quantity of liquid water. In the case of  $\eta=0.05$  the formation of  $[L\text{-serH}]_2[\text{ox}]\cdot 2\text{H}_2\text{O}$  form II was detected (in trace amount along with initial reactants) (see Fig. 1 in ESI). Increase of water added ( $\eta=0.1$ ) led to formation of the mixtures of  $[L\text{-serH}]_2[\text{ox}]\cdot 2\text{H}_2\text{O}$  polymorphs



**Fig. 4** XRPD patterns recorded at regular time intervals for the mixture of L-serine monohydrate and oxalic acid dihydrate (2:1) stored in a sealed vial (a). A gradual transformation from  $[\text{L-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$  form II (rhomb) to  $[\text{L-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$  form I (square) on storage manifests itself very clearly as a change in the relative intensity of selected reflections in the enlarged (10 – 11)  $2\theta$  region (b)

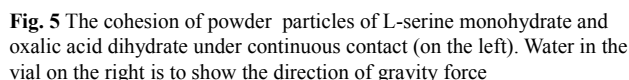
(see Fig. 1 in ESI). The LAG at  $\eta=0.25$  gave only  $[\text{L-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$  form I with significant amount of L-serine monohydrate (see Fig. 1 in ESI). Finally, almost complete transformation of initial components to  $[\text{L-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$  form I was obtained at  $\eta=1$  (Fig. 1b). Thus, interestingly, the amount of water in the system influences not the stoichiometry, but the crystal structure of the reaction product and the completeness of the transformation.

In order to separate the result of grinding from that of mere mixing the components, in another series of experiments the components were preliminary mechanically treated separately under the same conditions as the mixtures in the first series of experiments, after what mixed carefully manually (in the same molar ratio 2:1). Both L-serine and oxalic acid, as well as their hydrates, were stable under the chosen mode of mechanical treatment. None of the crystal hydrates dehydrated even partly on grinding. On storage at ambient conditions L-serine monohydrate is rather unstable and loses water easily on storage. Thus, for a single crystal the dehydration was observed already after 2 hours of storage at ambient conditions. For powder samples, the dehydration was followed by X-ray powder diffraction (see Fig. 2 in ESI). Anhydrous L-serine is not hygroscopic and does not tend to form the monohydrate on storage on air, but forms it easily if contacts with liquid water. The oxalic acid dihydrate does not lose water completely not only on storage, but also on heating, although some partial dehydration can be noticed with time. Anhydrous oxalic acid is extremely hygroscopic and forms hydrate readily when exposed to air at ambient conditions. It was shown that the dehydration of L-serine monohydrate proceeds faster at the contact with oxalic acid dihydrate (Fig. 3). After the components were preliminary ground separately,

the mixture was stored for 7 days at ambient conditions. This resulted in the transformation into  $[\text{L-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$  form II (systems 3 and 4) and  $[\text{L-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$  form I (system 5 for addition of water drop according to  $\eta=0.25$ ); the trace amounts of these salts could be observed already after the first hour of storage.

It became evident after these experiments, that the role of mechanical treatment of the mixture in inducing a reaction between L-serine and oxalic acid is in bringing the components into contact: reaction occurs as soon as a good inter-particle contact has been achieved. Water is released from the crystal hydrates faster in the presence of the second component that could then bind both water and the first component into one of the two polymorphs of the same salt hydrate.

The results of mechanical treatment at room temperature were compared with those of cryogrinding (at the liquid nitrogen temperature), when water could no longer be liquid but froze to solid ice. The outcome of co-grinding was exactly the same for system 3. However, for system 4, a mixture of the two forms of  $[\text{L-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$  was observed on cryogrinding, differently from pure  $[\text{L-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$  form I at ambient conditions (Fig. 2). Thus, even solid water seems to participate in the reaction between the components in this system. An alternative explanation could be that the condensation of liquid water at the surface of the reacting particles on ejecting the samples after cryomilling could not be completely avoided even when all operations were as fast as possible. The incomplete yield of the  $[\text{L-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$  polymorph I (in comparison with treatment under room temperature) can be explained by decreasing the mobility of molecular species and slowing down the diffusion of the



The results of all the series of the experiments could be interpreted assuming that  $[\text{L-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$  polymorph II forms *prior to* the  $[\text{L-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$  polymorph I as an intermediate phase (similarly to how bis-glycinium oxalate is an intermediate phase in the mechanochemical synthesis of glycinium semi-oxalate<sup>30</sup>). To check this hypothesis, a mixture of L-serine monohydrate and oxalic acid dihydrate was prepared (with the size of particles equal to 100-200  $\mu\text{m}$  as controlled by sieving). Then the mixture was carefully stirred manually by rotation in a glass vial, and XRPD patterns were recorded at regular time intervals. The accumulation of the  $[\text{L-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$  polymorph II started from the first moments of this experiment. Then a transformation of polymorph II to polymorph I occurred, thus confirming the original hypothesis (Fig. 4). An intense agglutination of particles was observed after storage of the mixture (in a sealed vial, to avoid condensation of water from the environment) during 7 days evidencing the reaction through dissolution and recrystallisation as is common for many crystal hydrates prone to “caking” (Fig. 5).

The dehydration of L-ser·H<sub>2</sub>O on co-grinding at chosen mode is noticeable only if the second reactant is present, so that the subsequent stages take place. Important to note is that

In order to understand why polymorph II of [L-serH]<sub>2</sub>[ox]•2H<sub>2</sub>O is the first one to form, we have compared the two crystal structures (Fig. 6).<sup>35</sup> The transformation from polymorph II to polymorph I of [L-serH]<sub>2</sub>[ox]•2H<sub>2</sub>O at the second stage occurred due to the rotation of molecular fragments («L-serine cation – oxalic acid dianion – L-serine cation» blocks) in the crystal structure relative to each other (Fig. 6). The process is accompanied by the formation of new hydrogen bonds between: a) the amino group of L-serine cation and the oxalic acid dianion (one new N-H...O bond), b) the carboxylic group of L-serine cation and the oxalic acid dianion (two new O-H...O bonds), c) the amino group of L-serine cation and the oxygen of water (one new N-H...O bond) (see ESI). The presence of water facilitates this process, therefore, polymorph I is formed only if sufficient amount of water is present in the system. At low temperatures, the process is also hindered, and the transformation of polymorph II into polymorph I is not complete. Therefore, cryogrinding gives a mixture of polymorphs I and II (Fig. 2).

One can notice some similarity with the case of bis-glycinium oxalate (also formed first and then transformed into glycinium semi-oxalate).<sup>30</sup> The polymorph II has a “block” structure, which looks as the result of a rapid formation of “primary clusters” which are then only loosely linked with

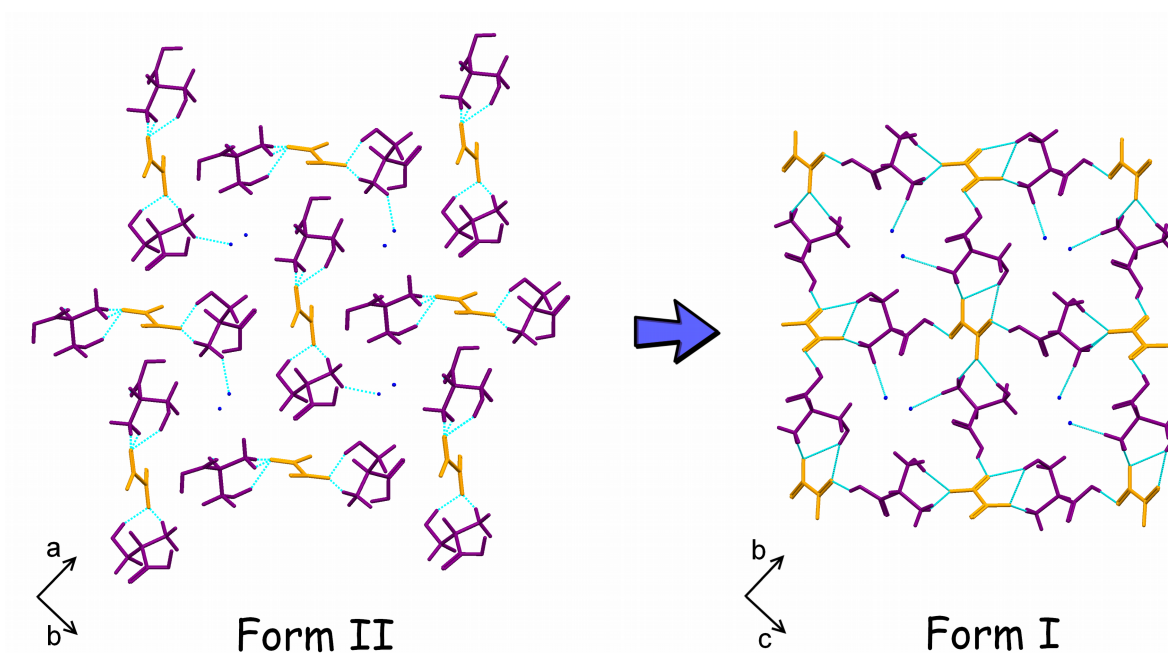


Fig. 6 A comparison of crystal structures of the two polymorphs of  $[\text{L-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$

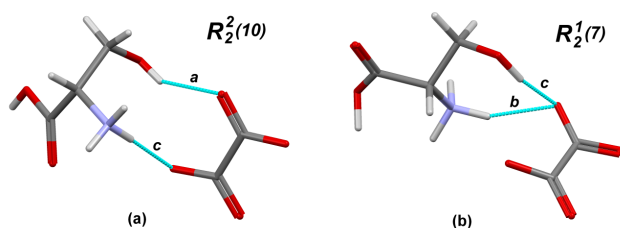


Fig. 7 Second level ring motifs in the structures of  $[\text{L-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$  polymorph I (a) and polymorph II (b)

each other (similar to bis-glycinium oxalate<sup>30</sup>). The crystal structure of polymorph I is additionally stabilised as compared with polymorph II of the same compound by extra hydrogen bonding, so that a 3D hydrogen-bond network with ring heterosynths  $R_2^2(10)$  instead of  $R_1^2(7)$  is formed (Fig. 7; Table 2, 3 in the ESI). The difference in the IR-spectra of the two polymorphs (Fig. 3, Table 1 in the ESI) agrees with the difference in the hydrogen-bond patterns: the decrease of the frequencies of O-H and N-H stretching modes corresponds to the strengthening of hydrogen bonds in the network.

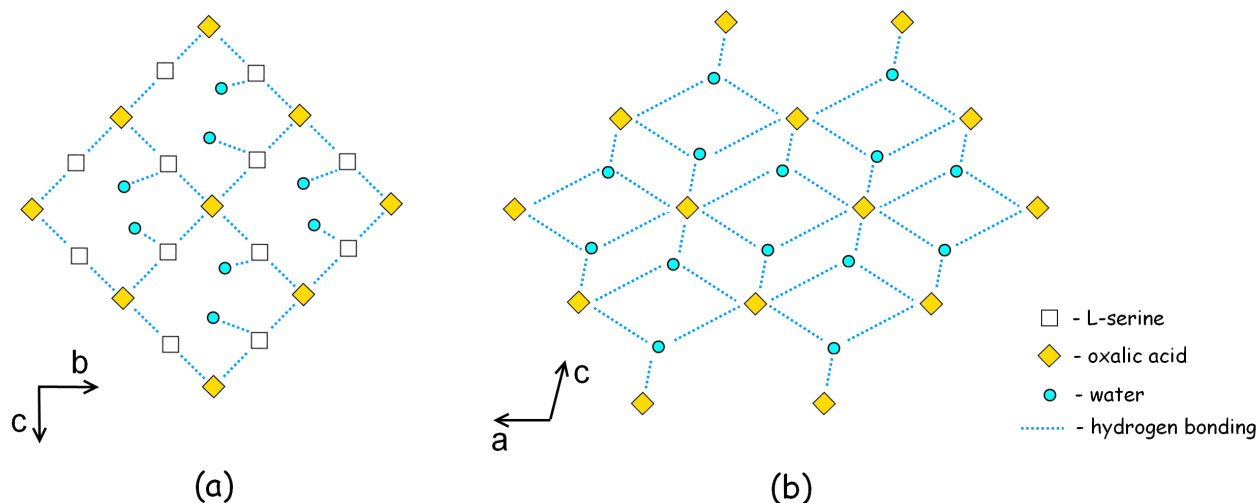
Interestingly, the crystal structures of  $[\text{L-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$  have some topological similarity with the crystal structure of the oxalic acid dihydrate: there are no homomolecular contacts in all these structures, and water molecules are located in the channels formed by other molecules (in the oxalic acid dihydrate water molecules act as bridges, in  $[\text{L-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$  they are bound to one of the serinium cations only) (Fig. 8). This contrasts with the crystal structures of both L-serine and L-serine hydrate, in which L-serine molecules are directly linked *via* hydrogen bonds with each other to form chains, layers, and (in L-serine) a 3D network. Thus, to form  $[\text{L-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$ , one has to break bonds

between serine molecules in the original structures of either L-serine, or L-serine hydrate.

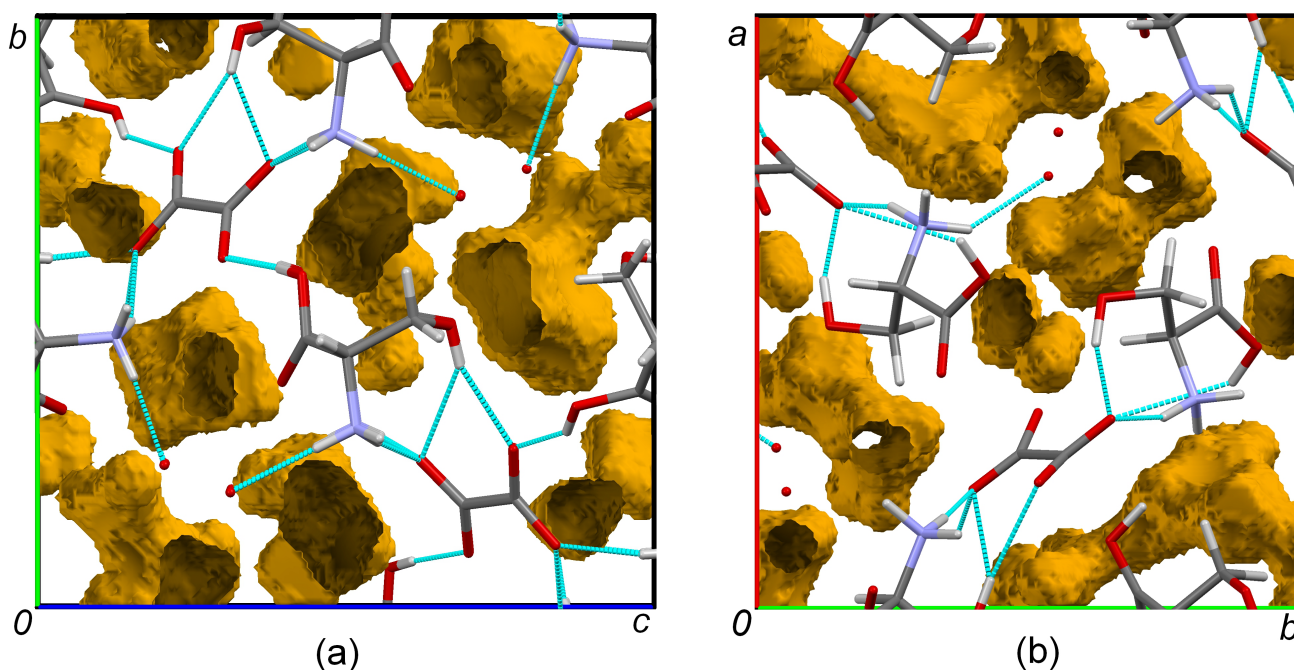
The bulk densities of the two polymorphs calculated from X-ray diffraction data are slightly different: form II is denser than form I ( $1.547$  and  $1.537 \text{ mg} \cdot \text{cm}^{-3}$ , respectively), although form I is the final product of mechanochemical reaction between L-serine monohydrate and oxalic acid dihydrate. The data do not correlate with the “density rule” that implicates the greater energetic stability for denser crystalline forms if van der Waals interactions dominate. The less dense form I is stabilised by additional hydrogen bonds, but their formation results in additional free space. An estimation of the free space inside the unit cells of the two forms of hydrated salts using Mercury programme<sup>51</sup> shows that form I has more voids ( $115.67 \text{ \AA}^3$  or  $15.9\%$  of the unit cell volume), than form II ( $97.98 \text{ \AA}^3$  and  $13.6\%$ , respectively) (Fig. 9), in agreement with the bulk density calculation. The total volume of free space in both hydrated salts is much larger than that in any of the initial components ( $52.36 \text{ \AA}^3$  ( $9.4\%$ ) for L-serine monohydrate and  $17.91 \text{ \AA}^3$  ( $7.0\%$ ) for oxalic acid dihydrate).

The products formed on grinding of solid mixtures were reported to correlate in some cases with those formed from solutions of the same components on fast crystallisation, *e.g.*, by antisolvent crystallisation, or by spray drying,<sup>30,32,52</sup> and to differ from those formed on slow evaporation of solutions.<sup>30,53</sup> In order to follow the results of “rapid” crystallisation in “L-serine – oxalic acid” system, spray drying of stoichiometric aqueous solution of L-serine and oxalic acid (molar ratio 2:1) was performed at different temperatures, taking into account the data on thermal stability of the two forms of  $[\text{L-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$ .<sup>35</sup> The experiments both at  $65$  and at  $80^\circ\text{C}$  (below and above the onset of melting point of form II at  $73^\circ\text{C}$ )<sup>35</sup> resulted in the formation of  $[\text{L-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$





**Fig. 8** Comparison of positions of water molecules in the structures of  $[L-serH]_2[ox] \cdot 2H_2O$  polymorph I (a) and oxalic acid dihydrate (b). In both structures water is located inside the channels and forms hydrogen bonds



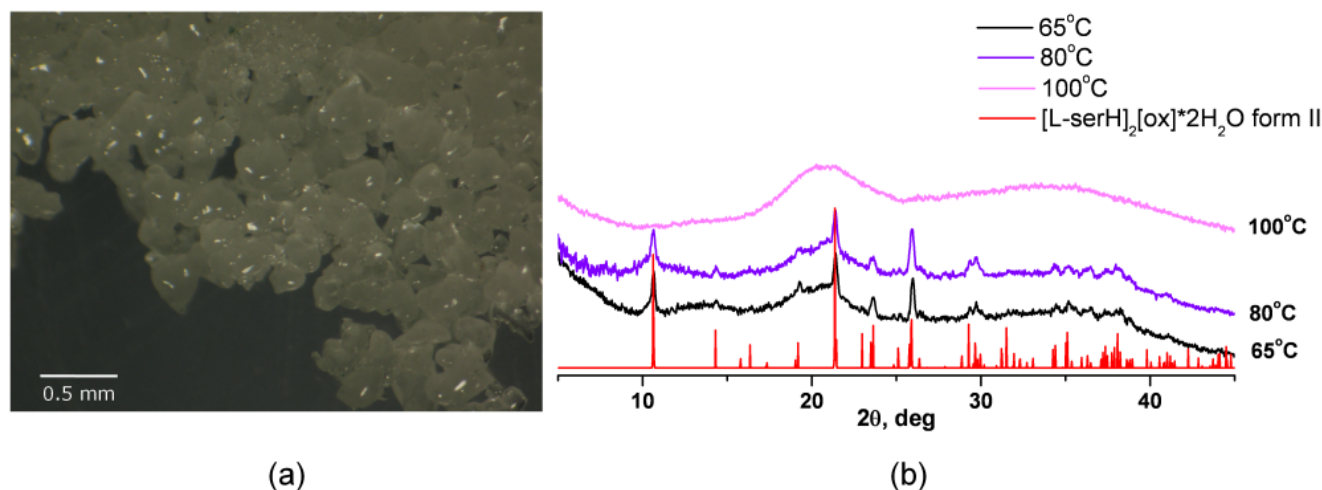
**Fig. 9** Visualisation of the voids in the structures of  $[L-serH]_2[ox] \cdot 2H_2O$  form I (a) and form II (b). Voids were found using the “contact surface” method with probe radius 0.5 Å and grid 0.1 Å<sup>51</sup>

polymorph II (partially X-ray amorphous products). One can interpret the fact as the formation of a kinetically controlled product: components of the system in question have no time to build the spacious network of hydrogen bonds and to assemble the structure containing “primary clusters”. Spray drying was often reported to give products different from those predicted by phase diagrams calculated for equilibrium slow crystallisation.<sup>54</sup> The spraying of feed solution under 100 °C gave us a completely amorphous pattern, apparently due to the

extreme drop of temperature (Fig 10).

The results of rapid precipitation in the same system (aqueous solution of L-serine and oxalic acid, molar ratio 2:1) induced by another technique, namely by antisolvent crystallisation, were compared with those on spray drying and on grinding. Acetone and ethanol were chosen as antisolvents. Interestingly enough, in both cases pure polymorph I of  $[L-serH]_2[ox] \cdot 2H_2O$  was precipitated. In contrast to the results reported previously for the system “glycine-oxalic acid”,<sup>30,55,56</sup>





**Fig. 10** Typical product of spray drying of L-serine-oxalic acid aqueous solution (a). The formation of  $[L\text{-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$  polymorph II on spray drying of aqueous solution of L-serine with oxalic acid (molar ratio 2:1) at 65 and 80 °C

the antisolvent crystallisation in “L-serine – oxalic acid system” gives not an intermediate, but the final product of the mechanochemical synthesis. It seems to happen due to the excessive amount of water in the system leading to the formation of  $[L\text{-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$  polymorph I similarly to the slow solution crystallisation<sup>30,48</sup> or LAG experiments (see above).

A comparison of the results of LAG, spray drying, antisolvent and slow evaporation of solutions shows that in “L-serine – oxalic acid – water” system the intermediate product of the reaction observed in the mixtures of solid powders coincides with that formed on spray drying, whereas antisolvent crystallisation and slow evaporation give the same polymorph as is eventually observed on LAG or on storage of a solid mixture.

## Conclusions

Summing up, for the chosen “L-serine-oxalic acid” system the outcome of the reaction on co-grinding is independent on the choice of which phase is taken as a crystal hydrate. This fact allows us to suggest that the seemingly solid-state reaction proceeds in fact in the liquid phase at a contact between the solid particles, and does not depend on the crystal structures of initial components. The role of mechanical treatment in inducing the synthesis of  $[L\text{-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$  on co-grinding of L-serine (hydrate) with oxalic acid (dihydrate) is merely bringing the reacting species into contact, improving their mixing. The reaction can be observed also on storage of mixtures, presumably *via* the intermediate aqueous solution formed at the contacts between particles. Most probably, water acts as a solvent, but possibly as well as a lubricant improving interparticle contacts, and a medium strongly affecting the dielectric permeability and polarisability of the mixture. The reaction in the mixture of two anhydrous components without any water added specially seems to account for surface water absorbed as a thin layer at the contacts between the particles.

The presence of water is very important for the reaction between the solid components in all the systems considered in this study. However, the state in which water is present seems to be not important, only its relative amount in the system matters. Though the stoichiometry of the product salt hydrate does not depend on the amount of water in the system or the temperature of co-grinding, different polymorphs (as pure forms or in a mixture) are formed.

The  $[L\text{-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$  polymorph II is formed as an intermediate phase in the reaction that gives  $[L\text{-serH}]_2[\text{ox}] \cdot 2\text{H}_2\text{O}$  polymorph I as the final product. This fact could be interpreted comparing the two crystal structures: the first-formed metastable crystal structure seems to have more stable “molecular clusters” whereas in the thermodynamically stable structure the complete crystal packing is optimised. In contrast to the case of glycine-oxalic acid system,<sup>30,55,56</sup> the structure that is formed first in the solid powder mixtures differs from the product of precipitation on antisolvent crystallisation from water solution, *i.e.* antisolvent crystallisation in this case gives the thermodynamically stable form.

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## Notes and references

<sup>a</sup> Institute of Solid State Chemistry and Mechanochemistry SB RAS, Kutateladze 18, Novosibirsk, 630128, Russia

<sup>b</sup> REC-008, Novosibirsk State University, Pirogova 2, Novosibirsk, 630090, Russia.

E-mails: losev.88@mail.ru, eboldyreva@yahoo.com; Fax: +7 8 383 363

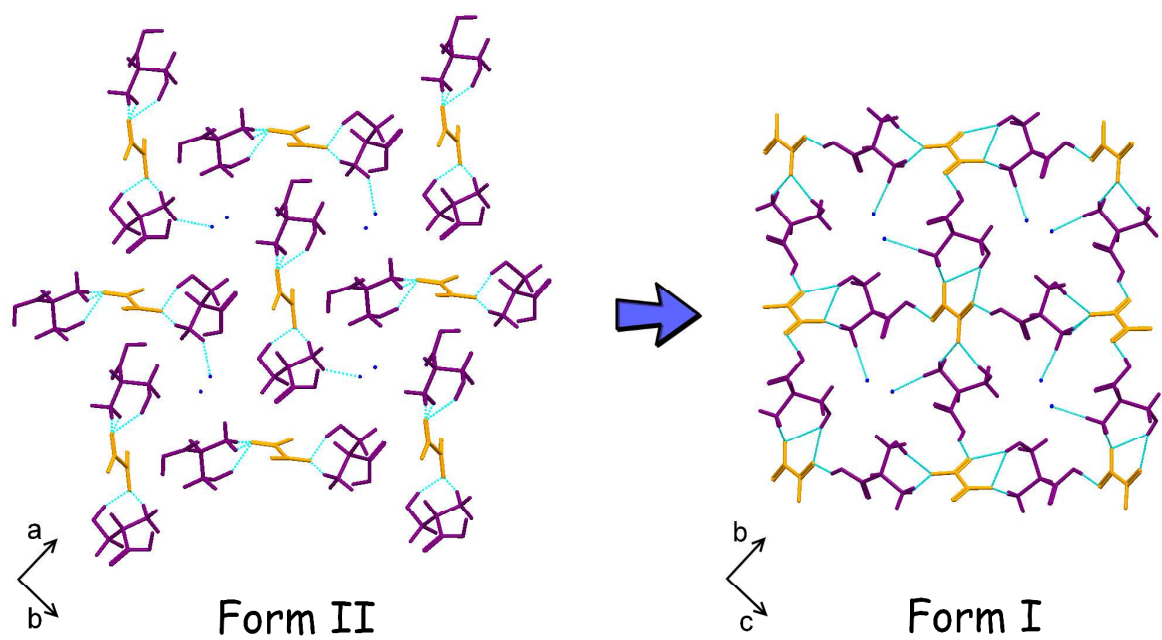
41 32; Tel: +7 8 383 363 42 06

† Electronic Supplementary Information (ESI) available: [ESI includes discussion of LAG experiments with various amount of water, comparison of IR spectra of two forms of [L-serH]<sub>2</sub>[ox]•2H<sub>2</sub>O, XRPD data on dehydration of L-serine monohydrate and comparison of crystal motifs in the structures of the two polymorphs of [L-serH]<sub>2</sub>[ox]•2H<sub>2</sub>O]. See DOI: 10.1039/b000000x/

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Graphical abstract



$[L-serH]_2[ox] \cdot 2H_2O$  form II proved to be an intermediate product in the reaction of obtaining the form I