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Mechanochemistry and co-crystal formation: effect of solvent on reaction kinetics†

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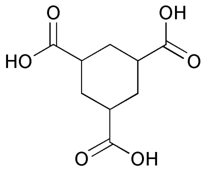
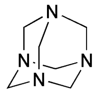
We demonstrate that significant improvements in kinetics of co-crystal formation by grinding can be achieved by the addition of minor amounts of appropriate solvent.

The synthesis of crystalline supramolecular structures mediated by hydrogen bonds is of considerable importance.[1–4] In the case of co-crystals, these are generally formed by dissolution and recrystallisation from a suitable solvent, although sublimation and growth from the melt are also used. The use of grinding a solid mixture has also been described. Solid-state grinding, *i.e.* the use of mechanical forces to create new molecular and supramolecular assemblies—mechanochemistry—can be regarded as an attractive and eco-friendly alternative route, avoiding the use of large amounts of solvent.[5–10] The utilisation of solid-state grinding, however, is limited. In certain instances, it is known that even though co-crystals are readily formed from solution, co-crystals are difficult to form even after extensive grinding.[11] Here, we report a significant increase in kinetics by the appropriate use of very small quantities of solvent.

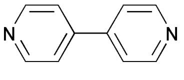
Several co-crystals of cyclohexane-1,3*cis*,5*cis*-tricarboxylic acid (**CTA**, $C_6H_9(COOH)_3$), the symmetry analogue of benzene-1,3,5-tricarboxylic acid ($C_6H_3(COOH)_3$, trimesic acid) which has been extensively employed as a building block in supramolecular chemistry,[12,13] have been synthesized using the solution-based method and their structures have been determined.[14]



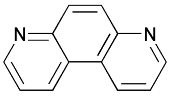
CTA



HTMA



Bipy



fPh

When a mixture of **CTA** and hexamethyltetramine (**HMTA**) are ground together in a ball mill for 20 min,[15] a distinct change in the powder X-ray diffraction pattern takes place.[16] Fig. 1 shows the powder XRD patterns of pure **CTA**, pure **HMTA** as well as the 1 : 1 mixture after 20 min grinding. Reflections associated with the reactants decrease in intensity while new reflections appear. The simulated powder pattern of **CTA·HMTA** (generated on the basis of its determined single crystal XRD structure[17]) and the pattern obtained show excellent agreement. The structures generated by grinding and from solution are, therefore, identical.

Co-crystallisation by simple grinding is, however, not always successful. The co-crystal structure of **CTA** and 4,4′-bipyridine (**Bipy**) has been determined by single-crystal X-ray diffraction analysis with co-crystals grown from MeOH solution.[18] When an equimolar mixture of **CTA** and **Bipy** is ground for 1 h, however, only partial reaction occurs. Reflections in the PXRD pattern of the ground sample associated with the original components are still clearly present. When the reaction of **CTA** and **Bipy** is repeated, however, but now with the addition of approximately 0.05 ml of MeOH,[19,20] co-crystallisation is found to be significantly accelerated such that complete conversion (as monitored by PXRD) is achieved in 20 min.†

For co-crystals of **CTA** and 4,7-phenanthroline (**fPh**), few reflections corresponding to the simulated **CTA·2fPh** PXRD pattern appear even after a considerable length of time grinding **CTA** with **fPh** (molar ratio of 1 : 2), despite the fact that the **CTA·2fPh** co-crystals can be readily obtained from MeOH solution. Fig. 2 shows the PXRD patterns of **CTA·2fPh** prepared by grinding with small amount of MeOH. After 5 min, reflections in the powder pattern associated with **CTA·2fPh** appear while the peaks matching the original reactants still remain but with diminished intensities. The observed PXRD pattern after 10 min is found to be very similar to the simulated PXRD pattern (Fig. 2(g)), and the reflections associated with **CTA** and **fPh** absent.

In order to rationalize how small amounts of solvent may influence the co-crystal formation, several different kinds of solvents have been tested. Water, in which **CTA** is very soluble but **fPh** only partially, is found to accelerate the reaction. Similarly, co-crystals were also formed by grinding using ethyl acetate in which **fPh** is soluble but not **CTA**. Acetonitrile, in which both **CTA** and **fPh** are only partly soluble, also accelerates the reaction. An important distinction, however, arises with cyclohexane—a liquid in which neither **CTA** nor

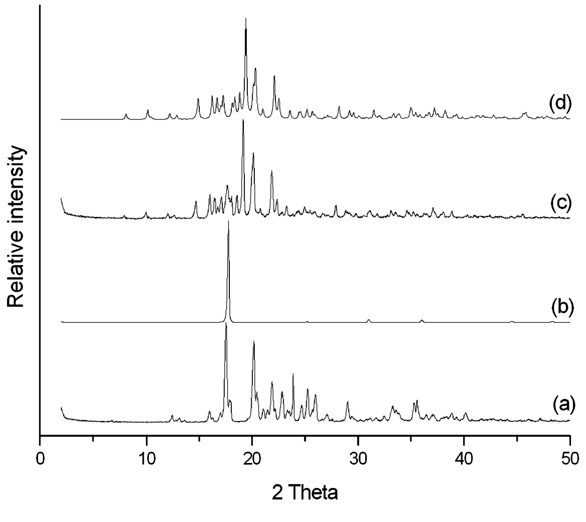


Fig. 1 Powder X-ray diffraction pattern of (a) **CTA**, (b) **HMTA**, (c) ground mixture of **CTA** + **HMTA** (20 min), (d) simulated pattern from single-crystal structure of **CTA·HMTA**.

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† Electronic supplementary information (ESI) available for PXRD profiles showing the grinding results for **CTA** + **Bipy** with and without solvent as well as **CTA** + 2**fPh** with different solvents. See http://www.rsc.org/suppdata/cc/b2/b207369m/

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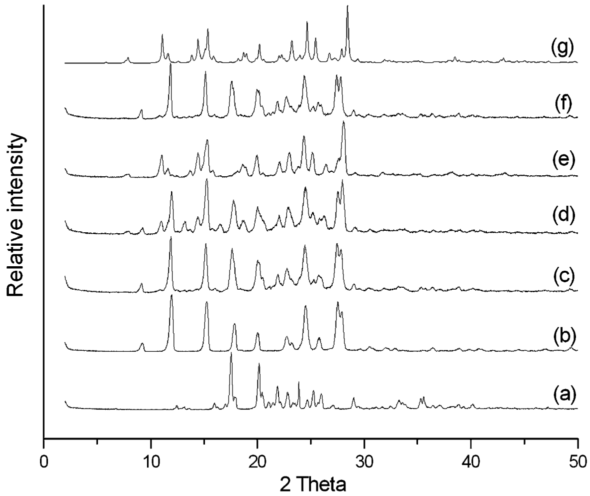

Fig. 2 Powder X-ray diffraction pattern of (a) **CTA**, (b) **fPh**, (c) ground dry mixture of **CTA** + 2**fPh** (1 h), (d) ground mixture of **CTA** + 2**fPh** with MeOH (5 min), (e) ground mixture of **CTA** + 2**fPh** with MeOH (10 min), (f) ground mixture of **CTA** + 2**fPh** with cyclohexane (1.5 h), (g) simulated pattern from single-crystal structure of **CTA.2fPh**.

fPh are soluble. In this case no kinetic enhancement is observed and no reaction occurs even after 1.5 hour grinding (Fig. 2(f)).

This paper reports the important observation that the addition of relatively minor amounts of a solvent can significantly enhance the rate of co-crystal formation. Whilst clearly of benefit to the organic solid-state chemists, it is likely to be of interest to all areas of chemistry where mechanochemistry methods are envisaged. The observed enhancement in kinetics might be rationalised by the additional degrees of orientational and conformational freedom open to molecules at the various interfaces as well as the enhancement of opportunities for molecular collisions. In addition, tiny co-crystal seeds may be envisaged to form within the solvent during the grinding process so that the rate of co-crystallisation can be increased. The choice of solvent used in grinding, therefore, should be one that is necessarily able to dissolve at least part of the original components. On the other hand, solid-state grinding involving small amount of solvents, might also be utilised to pre-test whether co-crystals can be synthesized from solutions. For instance, the co-crystal of **CTA** and phenazine, whose structure has not been reported in the Cambridge Structural Database[21] to date, cannot be synthesized from solution in our study. Interestingly, it cannot be obtained by grinding in the presence of various kinds of solvent either. Given the potential for tailoring solid-state properties *via* co-crystal formation, the use of small amounts of solvent allied with sample mechanical treatment may provide an important synthetic route in organic solid-state chemistry.

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15 Samples used for PXRD analysis were prepared using a Retsch MM 200 Mixer Mill, with oscillation frequency of 15 Hz. The mixtures used in grinding are *ca.* 200 mg in weight.

16 The PXRD pattern was recorded at room temperature using a Philips PW3710 diffractometer with Cu Kα radiation (λ = 1.5418 Å). Patterns were obtained using a 2-theta range of 2.00 to 50.00 degrees in increments of 0.02 degrees with a count time of 1.00 second per step.

17 Cerius,^{2} Accelrys Ltd., Cambridge, UK.

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19 All solvents introduced into the grinding system are *ca.* 0.05ml (2 drops from a pipette) in scale. The solvents have been evaporated at room temperature before the PXRD analysis.

20 **Bipy** and **fPh** are very soluble in alcohol (V. R. Lide, *Handbook of Chemistry and Physics*, CRC Press, Boca Raton, New York, 1997). In our test, **CTA** is found to be soluble in MeOH. The solubility of chemicals in different solvents is considered at room temperature.

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