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DEVELOPMENT OF LIQUID-ASSISTED GRINDING (LAG) FOR THE SYNTHESIS OF HYDROGEN-BONDED AND COORDINATION FRAMEWORKS

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Abstract

A brief overview is given on the use of the mechanochemical method liquid-assisted grinding as an alternative, clean and a rapid means to synthesise and screen for molecular inclusion and open frameworks based on hydrogen bonds and coordination bonds.

Introduction

Recent years have witnessed an explosion of interest in the use of mechanochemical methodologies [1] for chemical synthesis. Techniques based on grinding and milling have been successfully applied to the construction of diverse targets, ranging from organic molecules [2] and supramolecular assemblies [3] to metal-organic frameworks [4]. The principal reason underlying the sudden growth of interest in mechanosynthesis is the "green chemistry" aspect of developing faster, cleaner and more efficient approaches for the synthesis of molecules and materials [5]. Particularly, mechanochemical methods, such as neat grinding and liquid-assisted grinding (LAG) [6,7], provide significant advantages to conventional methods of synthesis in solution by avoiding elevated temperatures, large quantities of solvent, and providing desired products in short reaction times – frequently in quantitative reaction yields. In addition, mechanochemical methods are also likely to provide products that are difficult, or even impossible, to construct in solution [8]. We now provide a brief overview on the use of LAG (also known as solvent-drop grinding [9]) for the construction of molecular inclusion frameworks based on coordination and hydrogen bonds. In doing so, we will limit our review to the most recent contributions from our group in the context of metal-organic and organic host frameworks. For a broader overview of mechanosynthesis, we direct the reader to the recent excellent reviews [1,4].

Relevance of Mechanosynthesis to Cocrystals and Metal-Organic Frameworks

Whereas mechanosynthesis, i.e. the application of mechanical force to achieve a chemical transformation, has been extensively studied for transformations of covalent (e.g. carbon-carbon) bonds [2,10], its application to non-covalent interactions and metal-ligand coordination bonds became significant only recently.

Interest in the mechanosynthesis of non-covalent interactions, such as hydrogen [11] or halogen [12] bonds, has been inspired by the recognition of the role of cocrystals, i.e. multi-component molecular crystals [13], as novel functional materials. In particular, the ability to design cocrystals through the use of the supramolecular synthon [14] approach enables the construction, from molecular constituents, of cocrystals with interesting solid-state properties, such as optical [15], photo- [16] or thermo-reactivity [17], mechanical [18] or (semi)conducting 19] properties. Furthermore, the modular structure [20] of cocrystals allows the exchange of individual cocrystal components to modify a particular solid-state property in a systematic way. The most significant area of cocrystal application is in the context of pharmaceutical materials where cocrystal formation is recognised as an excellent alternative to salt formation in generating new pharmaceutical forms [21] of active pharmaceutical ingredients (APIs) with improved properties. Pharmaceutical cocrystals provide a particularly attractive area of application for mechanosynthesis, as grinding allows rapid screening for and synthesis of cocrystals, avoiding large quantities of solvent and elevated temperatures [22].

In the area of metal-organic frameworks (MOFs), the impetus to investigate the use of mechanochemistry for the construction of coordination bonds arises from the recent development of such three-dimensional (3-D) porous frameworks as designer materials for gas (hydrogen, methane) storage and catalysis [23]. Specifically, mechanochemical synthesis provides an attractive alternative to conventional, solvothermal methods that generally require high temperatures and pressures. Additionally, the use of grinding methods circumvents synthetic limitations imposed by the solubilities of reactant materials [24], in such a way as to allow the construction of porous MOF materials from less soluble, as well as less expensive starting materials, e.g. from metal oxides or carbonates as reactants [25,26]. Very recently, the application of liquid-assisted grinding to screen for coordination polymers [25] and for the construction of metal-containing derivatives of pharmaceutical compounds has been reported [27].

Neat vs. Liquid-Assisted Grinding

There are two important mechanochemical approaches that have been applied towards the construction of cocrystals and metal

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complexes: neat (dry) grinding and liquid-assisted grinding (LAG) [6,7]. Neat grinding consists of mixing the cocrystal components together and grinding them either manually, using a mortar and pestle, or mechanically, using a ball mill or a vibratory mill [6]. The LAG (or kneading [1]) technique requires the addition of a small (catalytic) amount [7] of a liquid to the grinding mixture. Originally, LAG was introduced as a means to increase the rate of cocrystal formation in the solid state, although it was soon established that it provided further benefits over neat grinding, including higher yield, higher crystallinity of the product, ability to direct specific polymorph formation and a significantly larger choice of reactants and products. Initially, the method was described as solvent-drop grinding, [9] but this name is no longer preferred, reflecting different ideas concerning the role of the liquid during grinding [28]. In the context of molecular materials, both neat and liquid-assisted grinding have been established as highly efficient methods to screen for cocrystals [22], salts [29] and polymorphs of pharmaceutical compounds [30]. Recently, liquid-assisted grinding of pairs of enantiomeric cocrystals has been introduced as a novel technique of cocrystal-cocrystal grinding for the synthesis and dismantling of cocrystals [31].

Characterisation of Products of Mechanosynthesis

For a product of a grinding reaction, the particle size usually prohibits structural characterization via single crystal diffraction. In some cases, however, the product obtained by grinding can also be formed by solution growth after testing a sufficient number of crystallization conditions. This allows the preparation of single crystals and structure determination by conventional single crystal diffraction methods. When grinding and solution synthesis consistently provide different products, it is sometimes possible to seed a supersaturated solution of the cocrystal components with the product of grinding [32], and induce the crystallization of the desired phase. Where solution growth and seeding experiments fail, recent advances in laboratory-based X-ray technology, data analysis software and structure solution algorithms [33] enable a fairly routine approach to crystal structure determination from powder data [34]. This approach can also be aided through crystal structure prediction (CSP) [35], as well as other techniques for solids analysis, e.g. CP-MAS NMR [36]. THz spectroscopy has recently been compared to PXRD and solid-state FT-IR in differentiating cocrystals of similar architectures [37].

Mechanosynthesis of Cocrystals and Metal Complexes

Cocrystal Mechanosynthesis

The ability to form molecular cocrystals [13] by grinding the individual components together has been known over a hundred years. Perhaps the earliest report of a neat grinding reaction to construct a hydrogen-bonded cocrystal dates from 1893, with the construction of the quinhydrone cocrystal by grinding together equimolar amounts of *p*-benzoquinone and hydroquinone (Figure 1) [38]. Quinhydrone is also most likely to be the first example of a cocrystal preorganized for a single-crystal-to-single-crystal chemical reaction, since its structure enables a reversible proton transfer to form the crystalline radical semiquinone [39]. However, the field of cocrystal mechanosynthesis first developed significantly through the efforts of Paul and Curtin [40] as well as Etter and co-workers [11,41], who demonstrated that supra-molecular synthesis in the solid state provides a degree of molecular recognition and a diversity of products that matched and, indeed, extended those observed in solution. In particular, the earliest reports that grinding can produce cocrystals that are not accessible from solution were provided by Patil *et al.* for the synthesis of quinhydrones [40], Toda and co-workers for the inclusion compounds of 1,4-naphthoquinone [42] and by Hollingsworth and co-workers who constructed urea inclusion compounds by grinding [43].

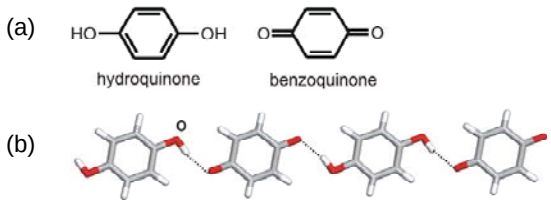


Figure 1. (a) Molecular diagrams of hydroquinone and benzoquinone and (b) fragment of a hydrogen-bonded chain in the hydroquinone-benzoquinone cocrystal

From the standpoint of molecular recognition and supramolecular chemistry, Etter and co-workers demonstrated that the assembly of adenine and thymine derivatives into hydrogen-bonded pairs can be achieved via solid-state grinding, as well as through a solution-based process.[41] The application of mechanochemical synthesis for the construction of multi-component hydrogen-bonded crystals of organometallic compounds has been extensively studied by Braga and co-workers.[1,44]

Investigation of the mechanism behind mechanochemical cocrystallisation, that was recently reviewed,[45] suggests that cocrystal formation via grinding can involve gas-phase transformations,[46] formation of an intermediate eutectic,[47] as well as partial or complete formation of an amorphous phase intermediate.[48] Overall, the increased efficiency of different grinding methodologies for cocrystal synthesis over solution-based approaches is most likely the result of avoiding the effects of solubility and solvent competition that affect solution crystallization.

Mechanosynthesis of Coordination Compounds

In contrast to mechanosynthesis of cocrystals, construction of coordination compounds by grinding is relatively new. In particular, the construction of a discrete, square-shaped, coordination complex by grinding the *cis*-protected platinum complex $Pt(NO_3)_2$(1,2-ethylenediamine) with 4,4'-dipyridyl (bipy) was reported by Orita *et al.* in 2002 (Fig. 2) [49].

Figure 2. Mechanochemical synthesis of a cationic molecular square, as reported by Orita *et al.* [49] For clarity, hydrogen atoms and anions have been omitted from the wireframe model

Moreover, grinding of an analogous palladium complex with a 1,3,5-tris(3-pyridyl)triazine ligand resulted in the solid-state self-assembly of a discrete hexanuclear molecular bowl. The construction of the molecular bowl was significantly more efficient by grinding than from solution, resulting in respective yields of 90 and 11 % after 10 minutes. A similar enhancement in the reaction yield was also observed in case of the molecular square. A particularly interesting application of mechanosynthesis to construct discrete metal complexes was recently presented by Braga *et al.*, who constructed two metal derivatives of the known API gabapentin by grinding the API with zinc and copper (II) chlorides [27].

Coincident with the work of Orita, Steed and co-workers reported the construction of a coordination polymer by grinding copper(II) acetate with 1,3-bis(4-pyridyl)propane[50]. Neat grinding resulted in the replacement of water molecules coordinated to the copper(II) acetate paddlewheel unit with pyridine groups, so as to form a one-dimensional (1-D) zigzag polymer (Fig. 3). The material obtained by grinding was found to be isostructural to the methanol inclusion complex of the same polymer, obtained by crystallization from solution. The isostructurality suggested that the water produced by the coordination of pyridine ligands to Cu^{II} ions remained included in the material as a guest [50]. Consequently, this mechanochemical reaction demonstrated not only the ability to construct extended architectures based on coordination bonds by grinding, but also that molecular inclusion can be achieved in the same manner.

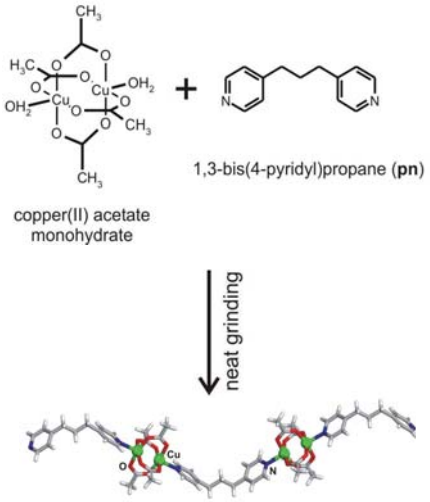


Figure 3. Mechanochemical construction of a 1-D coordination polymer, as reported by Belcher *et al* [50]

The ability to construct porous materials for molecular inclusion using neat grinding was demonstrated by Pichon *et al* [51] who utilized the mechanochemical reaction of copper(II) acetate with isonicotinic acid. In contrast to the coordination polymer synthesis involving 1,3-bis(4-pyridyl)propane (*vide supra*), the solid-state reaction of copper acetate and nicotinic acid resulted in ligand metathesis to form the three-dimensional (3-D) framework of copper(II) isonicotinate (Fig. 4). The reaction resulted in the formation of acetic acid and water byproducts, retained within the pores of the framework. The byproducts could be removed by heating to yield the porous evacuated material. A similar result was obtained by Pichon *et al.* in the reaction of copper(II) acetate and 1,3,5-benzenetricarboxylic acid. Neat grinding of the two substances resulted in the formation of the 3-D porous framework filled with molecules of water and acetic acid byproducts [51].

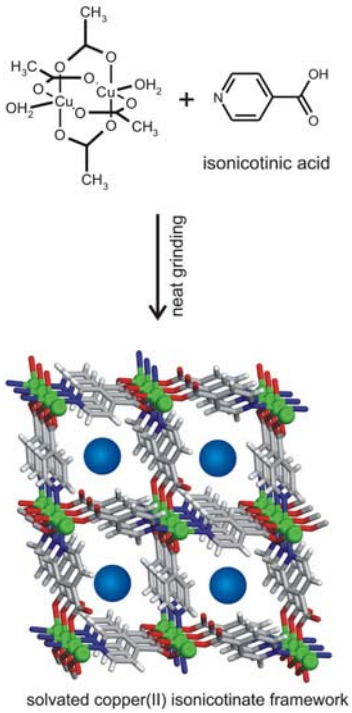


Figure 4. Mechanochemical construction of a porous 3-D MOF via neat grinding, as described by Pichon *et al* [51]

Mechanosynthesis using LAG

Cocrystal Mechanosynthesis

The addition of a small quantity of a liquid to the solid reaction mixture was found to significantly affect the course of cocrystal mechanosynthesis. The central benefit was identified as the liquid provided a notable accelerating effect [9]. Furthermore, LAG was also observed to lead to products more crystalline than those from neat grinding, as demonstrated by Nguyen *et al* [52] in a combined THz, PXRD and scanning electron microscopy (SEM) study of grinding cocrystallisation of phenazine and mesaconic acid. Neat grinding of the two cocrystal components for 60 minutes resulted in the maximum yield of the crystalline product of 55%. In contrast, addition of a few drops of either methanol, ethanol or *iso*-propanol resulted in the quantitative (100%) formation of the crystalline cocrystal. The liquid added to the reaction mixture in LAG can also exhibit a more profound effect on the course of mechanochemical reaction, as demonstrated by Trask *et al.* for the cocrystallisation of the model pharmaceutical compound caffeine and glutaric acid (Fig. 5) [53]. Grinding of the two components in the presence of cyclohexane resulted in the formation of the monoclinic form of the model pharmaceutical cocrystal (Form 1). In contrast, grinding with the addition of a small amount of chloroform produced the triclinic polymorph (Form 2). Cocrystallisation of glutaric acid and caffeine from a solution in chloroform produces both forms as concomitant polymorphs.

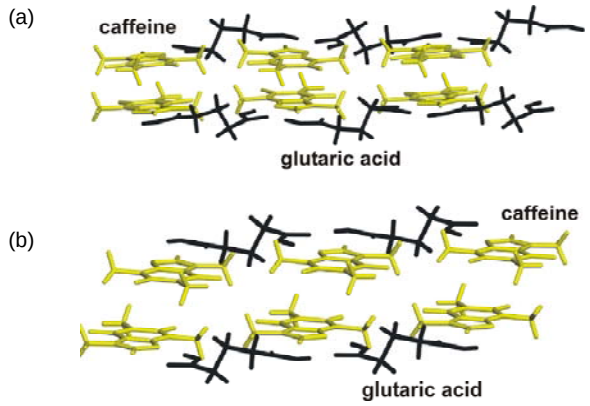


Figure 5. Fragments of crystal structures of the cocrystal of caffeine and glutaric acid (a) monoclinic polymorph obtained by cyclohexane LAG and (b) triclinic polymorph obtained by chloroform LAG, as reported by Trask *et al* [53].

The liquid added to the grinding experiment can also become incorporated into the final product. This was demonstrated by Karki *et al.* in the grinding reaction of the pharmaceutical compound theophylline and citric acid with the addition of a small amount of water [54]. LAG resulted in the formation of a three-component cocrystal hydrate, composed of mutually hydrogen-bonded molecules of theophylline, citric acid and water, in respective ratio 1:1:1 (Fig. 6)[54]. Interestingly, the same three-component material could also be obtained by neat grinding, by using the hydrated forms of either theophylline, or citric acid, or both, as the reactants.

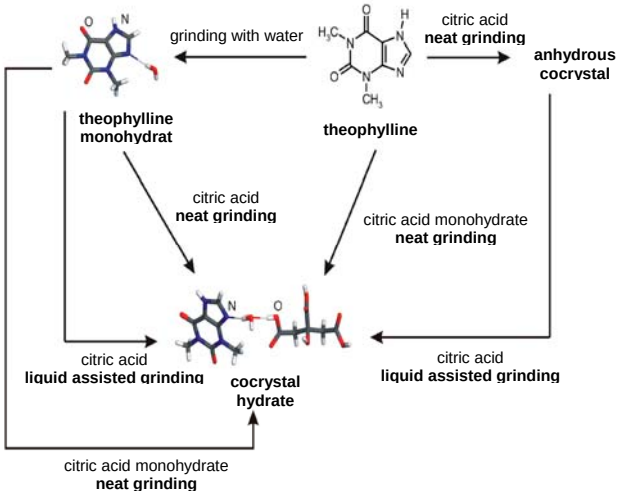


Figure 6. An overview of LAG and neat grinding reactions leading to the formation of a three-component crystal involving theophylline, citric acid and water (Karki *et al* [54])

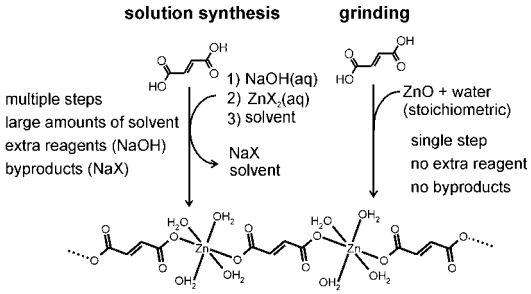
Coordination Polymers by LAG

The construction of coordination polymers using LAG was first demonstrated by Orpen and co-workers [55], who achieved the mechanochemical construction of a two-dimensional (2-D) sheet polymer by grinding together anhydrous cobalt(II) chloride ($CoCl_2$) with the bidentate bridging ligand 4,4'-dipyridyl (**bipy**) in the presence of a small quantity of ethanol. The reaction was also possible by neat grinding if cobalt(II) chloride hexahydrate was used as the precursor.

The addition of a small quantity of ethanol to the mixture of basic cobalt(II) carbonate and the hydrochloride salt of **bipy** enabled the LAG synthesis of the same coordination polymer, in a neutralisation reaction driven by the release of gaseous CO_2 [26].

Screening for Coordination Polymers using LAG

The ability to use a neutralisation reaction to drive mechanochemical synthesis of coordination polymers was combined with the ability to direct mechanochemical reactivity in LAG, so as to enable screening for different metal-organic architectures from the simplest metal precursors [25]. The use of a metal oxide reactant was expected to simplify the synthesis of a coordination polymer, as well as make it more environmentally friendly by avoiding additional reagents and solvents, as illustrated in Scheme 1 for a hydrated zinc fumarate polymer (Scheme 1).



Scheme 1. Comparison of a traditional solution-based synthesis of a coordination polymer with a LAG process involving a metal oxide [25].

LAG of zinc oxide with fumaric acid in the presence of methanol (MeOH) or ethanol (EtOH) was found to provide the anhydrous zinc fumarate polymer. Structure solution using PXRD data revealed zinc fumarate is a 3-D coordination polymer based on tetrahedrally coordinated zinc ions. In contrast, grinding of the same reactants in the presence of a 1:1 water:MeOH or water:EtOH mixture resulted in the formation of a previously unknown zinc fumarate dehydrate [25]. Structure solution from PXRD data revealed that the dihydrate is composed of 2-D coordination polymer sheets, based on octahedrally coordinated zinc ions, connected via O-H···O hydrogen bonds. Furthermore, grinding of equimolar quantities of ZnO and fumaric acid with either three or four equivalents of water resulted in the selective formation of the pure tetrahydrate and the pentahydrate, respectively, of the zinc fumarate polymer. Whereas the tetrahydrate is composed of linear 1-D chains of $Zn(H_2O)_4^{2+}$ ions bridged by fumarate ions bonded to the *trans*-positions of octahedrally coordinated zinc, the pentahydrate is a water inclusion compound of a zigzag variety of the same polymer, with fumarate ions bonded to the equatorial positions of $Zn(H_2O)_4^{2+}$ ions (Fig. 7). Crystallisation from solution provides both the tetrahydrate and the pentahydrate polymer [56].

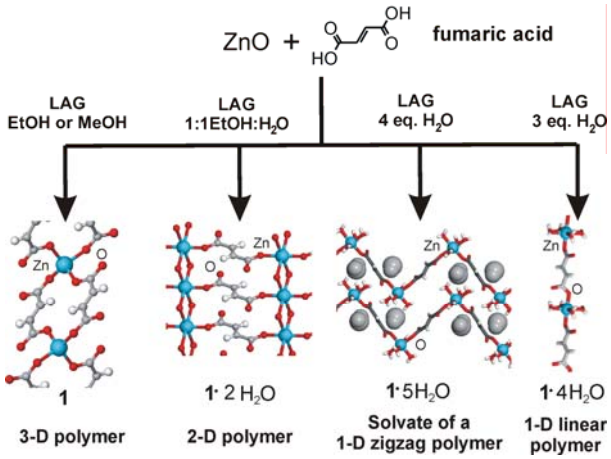


Figure 7. Screening for coordination polymers from ZnO, using LAG [25]

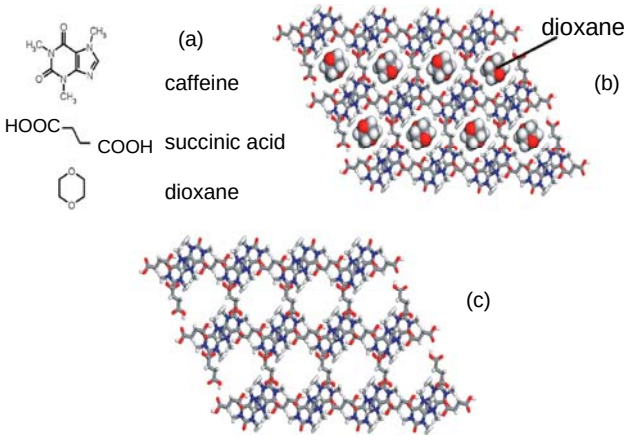


Figure 8. (a) Molecular diagrams of caffeine, succinic acid and dioxane; (b) fragment of the crystal structure of the (caffeine)·(succinic acid)·0.67(dioxane) ternary cocrystal and (c) the (caffeine)·(succinic acid) host, with guest molecules omitted for clarity [7]

Construction of Porous Frameworks via LAG

Overview

In addition to accelerating mechanosynthesis and controlling the polymorphic behaviour of the final product, the liquid added to the grinding reaction mixture provides an excellent means to induce the formation of porous structures. In such an approach, molecules of the liquid are expected to act as templates for the construction of a porous material and then be incorporated in the final product as losely bound guests. The following sections will discuss such LAG reactivity in the context of hydrogen-bonded cocrystals and metal-organic frameworks (MOFs).

Hydrogen-bonded frameworks

The ability to form porous structures using LAG was first indicated in grinding reaction of caffeine and succinic acid with the addition of a small amount of dioxane (Figure 8a).[7] Grinding resulted in the formation of a three-component solid, with the composition (caffeine)·(succinic acid)·0.67(dioxane). However, in contrast to the cocrystal hydrate obtained for theophylline and citric acid described earlier (Section 3.1.),[54] the structure of this dioxane solvate was found to consist of a two-component hydrogen-bonded framework of caffeine and succinic acid. The framework exhibited cylindrical channels of approximately 9 Å diameter that accommodated disordered molecules of dioxane (Figure 8b). That the dioxane molecules in the structure of (caffeine)·(succinic acid)·0.67(dioxane) are held only by weak van der Waals contacts suggested that this three-component cocrystal should be considered a lattice host-guest compound of a self-assembled two-component host framework (caffeine)·(succinic acid) (Figure 8c).[7] (caffeine)·(succinic acid)·0.67(dioxane) ternary cocrystal and (c) the (caffeine)·(succinic acid) host, with guest molecules omitted for clarity [7]

From this perspective, dioxane should be readily substituted with other molecules of similar shape and size. Indeed, substitution of dioxane with thioxane or nitromethane in the grinding mixture resulted in the formation of a material isostructural to (caffeine)·(succinic acid)·0.67(dioxane). Both ternary cocrystals could be obtained by crystallisation from liquid nitromethane or thioxane. Crystal structure analysis revealed inclusion of the two solvents within the same two-component framework as observed in (caffeine)·(succinic acid)·0.67(dioxane). The same three-component solid-state inclusion compound was subsequently obtained by LAG grinding with more than 20 guests that were liquids, solid, as well as gaseous at ambient conditions [7].

The versatility of the (caffeine)·(succinic acid) inclusion framework was also utilised to assess the relative efficiencies of neat grinding, LAG and crystallisation from solution in screening for hydrogen-bonded cocrystals. In this test, LAG has been demonstrated as the most efficient, providing a three-component cocrystal with 21 out of 30 potential guest molecules, while neat grinding was somewhat less successful (three-component cocrystal formation was observed in 16 out of 30 cases). The least efficient from a screening viewpoint was crystallisation from solution, indicating the formation of inclusion compounds in only 4 out of 30 test molecules (Table 1) [7].

In contrast to LAG, neat grinding of caffeine and succinic acid does not provide a cocrystal. Indeed, a simple two-component (binary) cocrystal of caffeine and succinic acid still remains to be synthesized. The comparison of the structure of (caffeine)·(succinic acid) inclusion host with the crystal structure of caffeine cocrystal with adipic acid [7,57] provided a rational as to why the formation of a three-component inclusion compound is preferred to the formation of a non-solvated binary cocrystal of caffeine with succinic acid. Both structures are composed of 1-D hydrogen-bonded polymers of the dicarboxylic (succinic or adipic) acid, with attached caffeine fragments. In case of adipic acid, the caffeine fragments of

neighbouring chains readily interdigitate to provide a close-packed structure. In contrast, the smaller length of the succinic acid molecules prevents complete interpenetration, resulting in cavities that enable guest inclusion to achieve a close-packed solid (Fig. 9).

Table 1. Efficiencies of solution crystallisation, neat grinding and LAG in the construction of ternary cocrystals involving caffeine, succinic acid and a guest. "Yes" and "No" indicate the formation, or lack thereof, of the ternary solid, respectively [7].

Guest	Guest state of aggregation	Solution	Neat grinding	LAG
	Liquid	Yes	Yes	Yes
	Liquid	Yes	Yes	Yes
	Liquid	Yes	Yes	Yes
	Liquid	No	Yes	Yes
	Liquid	Yes	Yes	Yes
	Liquid	No	No	Yes
	Liquid	No	Yes	Yes
	Liquid	No	Yes	Yes
	Liquid	No	Yes	Yes
	Liquid	No	Yes	Yes
	Liquid	No	Yes	Yes
	Liquid	No	Yes	Yes
	Liquid	No	Yes	Yes
	Liquid	No	Yes	Yes
	Liquid	No	Yes	Yes
	Liquid	No	No	No
	Liquid	No	No	No
	Liquid	No	No	No
	Liquid	No	No	No
	Liquid	No	No	No
	Solid	No	No	Yes
	Solid	No	No	Yes
	Solid	No	Yes	Yes
Ferrocene	Solid	No	No	No
	Solid	No	No	No

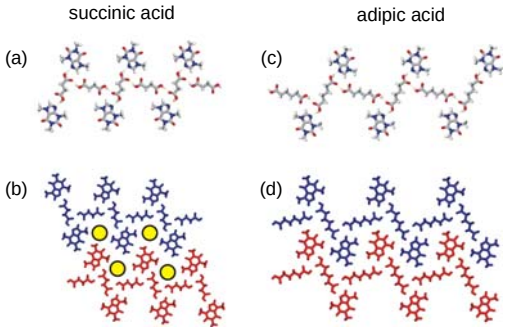


Figure 9. Rationalisation for the formation of ternary cocrystals involving caffeine and succinic acid. (a) and (b) 1-D hydrogen-bonded chains in the (caffeine)·(succinic acid) host and (caffeine)·(adipic acid) cocrystal, respectively; (b) and (c) assembly of hydrogen-bonded chains in the (caffeine)·(succinic acid) host and (caffeine)·(adipic acid) cocrystal, respectively. The remaining space for host inclusion is indicated by yellow circles [7,57]

Liquid Phase as the Template for the Formation of Porous Networks

Further exploration of potential guests for the (caffeine)·(succinic acid) framework lead to the discovery of a different inclusion framework.[58] This product was formed by grinding caffeine and succinic acid in the presence of chloroform. After considerable effort, the same material was obtained from solution in the form of single crystals. X-ray crystal structure analysis revealed a hydrogen-bonded framework of composition (caffeine)$_4$·(succinic acid) that exhibited channels filled with solvent $CHCl_3$ molecules. The channels of the (caffeine)$_4$·(succinic acid) framework have an irregular cross-section and are considerably wider than the ones in the (caffeine)·(succinic acid) framework, with approximate cross-section of approximately 14 Å × 7Å, that can fit two juxtaposed solvent molecules (Fig. 10).

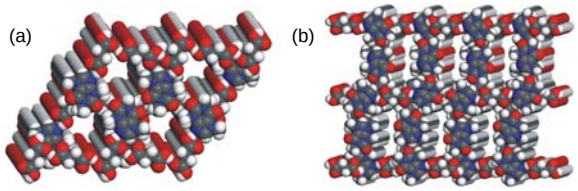


Figure 10. Space-filling models of inclusion hosts: (a) (caffeine).(succinic acid)[7] and (b) (caffeine)4.(succinic acid)[58]

In contrast to the (caffeine)·(succinic acid) framework, the chloroform guest in (caffeine)$_4$·(succinic acid) is attached to the inclusion channel walls through directional interactions. In particular, the $CHCl_3$ molecule is anchored to the channel wall through a weak (3.48 Å) Cl···N halogen bond interaction and a C-H···O hydrogen bond (3.02 Å) (Fig. 11(a)) [58]. Such attachment suggests that molecular recognition between framework constituents and guest molecules might play an active role in directing the formation of supramolecular frameworks. This was subsequently explored through LAG screening of a library of sixteen potential guest molecules, each

representing a different modification of the haloform structure (Scheme 2a).

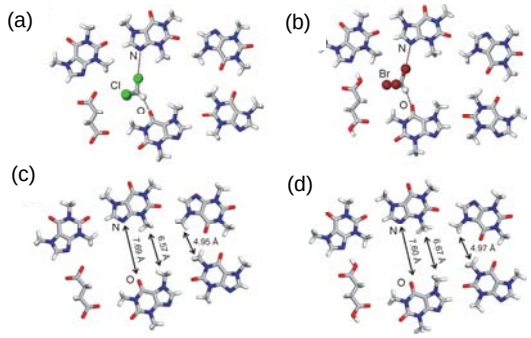
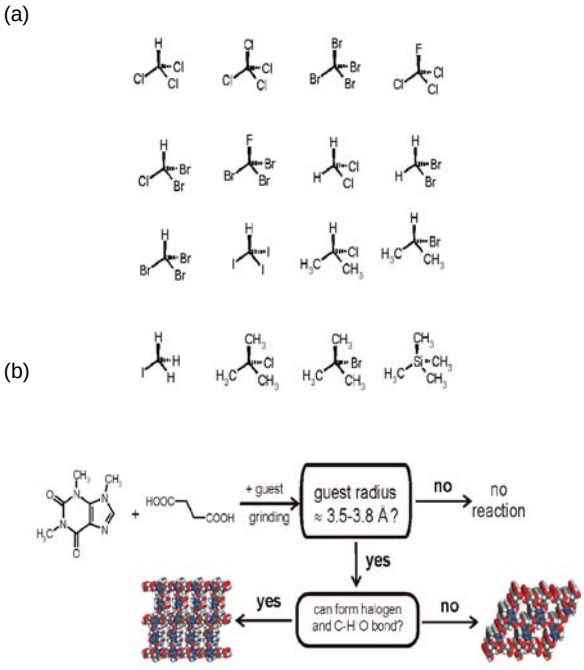


Figure 11. The bonding of chloroform (a) and bromoform (b) molecules in the channels of the (caffeine)$_4$·(succinic acid) framework; the dimensions of the channels in the (caffeine)$_4$·(succinic acid) host in case of $CHCl_3$ (c) and $CHBr_3$ (d) guest [58]

LAG screening of the library suggests two factors controlling the formation of different frameworks (Scheme 2b). First, the formation of any of the two frameworks is expected to occur only if the guest radius is in the range 3.5-3.8 Å. Second, the existence of a halogen atoms and a considerably acidic C-H group in the guest structure is expected to template the formation of (caffeine)$_4$·(succinic acid) framework. Absence of such groups will result in the formation of (caffeine)·(succinic acid) inclusion compounds (Scheme 2b).



Scheme 2. (a) Library of molecules employed to screen for the formation of different inclusion hosts of caffeine and succinic acid and (b) structural guidelines that determine the formation of a particular hydrogen-bonded host, established via LAG screening [7,58]

Crystal structure analysis of the (caffeine)$_2$·(succinic acid) inclusion compound with bromoform, $CHBr_3$, further confirmed the role of C-H···O and halogen bonding interactions in anchoring the guest molecule within the framework channels. Namely, the higher halogen-bonding propensity of bromine resulted in a stronger Br···N halogen bond (3.20 Å). The stronger interaction resulted in the shrinking of the inclusion channel diameter relative to the chloroform inclusion compound, despite the larger diameter of the bromoform guest (Fig. 11 (b)-(d)).

The Role of Supramolecular Shape in the Formation of Two-component Hydrogen-bonded Iinclusion Frameworks

The comparison (caffeine)$_4$·(succinic acid) [58] and (caffeine)·(succinic acid) [7] host structures revealed a more general interpretation of reasons for molecular inclusion. Both inclusion hosts exhibit a common structural motif, the hydrogen-bonded assembly (caffeine)$_2$·(succinic acid) (Figure 12). Structurally, this assembly resembles the ones observed in the cocrystal of caffeine and oxalic acid, that is readily made and does not exhibit inclusion properties. However, the higher length of succinic acid results in a more pronounced "wheel-and-axle" shape. Such shape is known to prevent the formation of close-packed structures [59], leading to the formation of solid-state host-guest complexes [60,61].

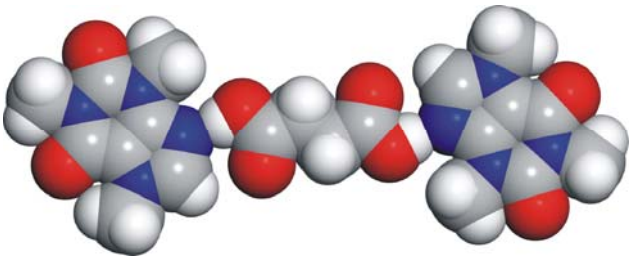


Figure 12. A space-filling representation of the "wheel-and-axle"-shaped (caffeine)$_2$·(succinic acid) assembly.[7,58]

Construction of metal-organic frameworks via LAG

Introduction

The ability to achieve molecular inclusion in coordination compounds through grinding was first demonstrated by Braga *et al* [62] who conducted the mechanochemical reaction of 1,4-diaminocyclohexane with copper(II) chloride to produce a 1-D coordination polymer Cu(1,4-diaminocyclohexane)Cl_2. Kneading of the reactants with water or S,S-dimethylsulfoxide (DMSO) resulted in the formation of a layered solid composed of alternating layers of solvent and juxtaposed 1-D chains of Cu(1,4-diaminocyclohexane)Cl_2. The sheet structure of this inclusion compound was compared to the sheet structure of clay minerals. Indeed, heating of the inclusion compound resulted in the removal of included solvent to product a material composed of polymer sheets. Kneading of the desolvated material, followed by suspension in a liquid resulted in the formation of sheet inclusion compounds with over 20 liquid guests, further augmenting the similarity to clays (Fig. 13).

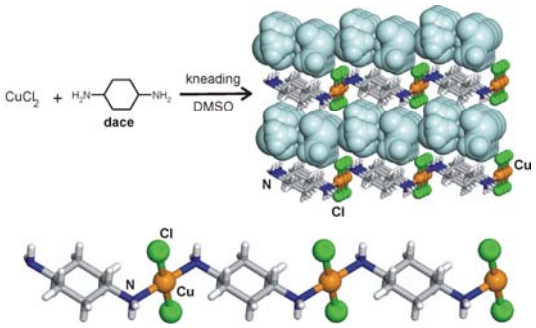
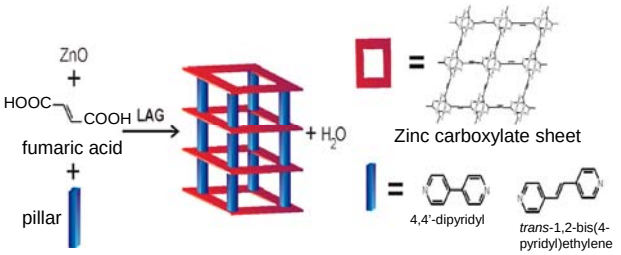


Figure 13. (a) Mechanosynthesis of a metal-organic clay mimic by kneading copper(II) chloride and dace with DMSO (or water) and (b) a single chain of Cu(**dace**)Cl_2 polymer [62]

Although this example does not illustrate the formation of a 3-D porous inclusion framework, it nevertheless demonstrates the ability to *in situ* include liquid molecules into the mechanochemically constructed metal-organic material.

Mechanochemical Construction of MOFs Directly from the Metal Oxide

The formation of a 3-D porous framework using LAG was achieved in the mechanochemical reaction of zinc oxide, fumaric acid and a bidentate bridging ligand, such as 4,4'-dipyridyl or *trans*-1,2-bis(4-pyridyl)ethylene (Scheme 3) [25]. Grinding of these three components in the presence of DMF resulted in the quantitative formation of a pillared MOF material, consisting of two-dimensional (2-D) sheets of zinc fumarate coordination polymer, pillared by bridging ligands.



Scheme 3. The formation of pillared MOFs from zinc oxide, using LAG [25]

The MOF obtained by using 4,4'-dipyridyl as the bridging ligand, Zn_2(fumaric acid)$_2$(4,4'-dipyridyl), was readily identified through its PXRD pattern, that corresponded to the one calculated from the known crystal structure[63] of the MOF with DMF guest included (Fig. 14(a)).

The MOF based on *trans*-1,2-bis(4-pyridyl)ethylene, Zn_2(fumaric acid)$_2$(*trans*-1,2-bis(4-pyridyl)ethylene), has not been constructed before. However, the PXRD pattern resulting from the LAG synthesis suggested isostructurality to the known copper(II) derivative [64]. Consequently, the structure of the previously unknown MOF Zn_2(fumaric acid)$_2$(*trans*-1,2-bis(4-pyridyl)ethylene) was solved and refined from PXRD data, using the copper analogue as the starting model (Fig. 14(b)) [25].

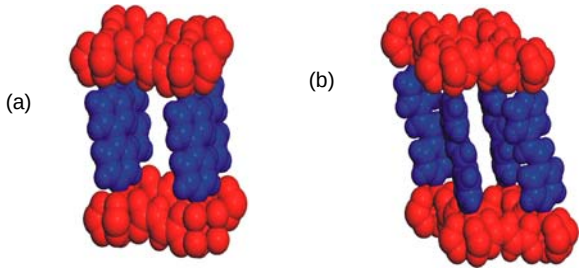


Figure 14. Fragments of the porous MOF structures: (a) Zn2(fumaric acid)2(4,4'-dipyridyl) and (b) Zn2(fumaric acid)2(trans-1,2-bis(4-pyridyl)ethylene). Zinc carboxylate sheets are shown in red, and bis(pyridine) pillars in blue

The MOFs prepared by 20 minutes grinding exhibited high crystallinity, demonstrated by the sharpness of the diffraction peaks, as well as SEM imaging that revealed crystallites with well-developed morphology and dimensions between 200 nm and 500 nm. In addition to DMF, both MOFs could be prepared directly from ZnO by grinding in the presence of small quantities of methanol, ethanol or *iso*-propanol, in that way inferring a more environmentally-friendly nature to the MOF synthesis process.[25] In all cases, the obtained MOF materials could be desolvated, without the collapse of their porous structure, by heating to 150 ^{o}C. Consequently, the application of LAG provided a route to construct porous MOFs with notable advantages to conventional synthetic methods: LAG avoids large amounts of solvents, high temperatures and pressures inherent to solvothermal synthesis, and also permits the construction of complex materials directly from a metal oxide, in that way avoiding the formation of acidic byproducts or additional neutralisation reagents.

Conclusion

We have provided a brief review of our own explorations in using small amounts of a liquid phase to enhance and steer the course of grinding reactions. But even by placing the focus of our review onto a limited subject, such as the role of a liquid phase in directing the formation of porous structure, we feel that this contribution provides plenty more questions than it does answers. To a certain extent, this can be explained by the fact that the application of mechanochemistry to molecular systems is very recent and, hence, a lot of fundamental questions regarding the mechanism and scope remain to be answered. In that sense, the pace of development of mechanochemistry, illustrated by the diversity of targets that have been constructed mechanochemically with equal, or better, success than by using conventional methods is impressive. Such rapid development is most likely the result of simplicity of the method and the speed through which different mechanochemical syntheses can be designed, conducted and evaluated. Indeed, perhaps the best advertisement for mechanochemical methods is the pace of its development, that promises that methodologies based on grinding will continue to play an increasingly important part of chemical synthesis in the future. We see liquid-assisted grinding as a central part in such development. Indeed, this expectation is confirmed by the recent development of methods for the rapid synthesis and screening of highly porous pillared MOFs and zeolitic imidazolate frameworks [65], as well as the synthesis of bismuth salicylate metallodrugs [66].

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