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## COMMUNICATION

Supramolecular metathesis: co-former exchange in co-crystals of pyrazine with (*R,R*)-, (*S,S*)-, (*R,S*)- and (*S,S/R,R*)-tartaric acid†

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Co-crystals of *dextro*-(*R,R*), *levo*-(*S,S*), *meso*-(*R,S*) and *racemic* (*R,R-S,S*)-tartaric acid with pyrazine were obtained by manual kneading and slurry experiments; subsequent reactions in the solid state between these co-crystals and the various forms of tartaric acid in the solid state and *via* slurry show that co-former exchange takes place according to the sequence of stability [(*R,S*)-ta]<sub>2</sub>·py > (*S,S/R,R*)-ta·py > (*R,R*)-ta·py or (*S,S*)-ta·py.

The paradigm of crystal engineering is the possibility of controlling the preparation of crystal phases of a given molecule by a choice of supramolecular bonding features. Molecules and ions are regarded as building blocks in the construction of periodical supramolecular frameworks.<sup>1</sup> The introduction of a new component in a single molecule crystalline material often allows the existence of materials with different free energy states, hence to potentially more stable crystal forms. Co-crystallization has been proved to be a route to the preparation of entirely new multi-component crystalline systems.<sup>2</sup> Clearly, the competition with kinetic factors, associated often to the nucleation stage of the crystallization process, needs also to be taken into account.<sup>3</sup> A way to overcome the thermodynamic-kinetic dualism is the “solvent-free” condition.

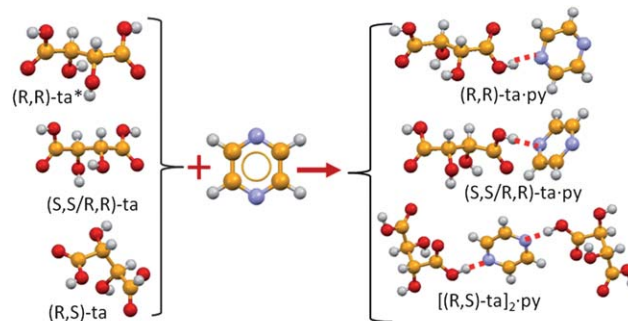
The number of papers reporting preparation of molecular co-crystals and salts *via* solid state techniques is constantly increasing. If not all, many processes can definitely be conducted in the absence of solvent or with solvent present in minimal “catalytic” quantity (*kneading* and *liquid-assisted grinding*).<sup>2i,4</sup> It has also been shown that in some systems chiral recognition can affect solid state reactions just as it does in solution chemistry, and that products of grinding and solution experiments can be different.<sup>5</sup>

In the present work we make use of mechanochemical methods to first obtain, then convert a co-crystal into a different one that shares a molecular component with the former. For this purpose *dextro*-(*R,R*), *levo*-(*S,S*), *meso*-(*R,S*) and *racemic* (*R,R-S,S*)-tartaric acid, C<sub>4</sub>O<sub>6</sub>H<sub>6</sub>, and pyrazine, C<sub>4</sub>N<sub>2</sub>H<sub>4</sub>, were chosen as starting materials. Pyrazine was chosen not only because it would easily bind to tartaric

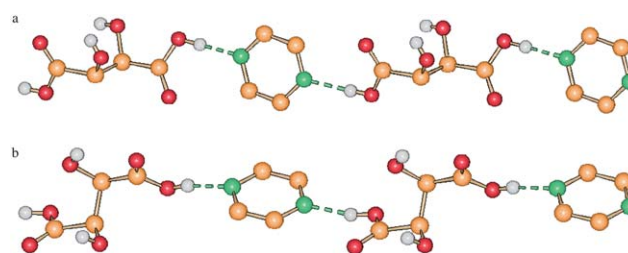
acid *via* N···H–O hydrogen bonds, but also because any unreacted pyrazine can easily sublimate at room temperature as a pure component,<sup>6</sup> thus simplifying analysis and characterization of the reaction product.

First co-crystals of (*R,R*)-, (*S,S*)-, *racemic* and (*R,S*)-tartaric acid and pyrazine, respectively called (*R,R*)-ta·py, (*S,S*)-ta·py, (*S,S/R,R*)-ta·py and [(*R,S*)-ta]<sub>2</sub>·py, were obtained from three different methods (see Scheme 1): (i) manual kneading of the solid pyrazine and tartaric acid reactants, (ii) slurry in ethanol and (iii) crystallization from ethanol solutions.<sup>‡</sup> This latter method allowed the growth of single crystals suitable for X-ray diffraction, thus providing not only complete characterization of the co-crystals, but also a control of the products purity that was performed *via* powder X-ray diffraction measurements accompanied by Rietveld refinements (see ESI†).§

Thermal stability of all compounds was checked by DSC measurements: above *ca.* 130 °C for (*S,S/R,R*)-ta·py, [(*S,S/R,R*)-ta]<sub>2</sub>·py (discussed below) and [(*R,S*)-ta]<sub>2</sub>·py, and *ca.* 120 °C for



**Scheme 1** Reactivity of the various forms of tartaric acid towards pyrazine, both in the solid state and in solution.



**Fig. 1** O(H)<sub>COOH</sub>···N hydrogen bonding interactions in (*R,R*)-ta·py (a) and in (*S,S/R,R*)-ta·py (b).

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(*R,R*)-ta·py the co-crystals are no longer stable, and separate out into the pure reagents; this is followed by sublimation of pyrazine.

X-Ray single crystal determinations were essential for the identification of the main hydrogen bonding features, responsible for the behaviour of these systems with respect to co-former exchange in kneading or slurry experiments.

In (*R,R*)-ta·py and (*S,S*)-ta·py the tartaric acid molecules link one to the other *via* O<sub>OH</sub>(H)···O<sub>OH</sub>/O<sub>CO</sub> hydrogen bonds, while the carboxylic OH group is employed only in the OH···N bonds with pyrazine (see Fig. 1a).

A similar arrangement, as far as the carboxylic groups are concerned, is observed in (*S,S/R,R*)-ta·py (see Fig. 1b).

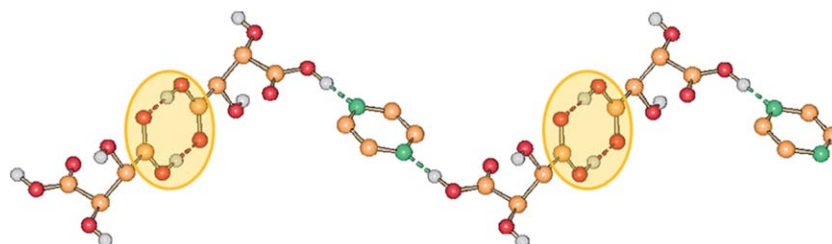
The pattern is completely changed, though, in [(*R,S*)-ta]<sub>2</sub>·py (Fig. 2), where the 2 : 1 acid : pyrazine stoichiometry, in a centrosymmetric space group, allows the formation of carboxylic dimeric rings (evidenced in yellow) in addition to the favourite (CO)OH···N hydrogen bonds. Structural effects of chiral *versus* racemic tartaric acid in the synthesis of adducts with diamines have also been investigated by Aakeroy *et al.*<sup>7</sup> and by Glidewell *et al.*<sup>8</sup>

Our co-crystals were then used as starting materials for slurry and kneading experiments,<sup>¶</sup> in the attempt of converting one phase into another by further reaction of pre-formed co-crystals with the

different forms of tartaric acid or by cross-reacting the preformed co-crystals. Kneading experiments were all conducted with an excess of pyrazine, and always led to quantitative co-crystal formation, since the excess of pyrazine sublimes. A list of experiments and stoichiometric ratios are reported in Table 1.

[(*R,S*)-ta]<sub>2</sub>·py was obtained from (*R,S*)-tartaric acid and (*R,R*)-ta·py or (*S,S/R,R*)-ta·py by kneading and slurry experiments. Interestingly, while (*R,R*)-ta·py and (*S,S*)-ta·py react in a slurry experiment to form (*S,S/R,R*)-ta·py, *i.e.* maintaining the stoichiometric ratio 1 : 1 between the acid and the base, manual kneading resulted in the formation of the 2 : 1 stoichiometry product [(*S,S/R,R*)-ta]<sub>2</sub>·py, with sublimation of the unreacted pyrazine. Recrystallization *via* seeding<sup>||</sup> of this co-crystal from an ethanol solution allowed complete structural characterization of the product by single-crystal X-ray diffraction. As observed in the case of [(*R,S*)-ta]<sub>2</sub>·py, the 2 : 1 stoichiometry allows the formation of carboxylic dimers in addition to the ubiquitous (CO)OH···N hydrogen bond (see Fig. 3).

This result provides further evidence to the fact that solid state reactions can rapidly produce pure phases in a solvent-free condition.<sup>9</sup> In this particular case the formation of the 2 : 1 product by manual kneading is probably due to partial sublimation of pyrazine during the kneading process; the same reaction conducted with

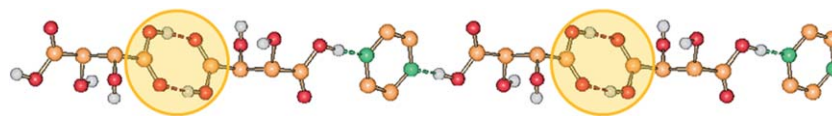


**Fig. 2** O(H)<sub>COOH</sub>···O<sub>COOH</sub> carboxylic dimeric rings are present in addition to O(H)<sub>COOH</sub>···N hydrogen bonding interactions in [(*R,S*)-ta]<sub>2</sub>·py.

**Table 1** Reagents stoichiometric ratio and products of kneading and slurry experiments

| Reagents   |             | Products (kneading)  | Products (slurry)  |
|--|-------------|--|--|
| Co-crystal <sup>a</sup> + tartaric acid                      | Molar ratio | Co-crystal + tartaric acid                                   | Co-crystal + tartaric acid                                   |
| ( <i>R,R</i> )-ta·py + ( <i>R,S</i> )-ta                     | 1 : 2       | [( <i>R,S</i> )-ta] <sub>2</sub> ·py + ( <i>R,R</i> )-ta     | [( <i>R,S</i> )-ta] <sub>2</sub> ·py + ( <i>R,R</i> )-ta     |
| ( <i>S,S/R,R</i> )-ta·py + ( <i>R,S</i> )-ta                 | 1 : 2       | [( <i>R,S</i> )-ta] <sub>2</sub> ·py + ( <i>S,S/R,R</i> )-ta | [( <i>R,S</i> )-ta] <sub>2</sub> ·py + ( <i>S,S/R,R</i> )-ta |
| [( <i>R,S</i> )-ta] <sub>2</sub> ·py + ( <i>R,R</i> )-ta     | 2 : 1       | No reaction  | No reaction  |
| [( <i>R,S</i> )-ta] <sub>2</sub> ·py + ( <i>S,S/R,R</i> )-ta | 2 : 1       | No reaction  | No reaction  |
| ( <i>S,S/R,R</i> )-ta·py + ( <i>R,R</i> )-ta                 | 2 : 1       | No reaction  | No reaction  |
| Co-crystal <sup>a</sup> + co-crystal                         | Molar ratio | Co-crystal   | Co-crystal   |
| ( <i>R,R</i> )-ta·py + ( <i>S,S</i> )-ta·py                  | 1 : 1       | [( <i>S,S/R,R</i> )-ta] <sub>2</sub> ·py <sup>b</sup>        | ( <i>S,S/R,R</i> )-ta·py <sup>b</sup>                        |
| ( <i>R,R</i> )-ta·py + ( <i>S,S</i> )-ta·py + py             | 1 : 1 : 10  | ( <i>S,S/R,R</i> )-ta·py <sup>b</sup>                        | ( <i>S,S/R,R</i> )-ta·py <sup>b</sup>                        |

<sup>a</sup> See the products in Scheme 1. <sup>b</sup> The 2 : 1 co-crystal could only be obtained *via* kneading, probably due to loss of volatile pyrazine during the experiment; in order to obtain the 1 : 1 co-crystal, an excess of pyrazine was used. Slurry experiments invariably yielded the 1 : 1 co-crystal.



**Fig. 3** The acid : pyrazine 2 : 1 stoichiometry in [(*S,S/R,R*)-ta]<sub>2</sub>·py allows the presence of O(H)<sub>COOH</sub>···O<sub>COOH</sub> carboxylic dimeric rings in addition to O(H)<sub>COOH</sub>···N hydrogen bonding interactions, contrary to what observed for (*S,S/R,R*)-ta·py (Fig. 1b).

a large excess of pyrazine (10 : 1, see Table 1) results in fact in the 1 : 1 co-crystal, as observed by slurry.

We assume that the products of slurry experiments represent the most stable forms, since the experimental time is much longer than manual grinding experiments (days *vs.* minutes). In terms of molecular recognition we may say that each pyrazine molecule has a chance to eventually pass from one crystal structure to a more stable one.

## Conclusions

We have shown that solid–solid reactions with co-crystals or between co-crystals can be used not only to produce new crystal forms with respect to conventional reactions in solution, but also to *interconvert* crystal forms, in a sort of supramolecular metathesis. The combined experiments suggest a scale of solid state stability  $[(R,S)\text{-ta}]_2 \cdot \text{py} > (S,S/R,R)\text{-ta} \cdot \text{py} > [(S,S/R,R)\text{-ta}]_2 \cdot \text{py} > (R,R)\text{-ta} \cdot \text{py}$  or  $(S,S)\text{-ta} \cdot \text{py}$ . The fact that pyrazine is volatile is instrumental to the preparation of pure phases because of the sublimation of the excess reactant.

## Notes and references

‡ **Co-crystals preparation.** *Crystallization from solution.*  $(R,R)\text{-ta} \cdot \text{py}$ ,  $(S,S)\text{-ta} \cdot \text{py}$ ,  $(S,S/R,R)\text{-ta} \cdot \text{py}$  and  $[(R,S)\text{-ta}]_2 \cdot \text{py}$  co-crystals were grown by crystallization from methanol solution. 1 mmol of tartaric acid (150 mg) and 3 mmol of pyrazine (240 mg) were separately dissolved in methanol and then mixed. The solution was allowed to evaporate at room temperature. *Kneading experiments.*  $(R,R)\text{-ta} \cdot \text{py}$ ,  $(S,S)\text{-ta} \cdot \text{py}$ ,  $(S,S/R,R)\text{-ta} \cdot \text{py}$  and  $[(R,S)\text{-ta}]_2 \cdot \text{py}$  co-crystals were obtained by kneading experiments using ethanol. 1 mmol of tartaric acid (150 mg) and 10 mmol of pyrazine (800 mg) were manually ground for 30 minutes after adding three to five drops of solvent. The powders were left at room temperature for at least 24 hours before XRPD characterization. *Slurry experiments.*  $(R,R)\text{-ta} \cdot \text{py}$ ,  $(S,S)\text{-ta} \cdot \text{py}$ ,  $(S,S/R,R)\text{-ta} \cdot \text{py}$  and  $[(R,S)\text{-ta}]_2 \cdot \text{py}$  co-crystals were obtained by slurry experiments using ethanol. 1 mmol of tartaric acid (150 mg) and 1 mmol of pyrazine (80 mg) were suspended in 15 ml of ethanol in a closed vessel, and stirred at room temperature for two weeks.

§ **X-Ray diffraction.** X-Ray data collected with an Oxford Diffraction Xcalibur diffractometer; Mo K $\alpha$  radiation ( $\lambda = 0.71073 \text{ \AA}$ ). *Crystal data.*  $(R,R)\text{-ta} \cdot \text{py}$ : chemical formula moiety  $\text{C}_4\text{H}_6\text{O}_6 \cdot \text{C}_4\text{H}_4\text{N}_2$ ,  $M = 230.19$ ,  $T = 293 \text{ }^\circ\text{C}$ , triclinic, space group  $P1$ ,  $a = 4.9179(5)$ ,  $b = 5.4897(7)$ ,  $c = 9.5322(7) \text{ \AA}$ ,  $\alpha = 92.426(9)^\circ$ ,  $\beta = 102.087(9)^\circ$ ,  $\gamma = 94.810(9)^\circ$ ,  $V = 250.28(5) \text{ \AA}^3$ ,  $Z = 1$ , 1460 independent reflections (1729 measured),  $R_{\text{int}} = 0.0168$ ,  $wR_2 = 0.0737$ ,  $R_1(\text{obs}) = 0.0375$ .  $[(R,S)\text{-ta}]_2 \cdot \text{py}$ : chemical formula moiety  $\text{C}_4\text{H}_6\text{O}_6 \cdot 0.5(\text{C}_4\text{H}_4\text{N}_2)$ ,  $M = 380.29$ ,  $T = 293 \text{ }^\circ\text{C}$ , triclinic, space group  $P1$ ,  $a = 4.9819(5)$ ,  $b = 5.3114(7)$ ,  $c = 14.748(2) \text{ \AA}$ ,  $\alpha = 89.543(12)^\circ$ ,  $\beta = 86.283(10)^\circ$ ,  $\gamma = 84.973(10)^\circ$ ,  $V = 387.91(9) \text{ \AA}^3$ ,  $Z = 1$ , 1726 independent reflections (2910 measured),  $R_{\text{int}} = 0.0178$ ,  $wR_2 = 0.1031$ ,  $R_1(\text{obs}) = 0.0419$ .  $(S,S/R,R)\text{-ta} \cdot \text{py}$ : chemical formula moiety  $\text{C}_4\text{H}_6\text{O}_6 \cdot \text{C}_4\text{H}_4\text{N}_2$ ,  $M = 230.19$ ,  $T = 293 \text{ }^\circ\text{C}$ , monoclinic, space group  $P2_1/n$ ,  $a = 11.4966(4)$ ,  $b = 5.1521(2)$ ,  $c = 17.0937(6) \text{ \AA}$ ,  $\alpha = 90^\circ$ ,  $\beta = 96.315(3)^\circ$ ,  $\gamma = 90^\circ$ ,  $V = 1006.34(6) \text{ \AA}^3$ ,  $Z = 4$ , 2258 independent reflections (4566 measured),  $R_{\text{int}} = 0.0207$ ,  $wR_2 = 0.0952$ ,  $R_1(\text{obs}) = 0.0491$ .  $[(S,S/R,R)\text{-ta}]_2 \cdot \text{py}$ : chemical formula moiety  $\text{C}_4\text{H}_6\text{O}_6 \cdot 0.5(\text{C}_4\text{H}_4\text{N}_2)$ ,  $M = 380.29$ ,  $T = 293 \text{ }^\circ\text{C}$ , triclinic, space group  $P1$ ,  $a = 4.9168(5)$ ,  $b = 5.4373(5)$ ,  $c = 14.7869(14) \text{ \AA}$ ,  $\alpha = 81.199(8)^\circ$ ,  $\beta = 83.738(8)^\circ$ ,  $\gamma = 88.135^\circ$ ,  $V = 388.28(6) \text{ \AA}^3$ ,  $Z = 1$ , 1726 independent reflections (2909 measured),  $R_{\text{int}} = 0.0222$ ,  $wR_2 = 0.1651$ ,  $R_1(\text{obs}) = 0.0568$ . SHELX97<sup>10a</sup> and SCHAKAL99<sup>10b</sup> were used for structure solution and graphical representation. Powder diffraction patterns over  $5^\circ$  to  $90^\circ$  in  $2\theta$  were collected on a PANalytical diffractometer with Bragg–Brentano geometry (Cu K $\alpha$  radiation, detector: X'celerator, step size  $\Delta 2\theta = 0.0167^\circ$ , and counting time per step = 50 s). The software GSAS<sup>10c</sup> was used for refinements. Rietveld analyses were

conducted starting from the crystal structures refined from single crystal data and treating the single molecules as rigid bodies. Shifted Chebyshev function with 6 parameters and Pseudo-Voigt function were used to fit respectively background and peak shape. An overall thermal parameter for each molecule was adopted. For  $(S,S)\text{-ta} \cdot \text{py}$  data crystal structure was derived from  $(R,R)\text{-ta} \cdot \text{py}$  co-crystal. Refinements of kneading experiment products for phases  $(R,R)\text{-ta} \cdot \text{py}$ ,  $(S,S)\text{-ta} \cdot \text{py}$ ,  $(S,S/R,R)\text{-ta} \cdot \text{py}$ ,  $[(S,S/R,R)\text{-ta}]_2 \cdot \text{py}$  and  $[(R,S)\text{-ta}]_2 \cdot \text{py}$  converged with  $R_{\text{wp}}$  respectively 14.80%, 11.68%, 11.58%, 14.62% and 9.91%, and  $R_{\text{F}}$  respectively 11.69%, 12.17%, 11.03%, 13.12%, and 10.99%. DSC measurements were performed with a Perkin-Elmer Diamond. Samples (3–5 mg) were placed in open aluminium pans. Heating was carried out at  $5 \text{ }^\circ\text{C min}^{-1}$  for all co-crystals and  $1 \text{ }^\circ\text{C min}^{-1}$  for  $(S,S/R,R)\text{-ta} \cdot \text{py}$  co-crystal, in the temperature range 25 to  $160 \text{ }^\circ\text{C}$ .

¶ **Metathesis experiments. Kneading experiments.** 1 mmol of tested co-crystal and tested isomeric tartaric acid in stoichiometric quantity (see Table 1) were manually ground for 30 minutes after adding three to five drops of ethanol corresponding to a few ml. 1 mmol of  $(R,R)\text{-ta} \cdot \text{py}$  and 1 mmol of  $(S,S)\text{-ta} \cdot \text{py}$  co-crystals with or without 10 mmol of pyrazine (see Table 1) were manually ground for 30 minutes after adding three to five drops of ethanol corresponding to a few ml. The powders were left at room temperature for at least 24 hours before XRD characterization. *Slurry experiments.* 1 mmol of tested co-crystal and tested isomeric tartaric acid in stoichiometric quantity (see Table 1) were suspended in around 15 ml of ethanol in a closed vessel, and stirred at room temperature for over two weeks. 1 mmol of  $(R,R)\text{-ta} \cdot \text{py}$  and 1 mmol of  $(S,S)\text{-ta} \cdot \text{py}$  co-crystals with or without 10 mmol of pyrazine (see Table 1) were suspended in around 15 ml of ethanol in a closed vessel, and stirred at room temperature for over two weeks.

|| **Seeding experiment.** 1 mmol of  $(S,S/R,R)\text{-tartaric acid}$  (150 mg) and 3 mmol of pyrazine (240 mg) were separately dissolved in methanol solution and then mixed. 100 mg of  $[(S,S/R,R)\text{-ta}]_2 \cdot \text{py}$  were suspended in the resulting solution. The solution was left to evaporate at room temperature.

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