Exploring cocrystal–cocrystal reactivity *via* liquid-assisted grinding: the assembling of racemic and dismantling of enantiomeric cocrystals†

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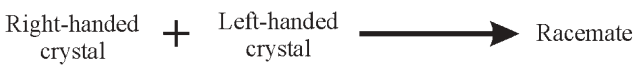
The reaction between pairs of enantiomeric cocrystals involving caffeine or theophylline and a chiral cocrystal former has been investigated by liquid-assisted grinding: we demonstrate two different outcomes for such cocrystal–cocrystal reactions.

The interest in cocrystals, driven largely by new opportunities in the design and construction of solid-state materials,[1] has also brought about an equally strong interest to discover new and efficient methods of cocrystal synthesis.[2] Specifically, in addition to the traditional means of constructing cocrystals by cocrystallization from solution, several research groups,[3–5] including our own,[6] have described the construction of two-component, or binary, cocrystals by grinding together the two cocrystal components.[7]

Whereas such grinding can be performed using dry reactants, the presence of a small amount of a liquid phase has been found to enhance the rate of cocrystal formation.[8] Indeed, we have recognized such liquid-assisted grinding as a powerful methodology to construct cocrystals in a rapid and quantitative fashion.

The facility of using liquid-assisted grinding to explore reactions that involve single-component solids as reactants led us to consider investigating the solid-state reactivity between multicomponent solids as the starting materials. Specifically, we decided to explore the outcome of the liquid-assisted grinding together of two binary cocrystals.

As our first entry into investigating such cocrystal–cocrystal reactivity, we have decided to focus on enantiomeric cocrystals as reactants. Our selection was guided by the relative simplicity of the system and the ability to compare the results with reactions involving enantiomeric single-component solids as reactants. Notably, grinding together of two single-component enantiomeric crystals has been known usually to result in the formation of a racemate, as reported by Toda *et al.* in the context of organic solids[9] and Nakamura *et al.* in context of metal–organic solids (Scheme 1).[10]



Scheme 1

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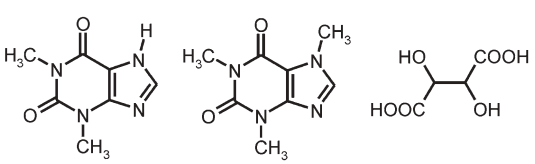
Recognising the major significance of cocrystals in the context of pharmaceuticals,[11] we have decided to focus on model pharmaceutical cocrystals,[12] *i.e.* solids that are composed of a model active pharmaceutical ingredient (API) and a cocrystal former. Following our previous work[13] on the design of pharmaceutical cocrystals, we have selected two methylated xanthines, theophylline and caffeine, as model API compounds. As a suitable chiral cocrystal former we have selected readily available tartaric acid (Scheme 2).

We now wish to report liquid-assisted grinding as a method of exploring the solid-state chemistry of chiral cocrystals. Specifically, we have observed that liquid-assisted grinding of two enantiomorphic cocrystals can lead to at least two possible results. One is the formation of a centrosymmetric three-component cocrystal, consisting of the left- and right-handed cocrystal former molecules and the model API. The second possibility is a dismantling reaction that yields the model API along with the racemic form of the cocrystal former.

The cocrystals of theophylline and caffeine with L- and D-tartaric acids were prepared by liquid-assisted grinding stoichiometric amounts of appropriate components. Nitromethane was used as the liquid phase in the grinding experiments and X-ray powder diffraction was used to monitor reaction progress. According to powder diffraction patterns, grinding together of theophylline and D- or L-tartaric acid produced cocrystals that contained theophylline and the cocrystal former in a 2 : 1 stoichiometric ratio, whereas caffeine and D- or L-tartaric acid produced cocrystals that contained the two components in a 1 : 1 ratio.

Since all attempts to obtain cocrystals of (theophylline)$_2$·(D/L-tartaric acid) from solution failed (the outcome was theophylline), it was not possible to elucidate the structure of the cocrystal using single crystal X-ray diffraction. Consequently, the crystal structure was determined from X-ray powder diffraction data using the program DASH.[14] The structure consists of staircase-shaped polymer ribbons that are held together by hydrogen bonds of O–H···N and N–H···O type.‡ The repeat unit of each ribbon contains two tartaric acid molecules and four molecules of theophylline (Fig. 1a). Tartaric acid molecules are located in the center of each ribbon, whereas theophylline defines the ribbon edges. The ribbons become triply interwoven through O–H···O



Scheme 2

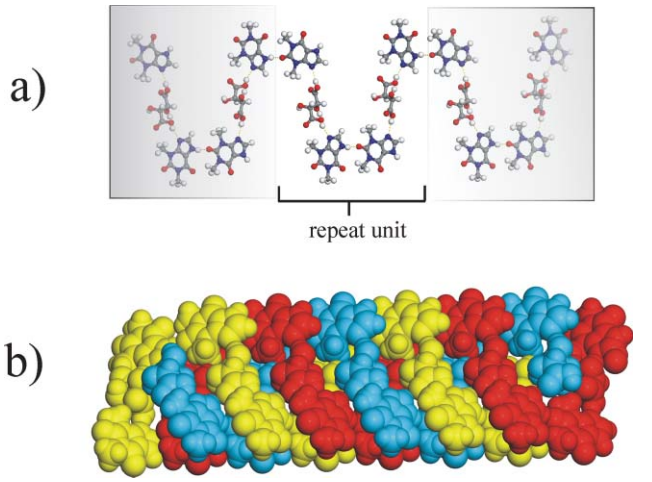


Fig. 1 (a) A ball-and-stick model of a single hydrogen-bonded polymer ribbon with the repeat unit of the polymer shown; (b) three interwoven ribbons in (theophylline)$_2$·(D/L-tartaric acid). For clarity, each ribbon is given a different colour.

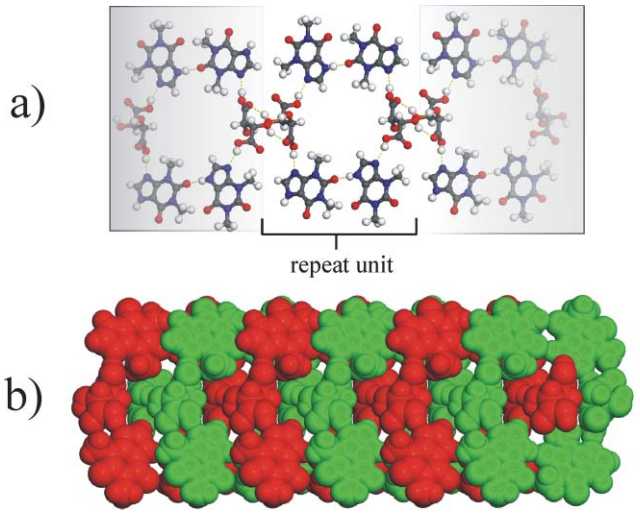


Fig. 2 (a) A ball-and-stick model of a single hydrogen-bonded polymer ribbon with the repeat unit of the polymer shown; (b) two interwoven ribbons in (theophylline)$_2$·(DL-tartaric acid). For clarity each sheet is given a different colour.

hydrogen bonds between tartaric acid molecules in neighboring ribbons (Fig. 1b). Neighboring ribbons also make side-on contact *via* N–H···O hydrogen bonds between theophylline molecules.

X-Ray powder diffraction was then used to study the liquid-assisted grinding of cocrystals of (theophylline)$_2$·(D-tartaric acid) and (theophylline)$_2$·(L-tartaric acid). The results indicated the formation of a new crystalline phase. After 20 min grinding no signals characteristic of the starting cocrystals remained in the powder diffraction pattern, suggesting complete conversion. Dissolving the ground material in a mixture of nitromethane and methanol, followed by slow evaporation at room temperature provided crystals suitable for single crystal X-ray diffraction. Crystal structure analysis revealed the cocrystals are centrosymmetric, containing both D- and L- forms of tartaric acid in equal amounts.§ The overall 2 : 1 ratio of theophylline to tartaric acid in the cocrystal is consistent with the ratio found in the starting cocrystals (theophylline)$_2$·(D-tartaric acid) and (theophylline)$_2$·(L-tartaric acid). Similar to the starting enantiomorphic cocrystals, the centrosymmetric cocrystal is built up of staircase-like hydrogen-bonded polymer ribbons. Moreover, a six-membered repeat unit, made up of four theophylline molecules, one molecule of D-tartaric acid and one molecule of L-tartaric acid can also be recognized in each sheet (Fig. 2a). The repeat unit is analogous to the repeat units found in (theophylline)$_2$·(D-tartaric acid) and (theophylline)$_2$·(L-tartaric acid). However, whilst the repeat units in the enatiomorphic cocrystals are open-ended, the repeat unit of the centrosymmetric cocrystal is cyclic. As a result of the cyclic structure of the repeat unit, a ribbon is formed by connecting together the centrosymmetric repeat units through O–H···O hydrogen bonds between opposite enantiomers of tartaric acid. The hydrogen-bonded sheets of the centrosymmetric cocrystal are doubly interwoven (Fig. 2b).

Simulation of the X-ray powder diffraction pattern of this centrosymmetric cocrystal revealed it to be identical to the material that was obtained by liquid-assisted grinding of (theophylline)$_2$·(D-tartaric acid) and (theophylline)$_2$·(L-tartaric acid). That enantiomeric cocrystals of theophylline and tartaric acid react by grinding to form a centrosymmetric cocrystal is consistent with the observed solid-state behaviour of single-component enantiomeric solids. Consequently, cocrystals of (theophylline)$_2$·(D-tartaric acid)·(L-tartaric acid) could be considered a racemic form of (theophylline)$_2$·(D/L-tartaric acid).[15]

In contrast to theophylline, however, cocrystals of caffeine with either D- or L-tartaric acid were readily obtainable both by liquid-assisted grinding and by cocrystallization from solution. Single crystal X-ray structure analysis revealed the cocrystals were made up of caffeine and the chiral tartaric acid in equimolar amounts.¶ The structure of the cocrystals is characterized by sheets of tartaric acid, held together by O–H···O hydrogen bonds. The edge of each sheet was found to be decorated by molecules of caffeine, held to tartaric acid molecules through O–H···N bonds (Fig. 3).

Unlike the case of theophylline cocrystals, liquid-assisted grinding of cocrystals of caffeine with chiral tartaric acids (*i.e.* grinding (caffeine)·(D-tartaric acid) with (caffeine)·(L-tartaric acid)) did not provide a new cocrystal. Instead, the components of the two enantiomeric cocrystals recombined to form crystalline β-caffeine and crystalline DL-tartaric acid. In that way, both cocrystals have effectively been dismantled into the model API and the cocrystal former in the form of a racemate. As far as we know, this is the first example of a mechanochemical reaction through which a cocrystal can be dismantled, rather

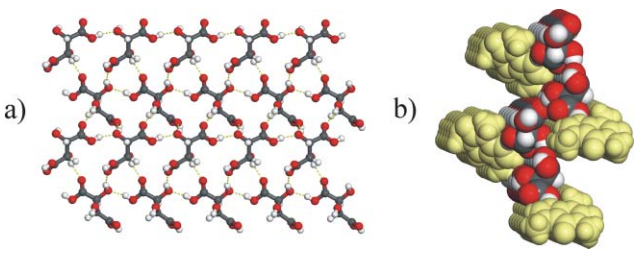
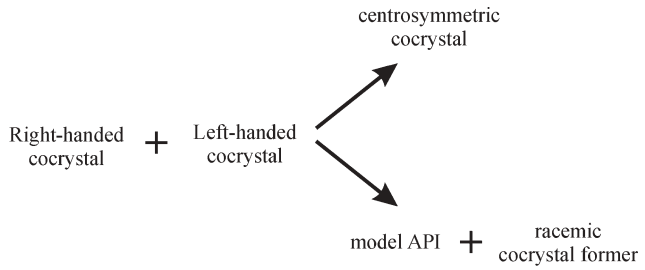


Fig. 3 Representations of a hydrogen-bonded sheet in the cocrystal of (caffeine)·(D/L-tartaric acid): (a) view perpendicular to the sheet, with caffeine molecules omitted for clarity; (b) view parallel to the sheet, with caffeine molecules shown in space-filling fashion.



Scheme 3

than assembled. The comparison of reactions involving pairs of enantiomeric cocrystals presented here allows us to delineate two distinct modes of cocrystal–cocrystal reactivity. In the first case, enantiomeric cocrystals react to form a centrosymmetric cocrystal. In the second case, the two enantiomers rearrange to provide individual cocrystal constituents (Scheme 3). Taking into account that a racemate is a two-component solid, then it can be stated that both observed cocrystal–cocrystal reactions have a common result of forming a centrosymmetric cocrystal.[16]

The inability of enantiomeric cocrystals of caffeine to form a centrosymmetric crystal on liquid-assisted grinding, as opposed to theophylline, led us to explore the solid-state reactivity of the two model APIs towards racemic DL-tartaric acid. As evidenced by X-ray powder diffraction, in both cases the liquid-assisted grinding of the model API with DL-tartaric acid provides an outcome identical to a cocrystal–cocrystal reaction between pairs of enantiomeric cocrystals. Specifically, theophylline and DL-tartaric acid yielded (theophylline)$_2$·(D-tartaric acid)·(L-tartaric acid), while in the case of caffeine no new crystalline phase was observed. Consequently, caffeine is able to differentiate between enantiomeric and racemic forms of a cocrystal former. Since neither the molecular or crystal structures of caffeine are chiral,[17,18] we assert that such discrimination is a result of a complex interplay of crystal packing forces rather than symmetry of the molecules involved. The assumption is supported by preliminary results that indicate caffeine forms a cocrystal with centrosymmetric *meso*-tartaric acid, as well as chiral and racemic forms of malic acid. Since theophylline forms a cocrystal both with chiral and racemic forms of tartaric acid, it is worth noting that the ability to discriminate between such forms of a cocrystal former has been brought about by simple methylation of a nitrogen atom in the model API.

In summary, liquid-assisted grinding provided evidence of two different cocrystal–cocrystal reactions involving enantiomeric pairs of cocrystals. Whereas the formation of a centrosymmetric solid from a pair of enantiomers is well-known in the context of single-component solids, we now provide evidence of such reactivity using cocrystals. On the other hand, we also provide the first observation of a mechanochemical reaction to dismantle a model pharmaceutical cocrystal by a cocrystal–cocrystal reaction involving cocrystals of opposite chirality. In that context, a chiral cocrystal of an API may be considered as a reagent to dismantle the cocrystal of opposite handedness. Whereas the examples of cocrystal–cocrystal reactivity reported herein are of largely academic importance, we foresee that the growing interest in cocrystals as pharmaceutical materials could provide practical significance to the understanding and control of such reactivity. With the intention to further explore the solid-state synthetic potential of liquid-assisted grinding and the possibility of establishing general rules of cocrystal–cocrystal reactivity, we are currently looking at further reactions involving model API compounds and chiral cocrystal formers.

Notes and references

‡ Crystal data for (theophylline)$_2$·(L-tartaric acid): monoclinic, $P2_1$, a = 8.9522(4) Å, b = 6.7582(5) Å, c = 18.876(1) Å, β = 100.685(4)°, χ_2 = 1.691, R_{wp} = 0.0619, R_p = 0.0468 and $R_{(Bragg)}$ = 0.0817. CCDC 620241. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b613073a

§ Crystal data for (theophylline)$_2$·(DL-tartaric acid): triclinic, $P\bar{1}$, a = 7.3102(1) Å, b = 8.3730(1) Å, c = 17.9724(3) Å, α = 98.294(1)°, β = 99.466(1)°, γ = 94.527(1)°, R_1 = 0.037 and wR_2 = 0.103 for 5302 reflections with $I \geqslant 2\sigma(I)$. CCDC 620242. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b613073a

¶ Crystal data for (caffeine)·(D-tartaric acid): orthorhombic, $P2_12_12_1$, a = 5.8024(1) Å, b = 10.0260(1) Å, c = 25.3674(4) Å, R_1 = 0.028 and wR_2 = 0.069 for 3218 reflections with $I \geqslant 2\sigma(I)$. CCDC 620243. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b613073a

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