Mechanochemistry: new and cleaner synthesis

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1. Introduction

1.1 General aspects

'Mechanochemistry' refers to reactions, normally of solids, induced by the input of mechanical energy, such as by grinding in ball mills. It is becoming more intensely studied partly because it can promote reactions between solids quickly and quantitatively, with either no added solvent or only nominal amounts. Historically it has been a sideline approach to chemical synthesis, and solution-based methods have been adopted by default. However, mechanochemistry could in future become a more mainstream technique for two reasons. Firstly, it is increasingly clear that is effective, and even advantageous, in ever-widening types of synthesis. Secondly, our current dependence on solvents appears increasingly unsustainable[1] since it is wasteful of fossil-derived materials (e.g. 85% of chemicals used in the pharmaceutical industry are solvents and even if recycled typical recovery rates are only 50-80%[1b]), environmentally problematic, hazardous and energy-demanding with regard to solvent production, purification and recycling.[2]

Here we provide a broad but digestible overview of mechanochemical synthesis (sometimes called *mechanosynthesis*) including the current state of the art, as well as opportunities and challenges to it becoming a mainstream synthetic technique. The review also covers industrial aspects, inorganic materials, cocrystals, pharmaceutical applications, organic synthesis, discrete metal complexes, extended metal-organic materials (MOFs) and characterization methods. It is aimed to be accessible to any chemist or engineer who has no prior knowledge of the subject.

1.2 A brief history

According to Takacs, the earliest documented mechanochemical reaction may have been grinding cinnabar with acetic acid in a copper vessel to give elemental mercury (4th century BC). This may also be the first documented method to obtain an elemental metal from a compound.[3] Another early reference point is a statement of Aristotle's, translated as 'no reaction proceeds in the absence of solvent'.[4] Presented in this way, his statement runs counter to the ease of many solventless mechanochemical reactions. However, an alternative translation, which is less specific and less contentious, is simply that 'liquids are the type of bodies most liable to mixing'.[5] In the middle ages mechanochemistry was also used in mining and metallurgy, further references to which can be found in ref.[6]

Michael Faraday conducted mechanochemical experiments, reducing AgCl to Ag with Zn, Cu, Sn or Fe in a pestle and mortar (1820).[7] However, it was work by Carey Lea in the 1890s which showed that mechanochemical reactions could give different products to thermal ones – favouring decomposition of mercury and silver halides to their elements rather than melting or sublimation.[8] This work can be seen

as the point at which mechanochemistry became a truly distinct sub-topic within chemistry. Wilhelm Ostwald (1853-1932) is credited by some with classifying mechanochemistry as one of four sub-disciplines of chemistry (alongside thermochemistry, electrochemistry and photochemistry) each based on a different type of energy input.[6a] According to Fernandez Bertran,[9] Walther Nernst (1864-1941, one of Ostwald's students), also advocated this classification. An early solvent-free organic mechanochemical reaction, probably a cocrystallization, comes from 1893 by Ling and Baker,[10] and during the 1920s research was done into reactions of organic polymers such as cellulose.[6a] However, where soluble reactants are concerned (generally speaking, molecular synthesis) solution-based reactions have been the default approach throughout the development of synthetic chemistry, and mechanochemistry has been limited largely to insoluble inorganic materials, such as alloys and metal oxides, i.e. perhaps employed only when there was no solvent-based alternative. Molecular mechanochemistry, particularly cocrystallization, developed significantly in the 1980s and 90s (Curtin, Paul,[11] Toda,[12] Etter,[13] Jones,[14] Hollingsworth[15] and Caira[16]). These studies showed that mechanochemistry was not only a general way to make cocrystals, but also that it could give products not obtainable by solution-based methods. Regarding *covalent* organic synthesis, in the 1980s and 90s Toda demonstrated several solvent-free reactions between solids,[17] although these often involved grinding followed by heating and may occur via molten phases.[18] Reports focusing on organic synthesis in ball mills have been scarce until recently.[19] In the areas of organic, metal-organic,[20] and supramolecular synthesis (including cocrystals)[21] the types of mechanochemical reactions done and the products obtained have broadened greatly in the last ten years. The methodology has also become more sophisticated. This more contemporary work is the focus of Sections 2-9.

1.3 Terminology

The term mechanochemistry is frequently used in a broad sense, covering *any* chemical reaction induced mechanically (e.g. by grinding etc.).[22] This is the sense in which it is used in this review. It has been argued elsewhere that this broad usage is incorrect,[19c] and that it should be used when mechanical energy directly ruptures strong bonds (for example in polymers, or indeed in single molecules[23]). This generates reactive centres (often radicals) which undergo further reactions. This more restrictive use of the term would exclude grinding reactions which may proceed largely due to an increase in the contact surface area between reactants (as the particles become smaller and more intimately mixed). IUPAC defines a mechano-chemical reaction (with hyphen) as a 'Chemical reaction that is induced by the direct absorption of mechanical energy' with a note that 'Shearing, stretching, and grinding are typical methods for the mechano-chemical generation of reactive sites, usually macroradicals, in polymer chains that undergo mechano-chemical reactions'.[22] Whilst the note gives guidance for its use in the context of polymers, the basic definition is broad and without restrictions as to the atomic-scale mechanism. Therefore, the general use of the term does appear justified.

Grinding is a general term describing mechanical action by hard surfaces on a material, normally to break up the material and reduce its particle size. It may therefore refer to manual methods (mortar and pestle) or non-manual methods such as ball milling, or extrusion etc. However, further terminology is associated with grinding solids in the presence of liquids. Very small amounts of added liquid can dramatically accelerate, and even enable, mechanochemical reactions between solids. Often the molar equivalents added are similar to those of the reactants themselves. Such reactions are therefore 'minimal solvent' rather than strictly 'solvent-free'. The original term to describe them, 'solvent drop grinding', has been superseded by 'liquid assisted grinding', (LAG) so as not to presuppose the role of the liquid (i.e. solvating or non-solvating). LAG is equivalent to the term 'kneading', also used in the same context. [21, 24]

There can also be confusion over what is meant by 'solvent-free'. Firstly, mechanochemistry and 'solvent-free' are not synonymous since mechanochemistry can be done in the presence of solvents. Even so, there remains more than one connotation of 'solvent-free'. It may indicate simply that no solvent was *intentionally* added to the reaction, e.g. stressing a practical advantage of the approach. However, in interpreting how such reactions proceed mechanistically (particularly how fluidity arises), it may be wrong to think of such a reaction as entirely solvent-free. Solvents can be present in the solid starting materials, such as in hydrated metal salts or in molecular solvates. There may even be (smaller) amounts of moisture in non-formally hydrated materials or in the atmosphere which aid the reaction. Further, species such as water, acetic acid etc. may be generated as condensates. Therefore, whilst use of the term 'solvent-free' is often accurate in a practical sense, care must be taken when making mechanistic interpretations.

In the same general context, while a reaction in itself may be described as 'solvent-free' (in the practical and/or mechanistic sense), purification may still be needed and this *may* require a solvent. Therefore a solvent-free reaction does not necessarily correspond to a solvent-free process overall (see also Section 10).

1.4 Mechanistic aspects

Mechanistic studies do not reveal a straightforward, or as yet complete, picture. The situation is complicated by the diversity of reaction types, reaction conditions and reactive materials (from metals and metal oxides to molecular crystals etc.). The difficulties of directly observing materials undergoing mechanochemical reactions at microscopic or molecular levels and the lack of studies of some reaction types are further factors. Each mechanistic model developed has a limited area of applicability, whilst more than one may apply to a given reaction. Here, we give an overview of the models developed, organized by the type of material undergoing reaction.

Most work has been done with inorganic materials (metals and metal oxides for example). Several models have been developed as discussed in ref.s [6a] and [25]. Those most widely referred to are hot spot theory and the magma-plasma model.

Hot spot theory originally developed by considering frictional processes between two surfaces sliding against each other. Small protuberances cause plastic deformations associated with dramatic raising of local (within ca. 1 μm^2) temperatures to above 1000^oC for short periods (10^{-3} – 10^{-4} seconds). More brittle (less plastic) materials would tend to crack under strain.[25] However, in brittle materials, hot spots can also occur at the tips of propagating cracks where local temperatures are thought to reach several hundreds or thousands of degrees Celsius for very brief periods.[6a, 25] There is experimental evidence for such high temperatures in the form of gaseous decomposition products from cracking crystals of metal azides as well as organic compounds such as $C(CH_2NO_3)_4$[25-26] and glucose.[6a]

The magma-plasma model arose from considering direct impacts rather than lateral frictional processes. It proposes that local temperatures greater than 10^4 ^oC, can be generated at impact points, associated with transient plasmas and the ejection of energetic species including free electrons. This model also was developed largely in the context of extended inorganic materials.[6a]

It seems unlikely that hot spots and magma-plasma sites are the *primary* sites of reactivity in *molecular* organic and metal-organic mechanochemical reactions. If they were, extensive decomposition would be expected. That such decomposition is not seen suggests that these phenomena may be too brief and/or too localized to be the primary reactive sites for molecular organic reactions. It is still possible that they do occur in molecular reactants under mechanochemical conditions and that they contribute to general frictional heating as the localized energy dissipates. Related to such dissipation, but again in the context of inorganic materials, a hierarchical system has been developed delineating several different processes, each with an associated timescale, which can occur under mechanochemical conditions following impacts or frictional processes.[6a] What would seem most relevant to common ball milling reactions of molecular reactants are the temperatures, pressures and processes occurring over larger areas of ca. $1mm^2$ as the ball impacts against reactants on the side of the vessel. However, models and measurements over these larger areas have not yet been applied to molecular synthetic reactions to our knowledge.

Mechanistic studies of cocrystal formation have recently been reviewed.[21] The models developed are different to those described above. On one hand, this distinction can be traced to the inherently different natures of the types of reactants, with molecular crystals being generally softer and more mobile on molecular scales. On the other, this also derives from the fact that the reaction conditions studied are not always actually mechanochemical (and therefore they may not explicitly consider the formation of hot spots). Work from several groups has been summarized under three generic mechanisms,[21] specifically i. molecular transport across surfaces,[27] through the vapour phase,[27-28] or through the bulk of a crystal,[29] ii. formation of liquid eutectic intermediate phases,.[30] and iii. reaction *via* an amorphous

intermediate phase.[31] The first relates to molecules only loosely held in their lattices, with, for example, significant vapour pressures (e.g. naphthalene).[27] The second relates to reactants which have low melting points or reaction mixtures which may form low-melting eutectics such as the diphenylamine-benzophenone mixture.[30] The third relates to molecules relatively strongly held in their lattice positions (e.g. through substantial hydrogen bonding) but whose reactivity is increased under mechanochemical conditions by forming amorphous phases. An example is grinding carbamazapine with saccharin to form a pharmaceutical cocrystal.[31] In the context of these three mechanisms, it is relevant to note the physical effects which grinding can have on molecular crystals. These include i. breaking down particles to smaller sizes, giving greater surface area and breaking up any product coating layers to expose fresh surfaces, ii. intimate mixing of reactants, iii. introducing defects and eventually amorphization of the material, and iv. frictional heating, both local and bulk. These physical effects can enable or accelerate each of the three mechanisms described above.

Liquid-assisted grinding (LAG) can accelerate cocrystallisation reactions and give products of higher crystallinity compared to neat grinding. LAG therefore seems to provide greater molecular mobility than does neat grinding. Although the term *liquid*-assisted grinding does not presuppose that the liquid added plays the role of solvent, correlations of reactivity with reactant solubility have been noted in some cases.[32] The nature of the added liquid can also determine the product obtained (without being included within it), again suggesting that solvation (and therefore solubility effects) can be significant.[33] Regarding molecular scale rearrangements, some crystalline intermediate phases have been observed and structurally characterised.[34]

Organic reactions in which covalent bonds are formed have been suggested to occur principally, or even exclusively, through bulk liquid eutectic states.[18] This mechanism is analogous to the second cocrystallisation mechanism described above. However, in some cases (certain Knoevenagel reactions under temperature-controlled ball milling,[35] and organic disulfide metathesis reactions[36]) it has been asserted that there was no bulk melt and the reaction was solid state. Further and broader studies of covalent organic reactions would be very valuable in giving a definitive view of the possible transport mechanisms, in particular how generally this type of reaction can proceed via bulk solid phases. However, the possibility that the eutectic mechanism is more dominant in covalent bond-forming reactions than in cocrystal-forming processes would be consistent with some inherent differences between these two reaction classes. In particular, covalent bond forming reactions are more likely to exhibit greater exotherms, to eliminate liquid or low-melting byproducts, and to have additional reactants present (bases, acids etc). Each of these aspects increases the potential of forming low-melting eutectic intermediate phases. In the solid state Knoevenagel reactions described above the condensate water is believed to be taken up by the crystals of the product.[35]

Mechanistic studies of metal-organic reactions are relatively sparse. This is also a highly diverse class of reactions. For example, the metal-containing reactant may be an extended covalent metal halide,

pseudohalide or oxide, a hydrated/non-hydrated ionic salt or a neutral molecular species. The bond enthalpies involved (and by inference the magnitude of any exotherm) and the labilities of reactants also span very wide ranges. With more labile, molecular examples, the reactions may share mechanistic similarities with cocrystallisations. In fact, coordination polymers can interconvert under liquid-assisted grinding (LAG) via crystalline intermediate phases – behavior which is reminiscent of mechanochemical cocrystallisations.[37] In studies of LAG reactions of Cu(SCN) complexes, the rate of reactant diffusion in a liquid inter-particle zone has been predicted to be extremely sensitive to the particle size (inversely proportional to the cube of the particle diameter). If the added liquid can dissolve one or both of the reactants, the very high speed of diffusion enabled by small particles may explain the fact that reactions between preground reactants merely placed in contact in the presence of a small amount of the liquid can also proceed at appreciable rates.[38] In reactions involving highly hydrated metal salts, or the elimination of condensates such as water or acetic acid, the presence of such 'internal solvent' naturally invites comparison with LAG reactions. The quantities of such internal solvent are similar to the amounts of liquids normally added in LAG. In fact, the generally high mechanochemical reactivity of metal acetates with carboxylic acids (favoured by the release of acetic acid as internal solvent) and the accelerating effects of water of crystallization have been noted.[39] Further, at least one reaction ($Cu(OAc)_2.H_2O$ + $NC_5H_4CO_2H$) which eliminates acetic acid as a condensate has been noted to be self-sustaining following a brief initiation by grinding.[40] This behavior is closely related to the Cu(SCN) system in which reactions between preground reactants merely placed in contact with a small amount of added liquid also proceed without further grinding.[38b] Whilst some metal-organic complexation reactions can give the product as a paste, which dries to a free-flowing powder after exposure to air (suggesting a eutectic-type mechanism is possible),[39] others appear to remain as free-flowing powders throughout the reaction.[39-40] With the less labile metal-ligand systems based on stronger bonds, there may be closer mechanistic similarities with covalent organic reactions. However, there are relatively few studies of the more inert systems. Possibly the least labile system studied is the reaction of $PtCl_2$ (a covalent polymer) with PPh_3 to give $PtCl_2(PPh_3)_2$, and the reaction of $PtCl_2(PPh_3)_2$ with K_2CO_3 to give $Pt(CO_3)(PPh_3)_2$.[41] The latter reaction is thought to be truly solid state because of the high melting points of the reactants compared to estimated local temperatures generated in the ball mill.

Overall, there is still clearly some way to go to obtain a cohesive and comprehensive picture of the mechanisms of mechanochemical reactions. Further progress is likely to require carefully designed experiments which can provide key insights, as well as a larger body of general observations on which to draw. In this regard, as mechanochemical synthesis continues to develop, it will be helpful to report and study reactions which do *not* proceed under any given mechanochemical conditions as well as those that do.

2. Industrial aspects of mechanochemistry

2.1 Introduction

The need for sustainability brought about by the Kyoto Treaty and the global demand for increasing numbers of products will inevitably lead to an increase in sustainable manufacturing processes which have lower environmental demands.[42] Increased sustainability can take the form of lower energy use, reduced waste, less organic solvents and improved selectivity. Big improvements have been made recently in solvent usage in several pharmaceutical processes.[43] The manufacture of Viagra (sildenafil) was improved to reduce solvent usage from 1700 to 7 l/kg.[44] A new route to metal oxides developed by Süd Chemie replaces dissolution in nitric acid followed by base precipitation with a mild aerobic treatment of the metal in aqueous carboxylic acid, reducing the process water by 95%.[45] Mechanochemical methods offer solvent-free (or minimal solvent) routes to industrial materials and are therefore of great interest in devising more sustainable processes.[9, 46] The potential to access materials not available by other methods is also of great interest.

2.2 Overview of patent activity

Figure 1a shows the growing number of patents filed per year that contain in the full description either of the terms “mechanochemistry” or “mechanochemical”.[47] There is little activity up to the mid 1980s at which point there is a dramatic increase. The plot also shows a slowing-off of overall activity since 2005, which merits a more detailed analysis. Patents are classified according to International Patent Classification Codes (IPC) designated by the World Intellectual Property Organization (WIPO), [48] which relate to the field of application and the types of inventions etc. and are used here in the four-character form. Figures 1b-i show the patent activity broken down into eight areas: (1b) A61K (medical and personal care); (1c) H01L (semiconductors and solid state devices); (1d) H01M (mainly batteries); (1e) C01B (compounds of non-metallic elements); (1f) B01J (catalysis); (1g) C01G (metal compounds); (1h) C04B (ceramics) and (1i) G03G (electric charge or magnetic mediated image creation for example in photocopiers). While some areas are static or declining (such as H01L, C01G, C04B and G03G) others are showing steep rises (in particular A61K, H01M, C01B and B01J). Three growth areas of medical/personal care, batteries, and compounds of non metallic elements will be explored in more detail.

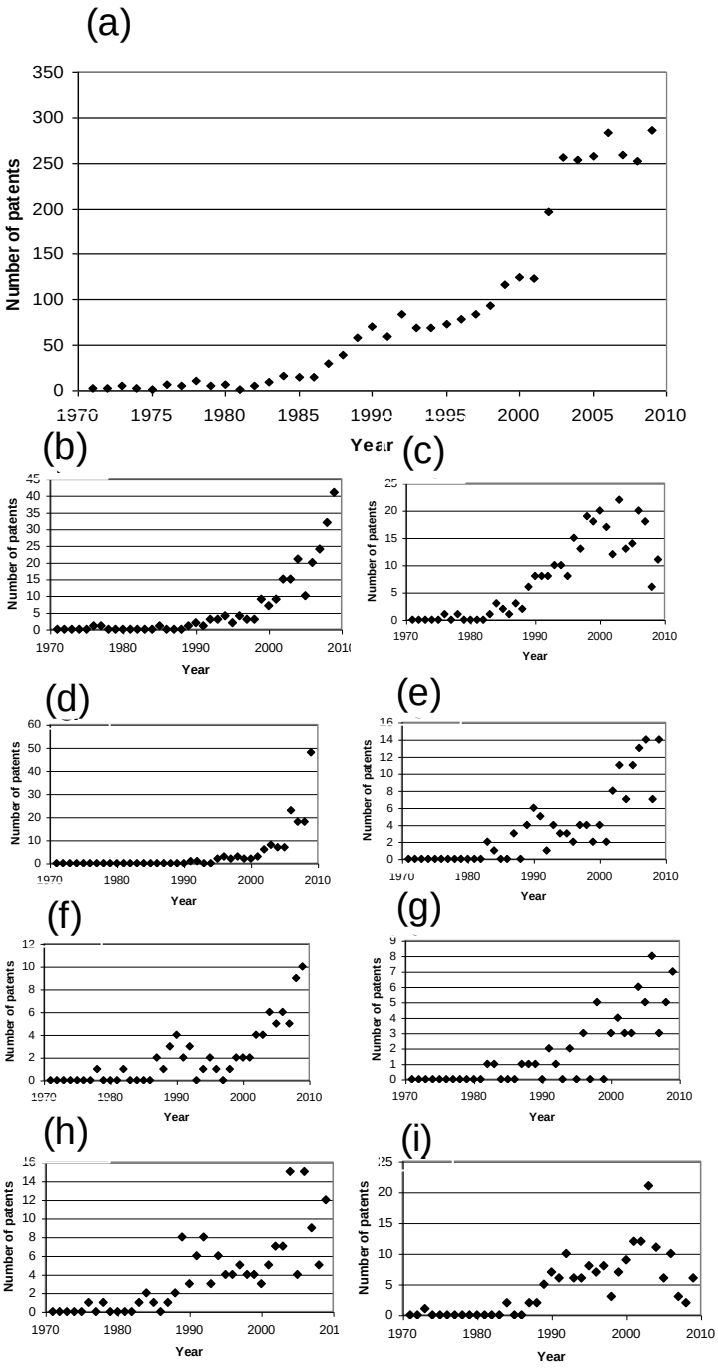


Figure 1 (a) Plot of number of patents vs. year for search terms “mechanochemical” or “mechanochemistry”, and plots showing occurrence of various IPC patent classification codes in patents relating to mechanochemistry; (b) A61K (medical and personal care); (c) H01L (semiconductors and solid state devices); (d) H01M (mainly batteries); (e) C01B (compounds of non metallic elements); (f) B01J (catalysis); (g) C01G (metal compounds); (h) C04B (ceramics) and (i) G03G (electric charge or magnetic mediated image creation for example in photocopiers). See text for full search details.

2.3 Medical/personal care

Iceutica have recently described a mechanochemical route to therapeutically active nanostructured compositions.[49] 20-30 nm nanoparticles of a pharmaceutical compound are synthesized in a stabilising matrix such as Na_2CO_3, NH_4Cl, $(NH_4)_2CO_3$ etc.. Significantly, this process has gone on to commercial scale in a GMP facility.[50]

A further example of production-scale mechanochemistry is by Vectorpharma Spa of Trieste, Italy, who prepared anti-inflammatory drug/carrier composites with β-cyclodextrin by high energy milling.[51] β-cyclodextrin finds use as a carrier for pharmaceuticals due to its lipophilic internal cavity and hydrophilic exterior, which allow the formation of soluble inclusion complexes.[52] The pharmaceutical/β-cyclodextrin complex helps to control the rate of drug delivery. Vectorpharma's mechanochemically-prepared composite shows different properties to those prepared by conventional routes, specifically much higher dissolution rates. The reaction between Nimesulfide and β-cyclodextrin was performed in a high energy vibration mill on pilot (0.5-2 kg) and production (20-50 kg batch) scales with the optimum processing time of a modest 3.5 hours. As an indicator of batch-to-batch reproducibility the residual crystallinity of the Nimesulide (an indicator of the amount of free Nimesulide present) was consistently 3-7%.

2.4 Batteries

Li-ion batteries are a major innovation in portable power solutions. They comprise a cathode material such as $LiFePO_4$ or $LiCoO_2$, and an anode material such as graphite.[53] Gillette have recently examined the mechanochemical synthesis of the cathode material $LiMnO_2$ from manganese dioxide and lithium hydroxide or lithium carbonate.[54] The work was done on the lab scale using a Turbula mixer containing 500g 1mm yttria-stabilized zirconia milling media over a 0.5-5 hour period. Calcination at 350-420°C removed residual water. Others have examined such an approach, and High Power Lithium, Lausanne, have also manufactured cathode materials for Li-ion batteries this way.[55]

2.5 Compounds of non-metallic elements

Diborane, B_2H_6, has been prepared mechanochemically without using a solvent for the semiconductor industry.[56] Also, silicon nitride is becoming popular for a number of applications such as bearings and high-temperature engine components because it is hard-wearing, lightweight and creep-resistant.[57] Commercially, Si_3N_4 is currently prepared by direct nitridation of silicon powder in the presence of a catalyst at 1200-1400°C.[58] The drawback is that the nitrogen pressure has to be controlled carefully

because of the large exotherm. There is also a need for low pressure routes to Si_3N_4 because high pressure N_2 is unattractive regarding safety and capital cost.[59] Li et al. with Fujian Sinocera Advanced Materials Co. have used mechanochemical treatment of silicon powder with NH_4Cl in steel milling media followed by calcination in the presence of low pressure N_2. Pilot work was performed at 400g scale. The NH_4Cl is added principally to improve the texture of the final Si_3N_4. However, it is possible that during milling it may also improve the characteristics of the silicon. The mechanochemical treatment gives small, highly defected silicon particles which leads to higher reaction rates even at low N_2 pressures (10 bar). Mechanochemical treatment reduces the silicon particle size (63nm after 8 hours milling compared to 58 nm after 12 hours). The process has been scaled to 3kg batches and is being transferred to industrial production.

2.6 Conclusion

The areas with increasing industrial interest, as indicated by patent activity, are currently medical/personal care, batteries, compounds of non-metallic elements and catalysis. These applications are founded on the types mechanochemistry which have been established for the longest time, *i.e.* synthesis of inorganic materials and non-covalent organic inclusion complexes/cocrystals (see Sections 3,4 and 5). Significantly, there are clear examples of processes going into production scale. Of additional interest in future will be patent activity based on more recently-developed uses of mechanochemistry in covalent organic and metal-organic chemistry (Sections 6,7 and 8).

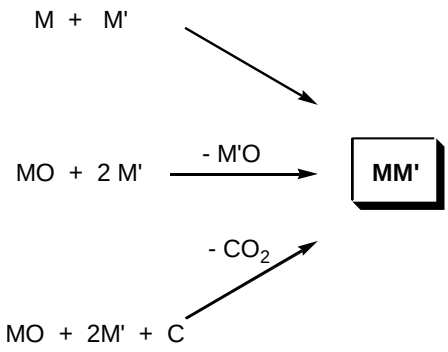
3. Inorganic materials

3.1 Introduction

Inorganic materials represent the most established area of mechanochemical synthesis. As mentioned above, the first recorded example of an entirely solventless mechanochemical reaction can be attributed to Faraday who in 1820 reduced AgCl to Ag using either Zn, Cu, Sn or Fe by grinding in a pestle and mortar.[7] Mechanochemistry in the modern era began with *mechanical alloying*, the process of combining elements or alloys to produce a single homogenous alloy, in high velocity ball mills. The term *mechanochemistry* is now also widely used to describe this process as well as other chemical reactions to produce alloys and inorganic compounds using ball mills. During such processes there is a significant reduction in crystallite and particle sizes, such that products are often either nanoparticles or amorphous phases,[60] which is sometimes desired as providing a top-down route to nano-materials. If more crystalline material is required the product of the mechanochemical process can be sintered.

3.2 Alloys

Mechanochemical techniques were first investigated to produce alloys and work in this area is ongoing. General routes are shown in Scheme 1. Recent work using the simple combination of alloys and elements in ball mills has produced Cu-Co,[61] Fe-Mo,[62] and Mn-Al alloys.[63] Elemental combination has also been used for boron-containing alloys in the Ni-Nb-B[64] and Ti-Al-B systems.[65] The risk of atmospheric oxidation of the metals means that these reactions are carried out under inert gas, typically argon. They generally require relatively long milling times (24 to 300hrs).[61, 63] An alternative to elemental combination is to combine a binary oxide powder and a reducing agent, which can be one of the metals to be alloyed, such as the reaction of TiO_2 and Mg to form TiMg,[66] or PbO and Te to form PbTe.[67] Alternately the reducing agent may not be intended for inclusion, such as carbon, which will be removed as a vapour (CO_2) – an example is the synthesis of brass from CuO, ZnO and PbO in the presence of graphite.[68]



Scheme 1 General ball milling routes to alloys.

3.3 Oxides

The mechanochemical synthesis of inorganic oxides can be conducted by several routes (Scheme 2). The simplest is the combination of different binary oxides – similar to the high temperature ceramic synthesis – but relying on the constant fracture and mixing of the grains to produce a homogenous product, as there will often be little thermodynamic driving force in the reaction itself. This method has been used to synthesize numerous materials including $CrVO_4$,[69] $LaVO_4$;[70] perovskites such as $LaCrO_3$,[71] $LaMnO_3$,[72] and $PbTiO_3$;[73] spinels like $MnFe_2O_4$,[74] $ZnFe_2O_4$,[75] and $NiFe_2O_4$;[76] and Ruddlesden-Popper compounds like $Sr_3Ti_2O_7$ and Sr_2TiO_4.[77] As for alloys this often produces nano-particulate (<10 nm) products.[69, 78] However, unlike the alloys, these reactions can be carried out under air, as all the materials are already fully oxidized. Milling times are also generally shorter, typically between 2 and 24 hours.[69-72, 75]

Direct combination of oxide powders to produce a homogenous phase is not always successful, but it can often still be used as an activation step allowing complete reaction at a lower temperature than in traditional ceramic synthesis. For example $CaZrO_3$ synthesized conventionally must be heated to >1100°C, but only to 800°C after mechanochemical activation.[79] The synthesis temperature of $ZrTiO_4$ could similarly be reduced from 1400°C to 1100°C.[80] This mechanochemical activation followed by sintering has also been used in the synthesis of $MgTa_2O_6$,[81] and the aurivillius phases $Bi_4Sr_{n-3}Ti_nO_{3n+3}$ (n = 4,5).[82]

An alternative mechanochemical approach involves providing a thermodynamic driving force to the reaction. One method is the presence of a reducing metal, intended for inclusion in the final product and requiring the use of an inert gas, but significantly reducing the necessary milling time – in some cases to 30 minutes. Examples include the use of titanium in the formation of $FeTiO_3$ and $FeTiO_4$,[83] iron in the formation of Fe_2GeO_4,[84] zinc in the formation of $ZnFe_2O_4$,[85] and aluminium in the formation of $FeAl_2O_4$.[86] In all these cases the reaction scheme must be devised, as in the case of oxide combination, so that there is a single product. Mechanochemical synthesis can, however, be used for reactions with multiple products as long as the solubilities of the product and by-products are different. An example is the production of silver nanoparticles by reduction of AgCl using either Na or Cu, with the CuCl and NaCl by-products removed by NH_4OH leaching and washing respectively.[87]

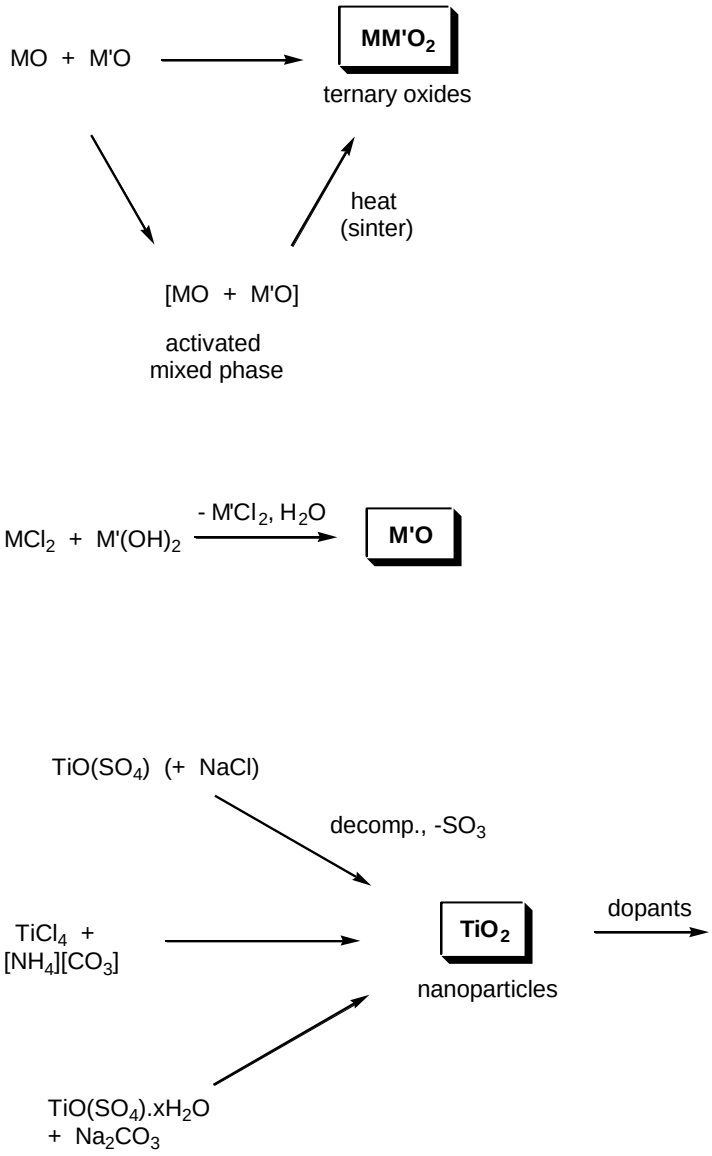
Multiple products are also formed in displacement reactions, which represent another method of introducing a driving force to a mechanochemical reaction. An example is the reaction of $ZnCl_2$ and $Ca(OH)_2$, to produce ZnO nanoparticles in a $CaCl_2$ matrix (with loss of water vapour).[88] The $CaCl_2$ can be removed and the ZnO nanoparticles isolated by washing with water. Similar displacement reactions with salt products have been used to synthesize ZrO_2,[89] Cr_2O_3,[90] $LaCoO_3$,[91] and Nb_2O_5.[92]

A number of researchers have used alkaline and alkaline earth carbonates to introduce Group 1 and 2 metals into compounds, such as $CaTiO_3$,[93] $Ba_{1-x}Sr_xTiO_3$,[94] and $NaNbO_3$.[95] with loss of CO_2, effectively generating MO or M_2O *in situ* for direct oxide synthesis.

The techniques outlined above represent the most common strategies for generating inorganic solids. They have been used to synthesise several potentially important materials for applications. The carbonate method has been used to synthesize $Ba_2ANb_5O_{15}$ (A = K, Na, Li)[96], while simple combination of oxides allowed the synthesis of $Bi_4Ti_3O_{12}$,[97] both of which are ferroelectric compounds, with potential use in memory devices. Mechanochemical methods have been used to synthesis solid state electrolytes (silver niobium oxyfluoride and silver molybdenum oxyfluoride[98][98]), fast ion conductors ($RbAg_4I_5$ and KAg_4I_5.[99]) and a lithium battery cathode material ($Li_2Mn_2O_4$[100]).

Another area in which mechanosynthesis has been used is titania based nanoparticles. TiO_2 is a widely used UV semi-conductor photocatalyst with applications in self-cleaning coatings, anti-microbial coatings and photo-activated water splitting.[101] Production of TiO_2 nanoparticles has been achieved by:

mechanochemical decomposition of titanyl sulphate using NaCl diluents;[102] reaction of $TiCl_4$ and ammonium carbonate;[103] displacement reaction of $TiOSO_4.xH_2O$ and Na_2CO_3. After annealing these particles had twice the activity of Degussa P25, the highly active industry standard.[104] Attempts to dope TiO_2 nanoparticles with carbon, sulphur and nitrogen have also been conducted by mechanochemical reaction of titania with adamantine, sulphur and ammonium carbonate with results indicating that visible-light photoactivity has been induced.[105] Fluorine-doped $SrTiO_3$ by has been prepared mechanochemically and this has also demonstrated visible light photocatalysis.[106]



Scheme 2 General ball milling routes to metal oxides.

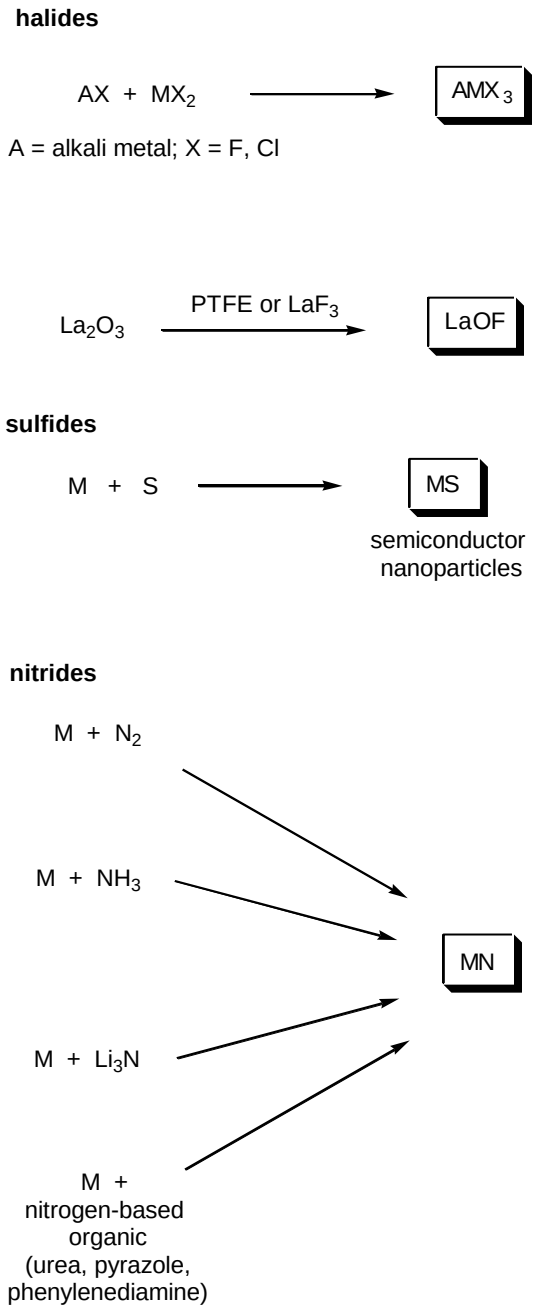
3.4 Halides, sulphides and nitrides

A number of compounds of the form AMF_3 have been produced by the mechanochemical combination of AF and MF_2, where A is an alkali metal and M is a divalent metal ion (Scheme 3), under inert gas, with milling times of 3-12 hrs. This has been successful for Na (M = Fe, Mn and Ni)[107] and K (M =Mg, Zn, Mn, Ni, Cu, Co and Fe).[108] Similarly, a series of chlorides $KMCl_3$ (M = Ti, Cr, Mn, Fe, Co, Ni, Cu and Zn) has been prepared[109] and direct combination of CaF_2 and LaF_3 produced $Ca_{1-x}La_xF_{2+x}$.[110] There has also been interest in mechanochemically synthesized halides as fast ion conductors, including $NaSn_2F_5$,[111] $RbPbF_3$,[112] and $Pb_{1-x}Sn_xF_2$.[113] The range of methods used in the synthesis of LaOF demonstrates a number of possible routes to the mechanochemical introduction fluorine; LaOF has been made by ball milling La_2O_3 with either PTFE,[114] poly(vinyldene fluoride)[115] or with LaF_3.[116]

Mechanochemical synthesis of sulphides has focused principally on semi-conductor nanoparticles, by direct combination of the metal and sulphur. This has been achieved for CdS,[117] $Cd_xZn_{1-x}S$,[118] and FeS.[119] Other sulphides of interest that have been investigated include fast ion conductors such as $(Ag_2S)_x(Sb_2S_3)_{1-x}$ and the purported anti-cancer agent As_4S_4 (realgar).[120]

For several metals nitrides can be synthesized simply by ball milling the metal under a high pressure of nitrogen for greater than 10 hours. This method has given TiN,[121] ZrN,[122] VN,[123] NbN[124] and CrN[125]. Similarly, ball milling the metal under the more reactive ammonia has given Mo_2N,[126] GaN,[127] BN,[128] Si_3N_4.[129] Alternative sources of nitrogen include Li_3N, which has been used to form GaN,[130] ZrN[131] and a range of lithium nitridometallates, LiNiN, Li_3FeN_2, and Li_7VN_5.[132] Its high reactivity can give complete mechanochemical reactions in as little as 7 minutes.[131] Ternary nitrides have been made by alloying a binary nitride (Mo_2N) with Fe or Co.[133]

Solid organic nitrogen compounds may also be used. Examples include reaction of urea with titanium to form TiN;[134] pyrazole and iron powder to give Fe_3N;[135] and phenylene diamine and iron to give Fe_2N_3.[136] This avoids the introduction of a gas, but requires removal with solvent at the end of reaction.



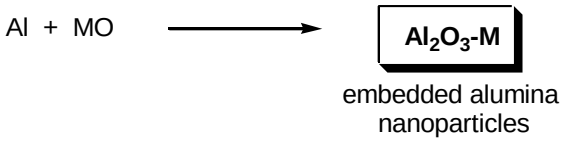
Scheme 3 General ball milling routes to halides, sulfides and nitrides.

3.5 Composites

For much of the chemistry described above, it has been important to design the reaction such that only a single inorganic product is generated, or if there are by-products, that they can be easily removed as gases or by extraction. However, two or more final products can be deliberately synthesized

simultaneously to produce a nano-composite. Most research conducted so far is for Al_2O_3 nanoparticles imbedded in a metal or alloy, to give improved mechanical properties (Scheme 4). Examples include Al_2O_3 in Zn,[137] Nb,[138] and Cu.[139] This is done by milling aluminium with the metal oxide, driven by the high heat of formation of Al_2O_3. Use of excess aluminium can give Al_2O_3 particles in aluminium-based alloys such as $TiAl_3$,[140] Al-Zn[141] and AlB_{12}.[142]

Mechanochemically-synthesized nano-composites have also been investigated as novel anode materials for Li ion batteries. These include a combination of Sn/C with either TiO_2 or Fe,[143] or LiH with either Mg or Ti.[144a]



Scheme 4 Synthesis of a composite material by ball milling.

A related aspect is the mechanochemical dispersion of metal particles on a pre-existing support, which provides a way to generate heterogeneous catalysts. This has been demonstrated for nanoparticulate gold dispersed on coordination polymers, carbon or metal oxides by Haruta using $Au(acac)Me_2$, which is readily vapourised, as the gold source.[144b] Some of the resulting materials exhibited high catalytic activities.

3.6 Conclusions

The historically most established application of mechanochemical synthesis is for inorganic materials and this continues for current and future technological applications. The formation of nanoparticulate phases and otherwise inaccessible composites are significant aspects. Interestingly it is also possible to react organic compounds with elemental metals. Many methods have been devised such that no separation of by-products is needed. This can be seen as an atom-economic approach, even if driven primarily by practical considerations. Analogous reconsideration of routes to organic products will be of interest in applying mechanochemistry to organic and metal-organic synthesis to avoid the need for separations (see Sections 6, 7, 8 and 10).

4. Cocrystals

4.1 Introduction

Although mechanochemical synthesis has not been applied as extensively to cocrystals as to inorganic materials, it does have a relatively long history in this context.[10] We adopt here the liberal definition of a cocrystal as a "multi-component molecular crystal".[145] This includes solvates and hydrates, and does not discriminate between formally charged systems (salts) versus neutral ones as defined by the extent of proton transfer along a hydrogen bond.[145c, 145d] The pharmaceutical applications of cocrystals[146] are discussed in Section 5. Mechanical mixing of molecular crystals, manually or by ball milling, is often effective for preparing cocrystals.[147] Often the best results are obtained by liquid assisted grinding (LAG, also called *kneading*) *i.e.* by grinding with a small amount of a liquid.[148] This method is complemented by approaches such as exposure of a solid mixture to solvent vapour[149] (vapour digestion) and heating solid mixtures[150] including screening by hot stage microscopy.[151]

4.2 Charge transfer cocrystals

Pioneering studies were carried out by Toda *et al.* in the preparation of crystalline host-guest inclusion compounds[152] and charge-transfer systems.[153] Formation of charge transfer cocrystals can often be followed by eye due to the change in color. Kuroda *et al*.[28, 154] obtained three-component cocrystals based on racemic bis-β-naphthol, benzoquinone and anthracene. Importantly, the resulting cocrystal could not be obtained from solution and so required structure determination from X-ray powder diffraction (see Section 9).[155] Sada *et al.*[156] formed brightly colored charge-transfer complexes by mixing a pale-colored electron donor, acting as an analyte, and a pale-coloured electron acceptor, acting as a probe, or vice-versa. A series of acceptor molecules was designed as probes to produce a 2D colorimetric indicator array which discriminated between isomers of organic molecules such as di-hydroxynaphthalene, using only the naked eye. All reactions were carried out in molten pastes. In 1 minute colour changes were visible but became much brighter after 10-15 minutes grinding. One probe molecule allowed discrimination between the eight isomers of di-hydroxynaphthalene.

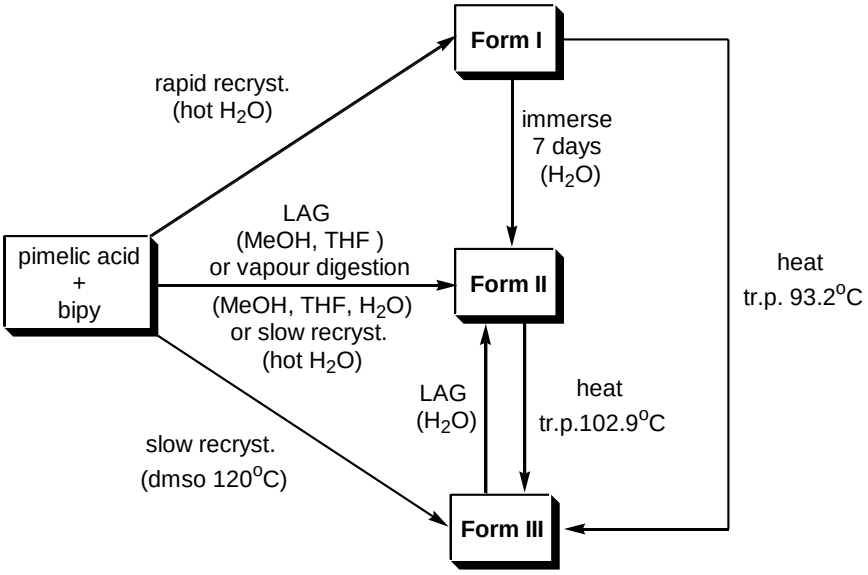
4.3 Acid-base cocrystals

1:1 cocrystals of variable chain length dicarboxylic acids $HOOC(CH_2)_nCOOH$ (n = 1-7) and 1,4-diazabicyclo[2.2.2]octane (dabco) have been prepared mechanochemically and investigated by X-ray diffraction and solid state NMR.[157] The melting points of the cocrystals were found to alternate as in the corresponding diacids irrespective of the salt/molecular nature of the cocrystals. It has been recently demonstrated that this behavior is also exhibited by cocrystals of these diacids with dipyridyl molecules 4,4'-bipyridine (bipy), 1,2-bis(4-pyridyl)ethane (bpa), and 1,2-(di-4-pyridyl)ethylene (bpe) which contain an

even number of C atoms between the two N atoms; while it is completely reversed in cocrystals with 1,2-bis(4-pyridyl)propane (bpp), which contains an odd number of (CH_2) groups.[158]

Competing solid-state exchange between cocrystal components by grinding has also been recently reported on cocrystals of *R*,*R*-, *S*,*S*-, racemic and *R*,*S*-tartaric acid (ta) with pyrazine (py).[159] "Supramolecular metathesis" was carried out in methanol slurry by reacting the cocrystal products, (*R*,*R*-ta)·(py), (*S,S*-ta)·(py), (*R*,*S*-ta)$_2$·(py) and (*R*,*R*/*S*,*S*-ta)·(py), with the different forms of tartaric acid showing that coformer exchange could take place according to the sequence of stability (*R*,*S*-ta)$_2$·(py) > (*R*,*R*/*S*,*S*-ta)·(py) > (*R*,*R*-ta)·(py) or (*S,S*-ta)·(py).

Formation and polymorphic transformation by grinding has been studied for 4,4'-bipyridine (bipy)/pimelic acid (H_2pma) cocrystals.[160] The structures of the three polymorphs (Form I, Form II and Form III) were determined from single crystals grown by seeding of solutions with the microcrystalline mechanochemical product. All polymorphs consisted of chains of alternating bipy and H_2pma molecules linked by O-H···N hydrogen bonds, but differed in the relative arrangements of the chains. Scheme 5 shows the various interconversions that were possible and illustrates how LAG can be important in enabling some transformations, complementing other more classical methods such as recrystallisation from solvents or from melts.



Scheme 5 Preparation and transformation conditions of the three crystal forms of (bipy)·(H_2pma) (tr.p.: transition point).

Grinding has also been used to gave a family of organometallic-organic cocrystals of the pyridyl ferrocene derivative Fe(η^5-C_5H_4-C_5H_4N)$_2$ ($Fcpy_2$) with dicarboxylic acids $HOOC(CH_2)_nCOOH_2$ of variable chain

length (n = 4-7). Compounds of general formula $(Fcpy_2)\cdot(diacid)$ were prepared by kneading of solid mixtures with MeOH. Interestingly, all compounds are discrete macrocycles $\{(Fcpy_2)\cdot(diacid)\}_2$ rather than extended networks except for the pimelic acid adduct (n = 5) (Figure 2).

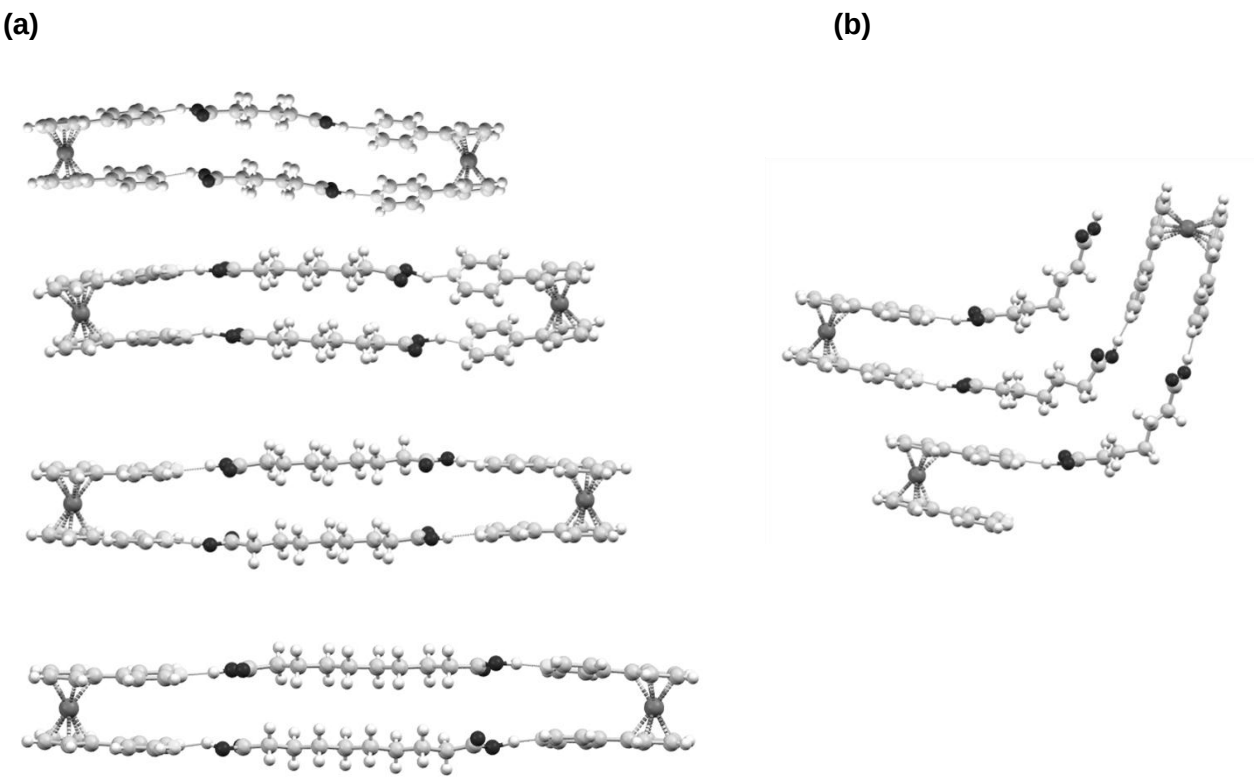


Figure 2 The supramolecular structures of the macrocycles $\{(Fcpy_2)\cdot(HOOC(CH_2)_nCOOH_2)\}_2$ (n = 4, 6, 7, 8) (a), and the zig-zag chain found when n = 5(b).

In the search for alternative polymorphs of the pimelic acid adduct vapour digestion of the solid mixture was attempted. The stoichiometry of the products was affected by the protic or aprotic nature of the solvent. The cocrystal with 1:1 stoichiometric ratio as observed in the grinding synthesis, was obtained by exposure to vapours such as CH_2Cl_2, $CHCl_3$, $(CH_3CH_2)_2O$, CH_3NO_2 and ethyl lactate, while a 1:2 cocrystal $(Fcpy_2)\cdot(HOOC(CH_2)_5COOH)_2$ was formed with protic solvents, such as CH_3OH, CH_3CH_2OH, H_2O and isopropyl alcohol.[149b] This indicates that the solvent used in the kneading is not an innocent spectator or lubricant in the diffusion process but takes an active part in the process very likely via subtle supersaturation levels over the grain surfaces, i.e. that dissolution, and therefore solubility, in the added liquid is important.

To explore the effect of the preparation method on the nature of the product, the cocrystallisation of $Fcpy_2$ and anthranilic acid, $(C_6H_4)NH_2COOH$, has been investigated.[149a] It has been shown that the same product can be obtained, quantitatively, by four different processes, namely kneading with methanol, wet

compression (*i.e.* pressure without mixing in the presence of MeOH), and vapour digestion,(*i.e.*placing a mixture of the solid reactants in an atmosphere of MeOH vapour) and by heating a mixture of the two solid reactants. In contrast, no reaction was observed by dry mixing or dry compression. This demonstrates not only the ability of small amounts of added liquids in LAG to direct the course of a cocrystallization but indeed also to enable cocrystallization. This dramatic influence of the added liquid in LAG is echoed in the mechanosynthesis of metal complexes including metal organic frameworks (Sections 7 and 8).

4.4 Ionic cocrystals

Recently it has also been shown that grinding or kneading of classical ionic crystalline materials (NaBr, KBr, CsI, RbBr etc.) with organic molecules, such as solid barbituric acid (H_2ba), gives a new class of "ionic cocrystals" in which BA is present as a neutral component.[161] Depending on the metal, hydrated forms were also observed. The structure of (H_2ba)·(KBr)·(H_2O)$_2$ is shown in Figure 3. An important aspect is the higher thermal stability and dissolution rates of the cocrystals compared to pure barbituric acid, illustrating that this unusual type of cocrystallization can alter the dissolution behaviour of organic molecules. This ability to modify the properties of organic molecules by creating novel solid forms is of key interest in the pharmaceutical area as expanded upon in Section 5.

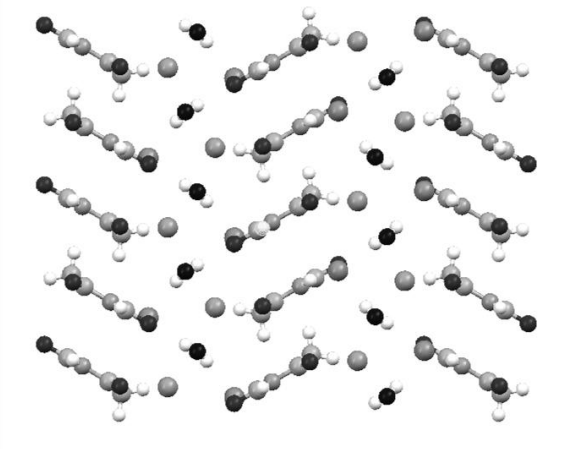


Figure 3 Packing of the ionic cocrystals (H_2ba)·(KBr)·(H_2O)$_2$.

4.5 Organocatalysis through cocrystallization

A cornerstone organic solid state reaction (not mechanochemical) is the [2+2] photo-induced dimerization of two double bonds in close proximity to one another.[162] MacGillivray *et al.* have used cocrystallization to direct such close arrangements of double bonds using resorcinol derivatives as directing agents.[163] Very recently this methodology has been extended to be *catalytic* by using mechanochemistry (Figure 4).[164] The method involves alternating grinding periods with exposure to UV light (which causes the

photochemical cyclisation) in the presence of a substoichiometric amount of a resorcinol directing agent. The catalytic resorcinol directing agent is able to dissociate from the reaction product, allowing it to be redistributed by grinding to complex to further reactant and so enabling catalytic turnover. This can be regarded as a more 'crystallographic' example of organocatalytic reactions in general which are discussed in Section 6.4.

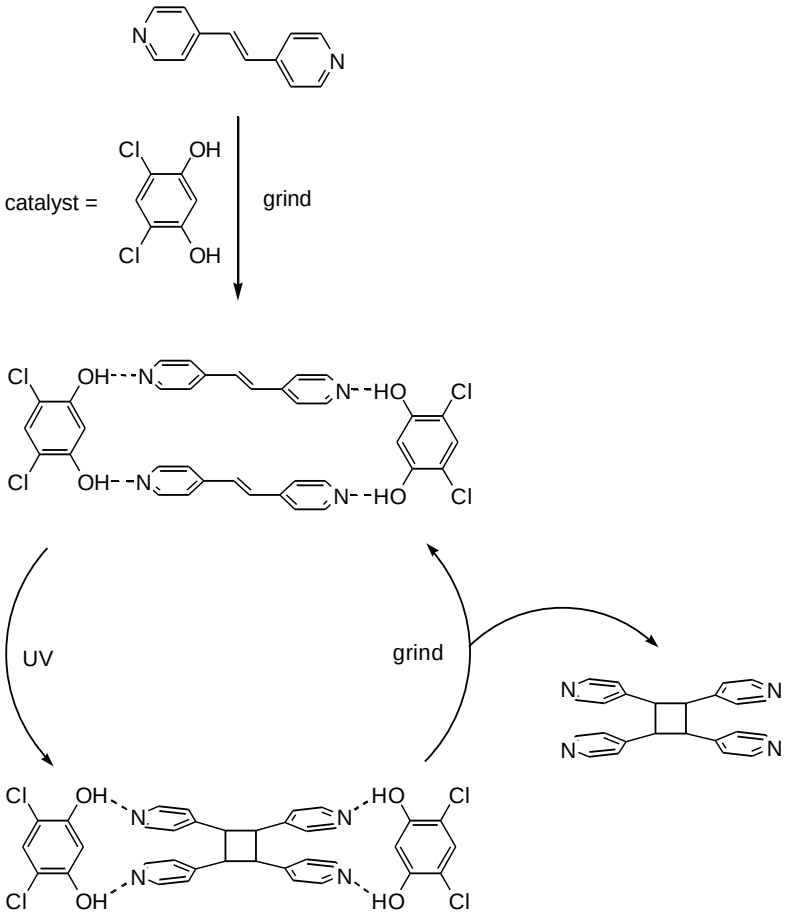


Figure 4 Solid state catalytic system which alternates UV irradiation and grinding-induced cocrystallisation.

4.6 Conclusion

Mechanochemistry is now recognized as one of the most effective ways to generate cocrystals. It is frequently effective regardless of the types of intermolecular interactions which are formed. Importantly, it can provide alternative structures to those obtained by solution crystallization. Whilst there are challenges to determining the structures of such cocrystals advances in structure solution from powder XRD data (see also Section 9) is successful in increasing numbers of cases.

5. Pharmaceutical aspects

5.1. Introduction

The discovery of new solid forms of pharmaceuticals (amorphous, crystalline, single and multicomponent) is an important application of mechanochemistry. Although most established for producing amorphous phases,[165] attention has recently been given to its use in cocrystallization (see also Section 4).[166] Cocrystallization is useful in this context because it provides a way to derivatize active pharmaceutical ingredients (APIs), by modifying their solid-state arrangements rather than their internal molecular structures. Modification of the crystal structure by cocrystallization can improve pharmaceutically relevant properties such as dissolution rate, solubility, thermal and hydration stability or compressibility.[167]

Pharmaceutical cocrystals generally consist of an API and one or more pharmaceutically acceptable molecules, known as the cocrystal formers or “coformers”, into a well-defined crystal lattice.[166b, 166c] The coformers are typically compounds "generally regarded as safe" (GRAS compounds). Greater thermodynamic stability[168] makes such cocrystals preferred over metastable amorphous forms and alternative polymorphs that may be of higher free energy. Since most pharmaceutical coformers are solids, pharmaceutical cocrystallization is also advantageous compared with solvate formation, since solvates inherently involve the risk of spontaneous desolvation. Finally, cocrystallization is more versatile than salt formation, as it does not require an ionisable centre in the API, and there are considerably more GRAS compounds than pharmaceutically acceptable salt formers. Because of the very large range of potential coformers, the efficiency and convenience of mechanochemical methods makes them particularly advantageous in screening amongst large numbers of potential coformers.

5.2 Pharmaceutical cocrystallization by neat grinding

The simplest mechanochemical method for pharmaceutical cocrystallization is by neat grinding of two or more cocrystal components.[169] The first examples were reported independently in 1993 by Caira [170] and Etter.[171] Caira ground the drug sulfadimidine with a variety of carboxylic acids, including benzoic, anthranilic, salicylic, and acetylsalicylic (aspirin) (Figure 5a).[170] Cocrystals were obtained in all cases, identical to those previously obtained by solution methods. First order kinetic behaviour was observed, interpreted as suggesting a random nucleation reaction mechanism. The exceptional stability of the sulfadimidine-anthranilic acid cocrystal (Figure 5b) was established through two types of mechanochemical competition experiments either using two different acids or grinding the preformed sulfadimidine cocrystals with an alternative carboxylic acid. The sulfadimidine-anthranilic acid cocrystal was always obtained.[170]

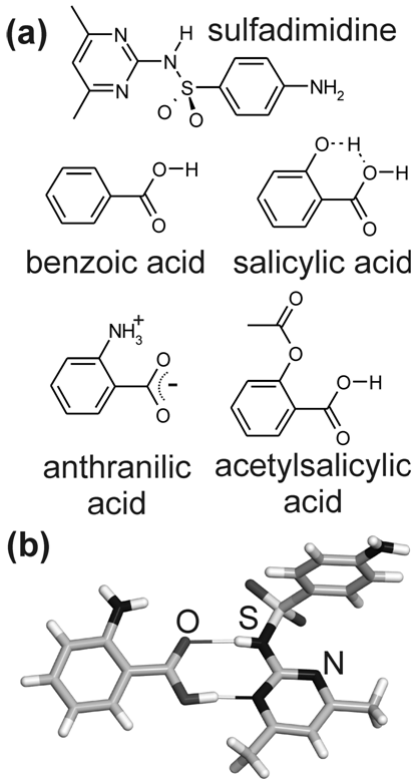


Figure 5 (a) Molecules used in mechanochemical synthesis of pharmaceutical cocrystals by Caira *et al.*; (b) fragment of the crystal structure of the cocrystal of sulfadimidine with anthranilic acid.[170]

Etter described the solid-state cocrystallization of 9-methyladenine and 1-methylthymine,[171] driven by the formation of hydrogen-bonded Hoogsteen complexes between the base pairs (Figure 6).[172] Although 9-methyladenine and 1-methylthymine are not API molecules *per se*, they are derivatives of biologically active molecules.

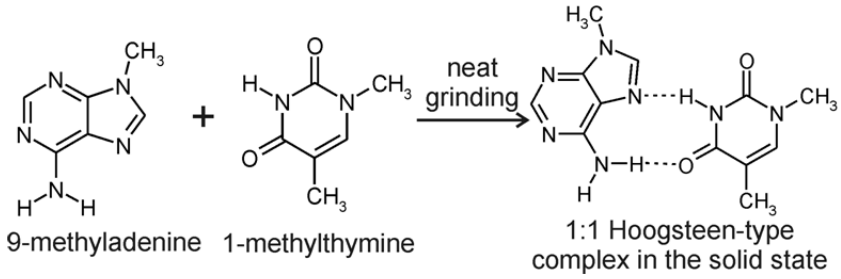


Figure 6 Mechanochemical reaction of 9-methyladenine and 1-methylthymine to form a cocrystal reported by Etter.[171-172]

In the later work of Rodríguez-Hornedo, the cocrystal of the API carbamazepine with the coformer saccharin was used to study the mechanism underlying neat grinding cocrystallization (Figure 7), [31, 173] which revealed an intermediate amorphous phase. The grinding reaction was faster at temperatures

close to the glass transition temperature (T_g) of the ground mixture. Cryogenic grinding, *i.e.* grinding at low temperatures, allowed observation of the intermediate amorphous phase which crystallized upon warming. Such behaviour is consistent with the mechanochemical behaviour of single-component solids, studied by Descamps *et al.*, i.e. that low temperature grinding leads to amorphization (vitrification), whilst grinding above T_g causes polymorphic transformations.[174] Mechanochemical cocrystallization was also accelerated by exposing the intermediate amorphous phase to water (in the atmosphere or as hydrated reactant), effectively lowering the T_g of the reaction mixture.[31, 173] Higher reactivity of hydrated carbamazepine compared to the anhydrous form was also observed by Rades *et al.* in mechanosynthesis of the (carbamazepine)·(nicotinamide) cocrystal.[175] Similar effects have been seen for caffeine and citric acid and their hydrates.[176]

The ability to scale mechanochemical cocrystal formation is important for industrial applications. This was recently addressed by Medina *et al.* who described a scalable continuous flow solvent-free process for pharmaceutical cocrystallization using twin screw extrusion.[177]

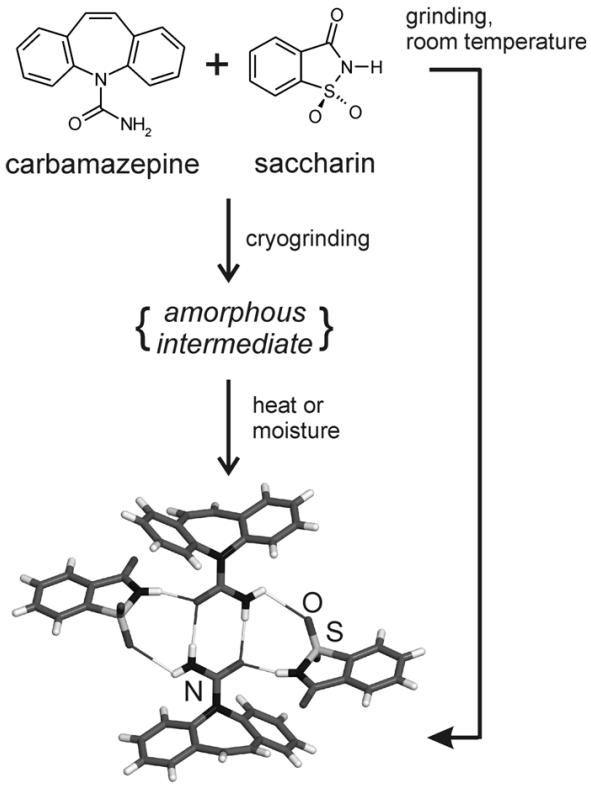


Figure 7 Mechanochemical cocrystallization by neat grinding of carbamazepine and saccharin,[31, 173] involving an amorphous intermediate.

5.3 Screening for pharmaceutical cocrystals by liquid-assisted grinding (LAG)

Since the interaction between the components of a pharmaceutical cocrystal is generally based on hydrogen bonding that is likely to be disrupted by interaction with the solvent, cocrystal screening using conventional solution-based methods is not efficient. For example, solution methods are likely to fail in screening for cocrystals of low-solubility APIs, as attempts to form the cocrystal often result in the separation of the solid API with the more soluble coformer retained in solution.[178] In such cases, mechanochemical neat grinding[179] or liquid-assisted grinding (LAG, also known as kneading or solvent-drop grinding) represent obvious alternatives.[180] LAG is preferred to neat grinding in that it is more general, faster (typically 20 minutes) and gives more highly crystalline products.[181] For example, while caffeine and citric acid do not form a cocrystal upon neat grinding, LAG with water or organic solvents gives the pharmaceutical solid (caffeine)·(citric acid).[176] The advantage of LAG was also observed in screening for cocrystals of piroxicam.[182] The study by Childs, Rodríguez-Hornedo *et al.* established that LAG was of comparable efficiency to solution-based and thermal methods for cocrystallization of carbamazepine.[183] Karki *et al*. demonstrated that mechanochemistry was more effective than solution- and melt-based methods in screening for cocrystals of nicotinamide.[184]

The application of LAG to form cocrystals of low-solubility APIs was demonstrated using theobromine (Figure 8). Grinding with trifluoroacetic or malonic acids resulted in cocrystals, while none were obtained by crystallization from solution.[185] Additionally, because of the high melting point (>400 ^{o}C) of theobromine the two cocrystals could not be obtained from the melt. The failure of solution crystallization also prevented their structural characterization by single crystal X-ray diffraction but characterization was achieved from powder X-ray diffraction (PXRD) data.[185] The combined approach of solid-state synthesis and powder structure analysis was also applied to the study of cocrystals of theobromine with acetic acid,[186] and of theophylline with chiral and racemic malic acids.[187] Among further pharmaceutically interesting molecules that were recently explored through LAG cocrystal screening are the cases of dihydrocarbamazepine,[188] indomethacin[189] and the drug candidate AMG 517.[190]

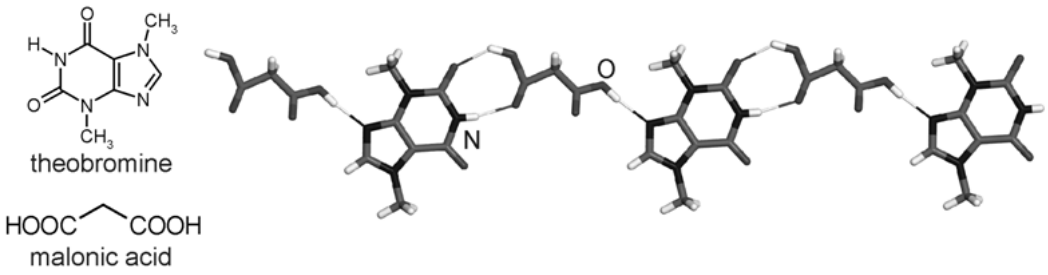


Figure 8 Pharmaceutical cocrystal components and a fragment of crystal structure for theobromine and malonic acid formed by LAG.[185]

Zaworotko explored the mechanochemical formation of 25 model cocrystals previously obtained from solution.[32] In each case, the cocrystal was successfully obtained using only 4-20 μL of the liquid per 100 mg of the solid. Furthermore, LAG was also shown to be advantageous to cocrystal screening from the melt, as it avoids exposing thermally-sensitive APIs or coformers to high temperatures. This was demonstrated in screening for cocrystals of the model API nicotinamide with dicarboxylic acids: Screening from the melt was not possible with thermally sensitive oxalic acid,[184] or the high melting fumaric acid.[191]

Another potentially interesting role for LAG in the context of pharmaceutical solids is for conducting cocrystal-cocrystal reactions involving chiral and racemic solid forms. In particular, LAG reactions between left- and right-handed pharmaceutical cocrystals of theophylline with tartaric acid were found to give a racemic pharmaceutical cocrystal. In contrast, LAG of left- and right-handed cocrystals of caffeine with tartaric acid decomposed the cocrystal and racemic tartaric acid and solid caffeine separated. This represents a unique example of a solid-state separation of a pharmaceutical cocrystal into the solid active ingredient and the cocrystal former.[192]

5.4. Control of stoichiometric composition and polymorphism

An attractively versatile aspect of cocrystallization in the synthesis of new API forms is the possibility to form cocrystals containing identical constituents in different stoichiometric ratios.[193] Mechanochemistry can often provide such stoichiometric variations by simply grinding different amounts of starting materials. This was first demonstrated for the model API caffeine upon cocrystallization with acetic acid.[193] Crystallization of caffeine from liquid acetic acid gives cocrystals of composition (caffeine)·(acetic acid)$_2$. The same product is obtained by grinding the two components in the appropriate ratio. Grinding equimolar amounts of caffeine and acetic acid, however, gave a cocrystal with composition (caffeine)·(acetic acid).[193] Stoichiometric variations were also systematically investigated for cocrystals of nicotinamide with dicarboxylic acids and, while readily accomplished mechanochemically, this could not be easily achieved from solution or a melt.[100a, 184, 194]

The ability to vary the added liquid in LAG allows control over the polymorphic behaviour of mechanochemically obtained cocrystals as noted in Section 4. In the pharmaceutical context this was demonstrated by Trask *et al*.[33, 195] Cocrystallization of caffeine with glutaric acid in chloroform solution provided the cocrystal (caffeine)·(glutaric acid) as two concomitant polymorphs. However, LAG with either chloroform or cyclohexane gave each form selectively.[196] Such mechanochemical control of polymorphic behaviour was has also been observed in other systems.[182, 195]

5.5 Pharmaceutical cocrystals with improved properties

In principle, the formation of pharmaceutical cocrystals can be guided by the concept of supramolecular synthons. However, the physicochemical properties of the resulting material cannot be readily predicted. Furthermore, since the synthon-based approach considers only specific recognition between selected functional groups, its usefulness in fully predicting the three-dimensional structure of the cocrystal is limited. Additionally, the synthon approach is sensitive to competition between different functional groups.[196-197] Consequently, pharmaceutical cocrystals with improved properties must be discovered in a trial-and-error process which is strongly assisted by efficient screening methods such as LAG. An example, is the use of cocrystals to enhance the hydration stability of a solid API as first demonstrated for model APIs caffeine or theophylline by forming cocrystals with dicarboxylic acids.[167c] Cocrystallization with oxalic, malonic, maleic and glutaric acids provided cocrystals based on expected $R_2^2(7)$ carboxylic acid-imidazole heterosynthons. In both cases, the cocrystal with oxalic acid demonstrated much greater hydration stability compared to the pure APIs.[167c]

LAG was used to construct cocrystals of nicotinamide with the low melting APIs *S*-ibuprofen and *RS*-ibuprofen.[179] It was anticipated that cocrystallization would give solid forms with higher melting points, due to extended hydrogen bonding in amide-amide $R_2^2(8)$ homosynthons. Cocrystals with significantly higher melting points compared to the parent APIs were indeed obtained. Single crystals were subsequently grown from solution and structurally characterized, confirming the presence of the expected networks (Figure 9a).[198]

Mechanochemical cocrystallization has also been exploited in the synthesis of readily compressible and thermodynamically stable forms of the API paracetamol.[167e] While tablet formation using the thermodynamically stable paracetamol polymorph is difficult, the metastable orthorhombic polymorph yields tablets much more readily due to its layered crystal structure. Consequently, it was expected that cocrystals having a similar layered structure would also be readily compressible. Screening by LAG revealed four cocrystals of paracetamol with improved ability to compress into tablets. Structural characterization and DFT calculations revealed that enhanced compressibility was indeed related to sheet structures (Figure 9b-e).[167e]

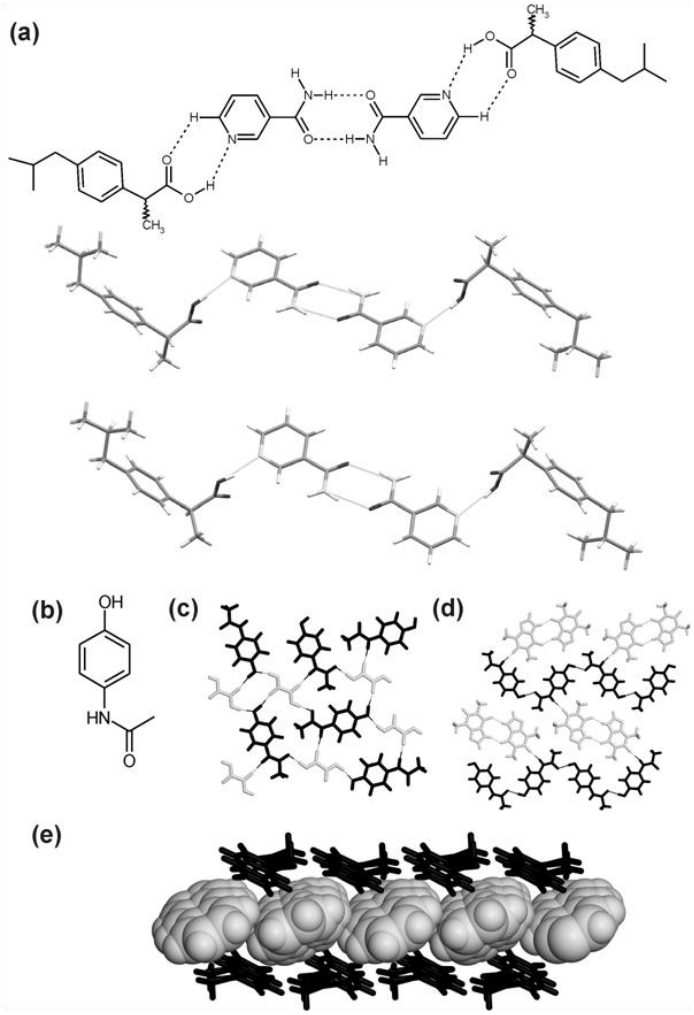


Figure 9 (a) Expected hydrogen-bonded assembly[179] (top) and corresponding fragments in observed[198] crystal structures of nicotinamide cocrystals with *RS*- (middle) and *S*-ibuprofen (bottom); (b) molecular diagram of paracetamol; (c) single layer in the crystal structure of the paracetamol cocrystal with oxalic acid; (d) single layer in the crystal structure of the paracetamol cocrystal with theophylline and (e) stacked layers of paracetamol and naphthalene in the cocrystal. Molecules of paracetamol are shown in black and the molecules of the coformer in grey.[167e]

5.6 Three-component pharmaceutical solids

Cocrystals of pharmaceutically relevant molecules can contain more than two components. This was first demonstrated with three-component (ternary) inclusion compounds involving a guest molecule within an open hydrogen-bonded host consisting of caffeine and succinic acid (Figure 10a).[180] The formation of ternary solids was attempted with 25 potential guest molecules using solution crystallization, neat grinding and LAG. Solution crystallization provided ternary inclusion compounds in four cases, neat grinding in 15,

and LAG in 18 (Figure 10b).[180] Ternary phases of the antibiotic pleuromutilin with succinic acid and methanol or water were studied by Clawson *et al.*.[199] From solutions or slurries ternary solids with succinic acid:pleuromutilin ratios between 1:2 and 1.4:1 were obtained, while LAG allowed the construction of materials with a ratio of up to 2:1.[199] Solid-state NMR and X-ray crystallography revealed that the material with the 1:2 ratio consisted of a host lattice of protonated pleuromutilin with included succinate anions and solvent. Increasing the relative amount of succinic acid resulted in the progressive replacement of solvent guests with neutral molecules of succinic acid, accompanied by a change in space group.[200]

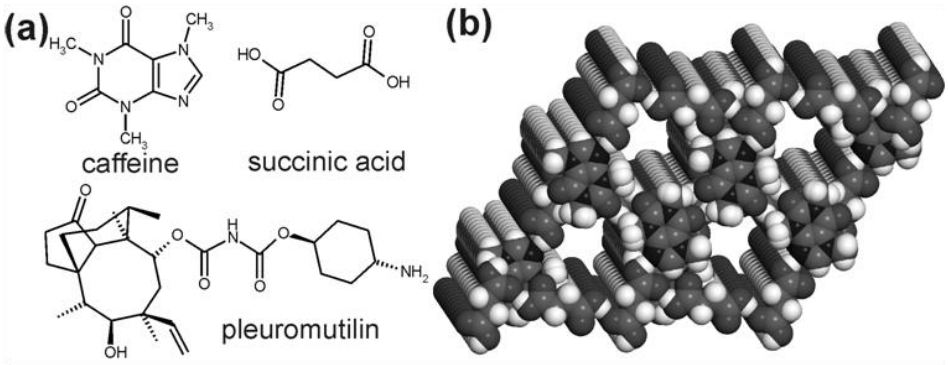


Figure 10 (a) Molecular diagrams of caffeine, succinic acid and pleuromutiline; (b) two-component host of caffeine and succinic acid.[180]

A three-component pharmaceutical cocrystal hydrate was obtained while comparing anhydrous and hydrated reactants in mechanochemical cocrystallization of theophylline and citric acid.[177] Whereas grinding anhydrous theophylline with anhydrous citric acid gives a binary cocrystal (theophylline)·(citric acid),[200] hydrated reactants lead to a ternary solid (theophylline)·(citric acid)·H_2O.[177]

5.7 Pharmaceutical salts

In addition to cocrystallization, LAG is also effective in screening for pharmaceutical salts. In particular, Trask *et al.* compared LAG and neat grinding in screening for salts of APIs trimethoprim and pyrimethamine.[201] LAG was more efficient in forming salts or salt polymorphs. Recently, LAG was used by André *et al.* to screen for new solvate and salt forms of the antibiotic 4-aminosalicylic acid.[202]

5.8 Conclusion

Mechanochemistry and cocrystallisation are, in tandem, becoming increasingly established as versatile approaches to discovering new solid forms of pharmaceutically active compounds. Mechanochemistry is often preferable to solution or melt-based approaches as a more efficient and general way to screen for potentially new cocrystal forms of APIs.

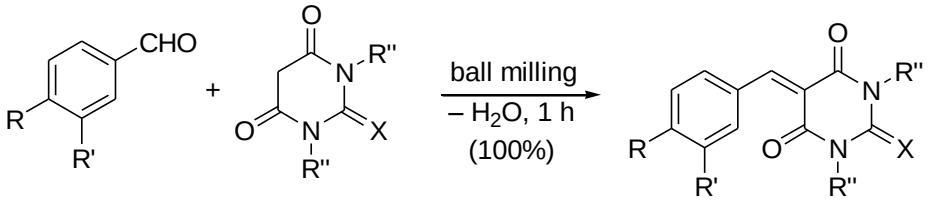
6. Ball milling in organic synthesis: C-C- and C-X-bond formations

6.1 Introduction

Organic synthesis has almost exclusively been restricted to solution-based methods during its development through to the present day. The use of ball mills in solvent-free organic synthesis has recently, however, begun to attract significant attention, and several reviews are now available.[19] Concentrating on C-C and C-X bond formations, including catalysed reactions, this section highlights selected examples which show the progress and potential of ball milling in organic synthesis generally.

6.2 Stoichiometric organic reactions in ball mills

The Knoevenagel condensation is an important C-C-bond forming reaction, giving access to α,β-unsaturated carbonyl compounds. In 2003, Kaupp introduced a solvent-free version of this reaction carried out in a ball mill (Scheme 6).[35] The use of stoichiometric amounts of starting materials led to a quantitative yield of the desired products. Here, as well as in the reported Michael additions, no work-up was required, rendering these waste-free approaches sustainable and eco-friendly.

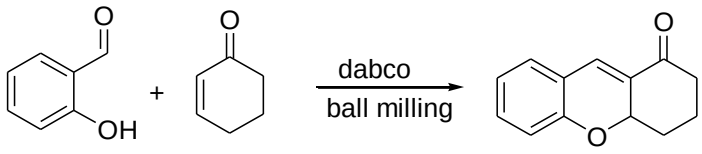


R = NMe_2, OH; R' = H, OMe; R'' = H, Me, Et; X = O, S

Scheme 6 Knoevenagel condensation.

The temperature increase resulting from friction during the milling process was an important factor in the success of these reactions. Various reaction conditions were applied, and a comparison to microwave-accelerated Knoevenagel condensation reactions revealed the superiority of the mechanochemical activation with respect to the energy consumption.

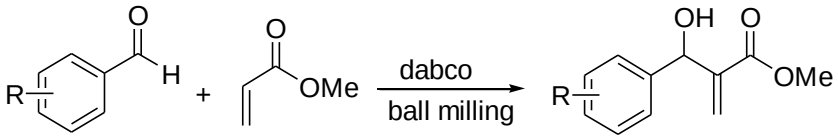
Bräse developed an easy and rapid access to xanthones, a structural motif, which can be found in several natural products.[203] A thorough investigation of the reaction between salicylaldehyde and cyclohexenone was performed in the presence of dabco (50 mol%). This report included an optimization of the reaction conditions with respect to time, ratio of starting materials, rotational frequency and number of balls used in the milling process. A fine-tuning of these factors led to a transformation affording tetrahydroxanthenone in 66% yield (Scheme 7).



Scheme 7 Domino oxa-Michael-aldol reaction.

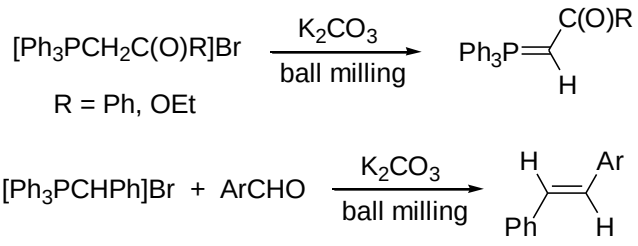
Although the yields of this mechanochemically-induced domino oxa-Michael-aldol reaction were not as high compared to those obtained in solution, the impact of the ball-milling parameters on the yield and chemoselectivity was clearly demonstrated.

Mechanistically related is the Morita-Baylis-Hillman reaction, studied by Mack under ball milling conditions (Scheme 8).[204] Using dabco (20 mol%) as the catalyst, a major rate enhancement was observed, producing products in high yields after a short reaction time (30 min).



Scheme 8 Morita-Baylis-Hillman reaction.

Wittig olefination is important for the formation of alkenes. Balema and Pecharsky showed that various types of phosphorus ylides could be generated mechanochemically in the solid state (Scheme 9).[205] Stabilized ylides were isolated in pure form and semi- and non-stabilized ylides directly reacted with solid organic carbonyl compounds. By this approach, phosphoranes were obtained in yields up to 99%, and "one-pot" Wittig reactions afforded olefins in up to 93% yield.

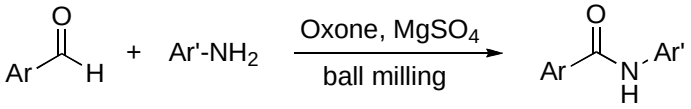


Scheme 9 Wittig reaction.

It is noteworthy not only that this was done under solvent-free conditions, but also that K_2CO_3 was basic enough to deprotonate the phosphonium salt; in solution commonly much stronger bases are required. It

can be noted that our common scales of basicity and acidity are normally solvent-specific, and clearly under solventless conditions acidities and basicities may differ from those expected.

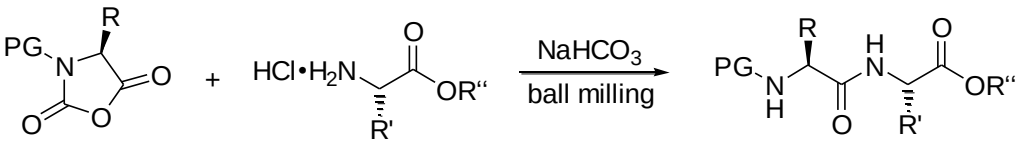
Amides play an important role in synthetic and biological chemistry. Traditional methods for the introduction of the amide function often need expensive transition metal catalysts and/or toxic reagents. To overcome these problems Wang developed a solvent-free route for the direct amidation of aryl aldehydes with anilines in a ball mill (Scheme 10).[206]



Scheme 10 Direct oxidative amidation.

It was found that under those conditions in the presence of $MgSO_4$, Oxone® (potassium peroxymonosulfate, $2KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$) promoted the oxidative coupling in moderate to good yields (up to 78%). For comparison, in acetonitrile and toluene the yields were much lower. Also, in the ball mill the chemoselectivity of the oxidant was higher, with only trace amounts of acid (from the oxidation of the corresponding air-sensitive aryl aldehydes with Oxone®) observed.

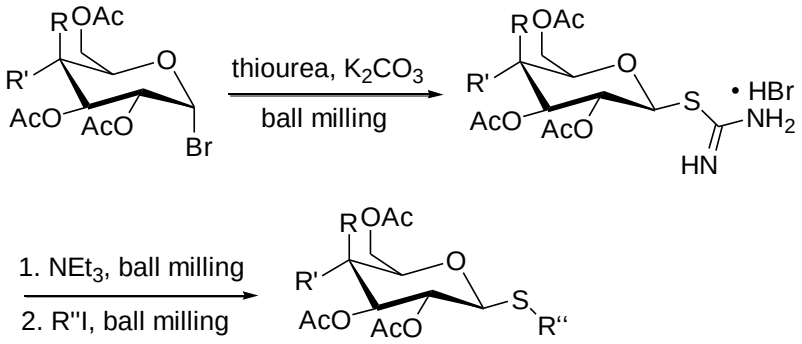
Although the field of peptide synthesis has made significant progress over the last few decades, major challenges remain. One is to reduce the amount of solvents used. Lamaty studied the opening of urethane-protected α-amino acid *N*-carboxyanhydrides with α-amino acid derivatives to afford peptidic products under solvent-free conditions in a ball mill (Scheme 11).[207]



Scheme 11 Solvent-free peptide synthesis.

With $NaHCO_3$ as base, a variety of di- and tripeptides were prepared in high yields. It is significant that educts with a wide range of protecting groups (PG) could be applied and that no epimerization was observed.

Thioglycosides are of interest in oligosaccharide synthesis and as enzyme inhibitiors. A solvent-free approach towards such compounds under ball milling conditions was reported by Kartha (Scheme 12).[208]

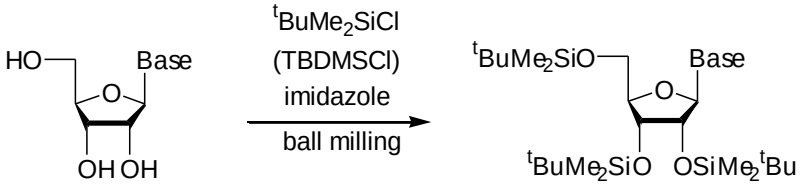


R, R' = H, OAc, R'' = Et, 2,4-di-NO_2-Ph, Ac_4Gal*p*-β-D-

Scheme 12 Synthesis of thioglycosides.

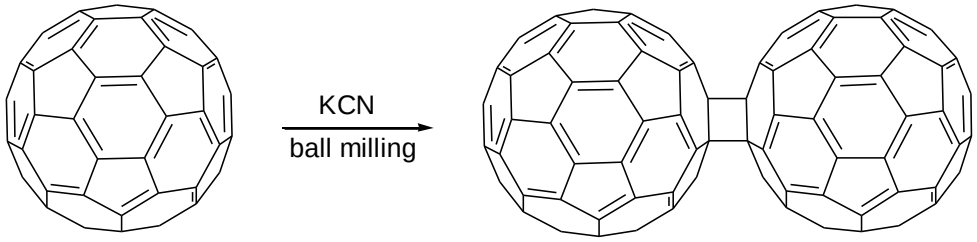
Of particular interest is that alkyl, aryl and glycosyl thioglycosides could be accessed without the need for aromatic solvents, toxic thiols or phase transfer catalysts. A key intermediate in this process was glyosyl thiuronium hydrobromide salt, which allowed a "one-pot" preparation of all products in high yields.

Vyle *et al.* have suggested that ball milling may provide advantages in organic synthesis with biological molecules quite generally.[209] This is because the characteristically poor solubilities of nucleosides, nucleobases, sugars etc. have traditionally required the use of polar aprotic solvents such as DMF (dimethylformamide) or pyridine, which are often toxic or carcinogenic. Solventless ball milling has been used effectively for the addition of TBDMS (^{t}butyldimethylsilyl) protecting groups to phenols as well as a range of nucleosides, avoiding the need for DMF or pyridine altogether (the usual method of purification by chromatography with ethyl acetate and hexane was still required) (Scheme 13).[209] Isolated yields were generally at least 95%. Another advantage of using ball milling was that the starting nucleosides did not need to be predried, which further simplifies the overall process. The conditions were also compatible with trityl protecting groups, and one-pot double protections could be done, in particular *O*-silylation followed by *N*-benzylation.



Scheme 13 Protection of nucleosides without using DMF or pyridine.

Remarkable results have been achieved in reactions of fullerenes under ball milling conditions.[210] Whereas Wudl demonstrated that cyanide added to C_{60} in toluene/DMF,[211] Komatsu found that a C_{120} dumbbell dimer formed in reactions performed under high-speed vibration milling in the absence of solvent (Scheme 14).[212] Other potassium salts such as potassium carbonate and acetate also promoted the reaction, which when optimized gave the dimer and unchanged C_{60} in a ratio of ca. 3:7.

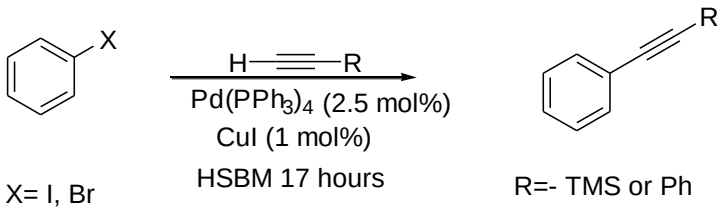


Scheme 14 Fullerene dimerization.

6.3 Metal-catalyzed organic reactions in ball mills

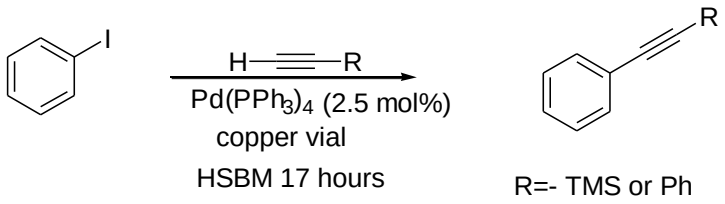
Coupling reactions such as the Suzuki,[213] Heck,[214] Sonogashira[215] and many others have become critical to the synthesis of a variety of organic molecules including organic polymers, natural products and organic light emitting compounds. They are especially useful reactions for the synthesis of carbon based building blocks such as graphene and other nanomaterials. Many of these coupling reactions have been shown to be successful under a variety of alternative methods such as in ionic liquids,[216] microwave reactors[217] or water.[218] This section will focus on the reactions of metal-catalyzed reactions that have been performed under solvent-free ball milling conditions.

The Sonogashira coupling reaction makes a carbon-carbon bond between the sp^2-hybridized carbon of an aryl or alkenyl group with the sp-hybridized carbon of a terminal alkyne. It is typically conducted with an aryl halide (or triflate), a terminal alkyne, and a base in the presence of copper iodide and a palladium catalyst. This reaction was shown to be successful under solvent-free ball milling conditions in high yields with a Spex 8000 M vibratory mixer/mill (Scheme 15).[219] Aryl iodides and bromides gave high yields of coupling products with phenyl acetylene and trimethylsilyl acetylene using palladium tetrakis triphenyl phosphine and copper iodide as catalyst and potassium carbonate as base. Following normal reactivity trends in solution, aryl chlorides were unreactive.



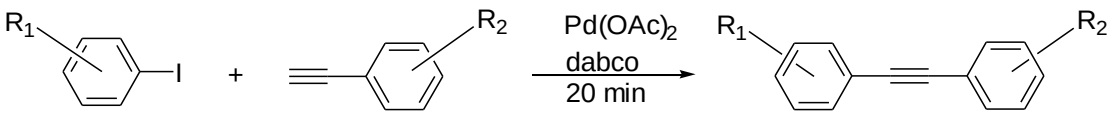
Scheme 15 Sonogashira reaction under solvent-free high speed ball milling conditions

Palladium tetrakistriphenylphosphine and many other palladium(0) catalysts used in coupling reactions are air- and moisture-sensitive. When the Sonogashira reaction is performed in solution, dry solvents and inert atmospheres are needed. However under solvent-free ball milling conditions these reactions can be conducted in an aerobic environment. Most ball milled reactions are carried out in a stainless steel vial with stainless steel balls. When the Sonogashira reaction is ball milled in a stainless steel vial without copper iodide, it proceeds in moderate yield. However if the reaction is conducted in a copper vial it gives the product in high yield (Scheme 16). This demonstrates that the material of the vial and/or ball can be a source of the catalyst.



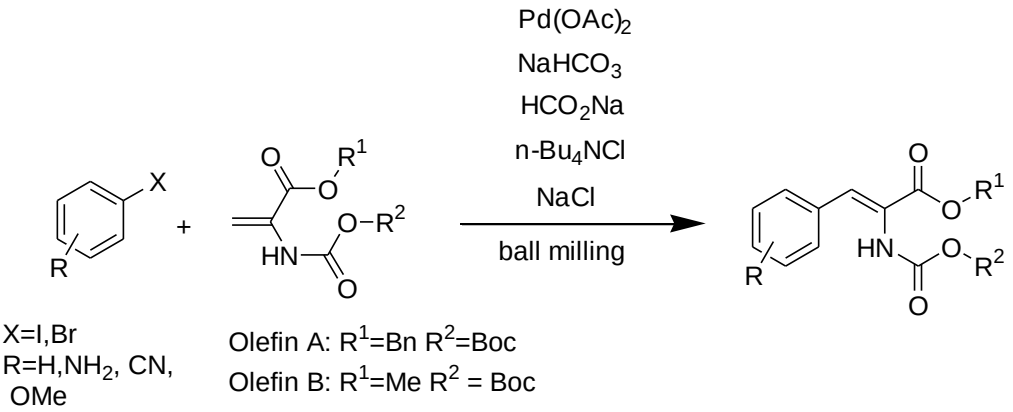
Scheme 16 Sonogashira reaction using a copper vial as the catalyst

Ondruschka demonstrated that the Sonogashira reaction can be conducted under ball milling conditions using more robust palladium(II) catalysts such as palladium acetate and palladium chloride.[220] These reactions were conducted in the absence of additional ligands and copper. The reaction was completed in 20 minutes using (Scheme 17). This catalytic system was successful with aryl iodides but not with aryl bromides. The rate and yield were highly dependent upon the substrate, grinding media and catalyst used.



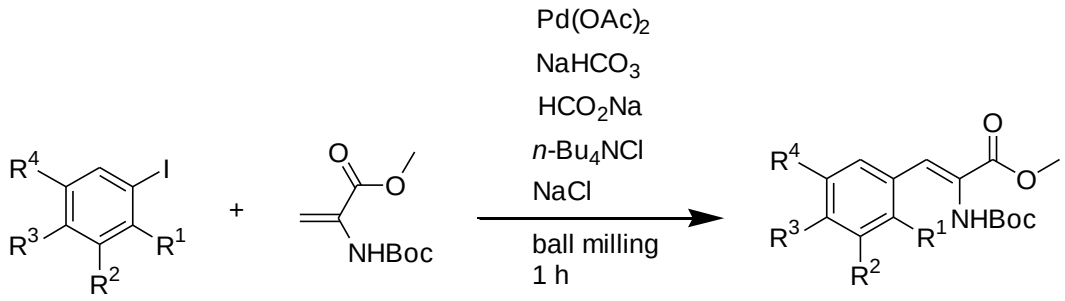
Scheme 17 Ligand- and copper-free Sonogashira reaction under planetary milling

The Heck reaction is an important palladium-catalyzed coupling and can be used to synthesize many important compounds such as unsaturated and unnatural amino acids. It forms a carbon-carbon bond between an aryl halide (or triflate) and an olefin. Frejd demonstrated the Heck reaction under solvent-free ball milling conditions (Scheme 18).[221] Using various aryl compounds to couple with olefins (A and B) they were formed variety of organic products. Using sodium formate as a reductant for the Pd(II) catalyst improved yields. Similar to solution reactions, aryl iodides were better coupling partners than bromides. Approximately 5 mol% catalyst loading is optimal. The product formed was the Z isomer, showing that diastereoselectivity can still be observed under energetic ball milling conditions. The ball milling conditions gave higher yields than alternative methods. Coupling of iodobenzene and methyl-2-[(*tert*-butoxycarbonyl)-amino] acrylate gave 77% yield by ball milling, whereas using a hydraulic press to reach pressures of 200 kg/cm^2 gave 13% yield. Heating to 80°C with and without stirring gave 33% and 18% yields respectively. Microwave experiments also generally gave lower yields than in the ball mill. It was concluded that it must be the combination of pressure, heat, grinding, and stirring in the ball mill that accounted for the success of the reaction and not just one of those components individually.



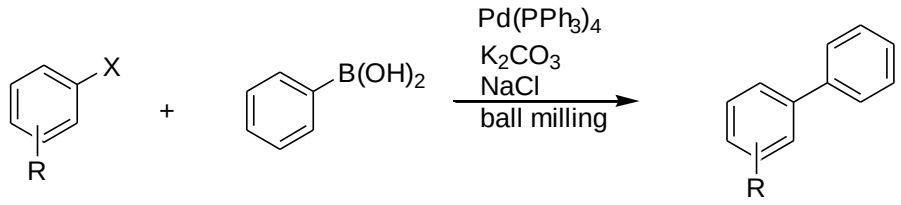
Scheme 18 An example of the ball milled Heck reaction

Various amino- and hydroxyl-substituted dehydrophenylalanine derivatives could also be made from amido acrylate in modest to good yields under Heck-Jeffery conditions (Scheme 19).[222] The system requires a stoichiometric amount of tetraalkylammonium salt but is both solvent- and phosphine-free.



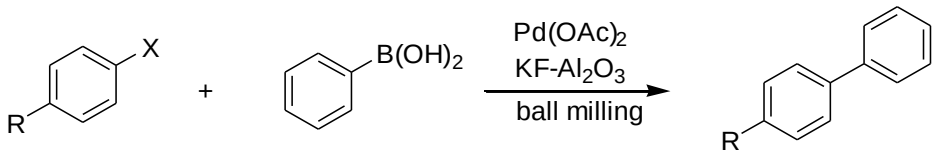
Scheme 19 General scheme for the Heck reaction under ball milling conditions

The Suzuki reaction couples boronic acids with aryl halide, typically iodides or bromides. Peters *et al.*[223] demonstrated this reaction under solvent-free, ball milling conditions (Scheme 20).



Scheme 20 Suzuki reaction using potassium carbonate and sodium chloride

Recently, Ondruschka and coworkers[224] found that potassium carbonate (base) and sodium chloride (grinding medium) could be replaced with potassium fluoride supported on basic alumina (Scheme 21).

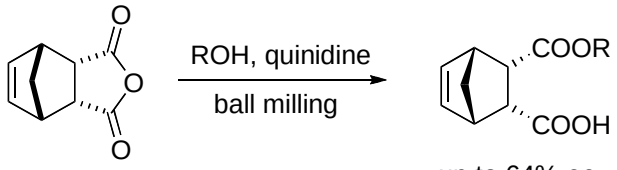


Scheme 21 Suzuki reaction in the presence of $KF\text{-}Al_2O_3$

Ondruschka also found that under ball milling conditions aryl bromides were more reactive than aryl iodides, which contrasts with Suzuki reactions in solvents. It was also found that the greater water content of the alumina, the greater the reaction.[225]

6.4 Organocatalytic asymmetric reactions in ball mills

The asymmetric opening of *meso*-anhydrides has been in the focus of several investigations.[226] Using alkaloids or their derivatives as catalysts, high enantioselectivities have been achieved providing synthetically highly useful products. Commonly, the reactions are performed at low temperatures (ambient to –50°C), and significant amounts of non-polar solvents such as toluene are used.[227] Studies of asymmetric anhydride openings with quinidine in a ball mill were performed by Bolm *et al.* (Scheme 22).[228]



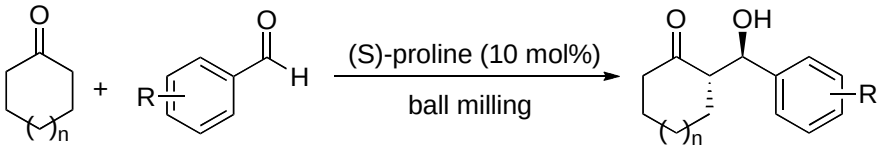
up to 64% *ee*

ROH = benzylic or aliphatic alcohols

Scheme 22 Organocatalytic asymmetric anhydride openings.

Compared to the analogous reactions in toluene, where *ee*-values of up to 99% had been achieved, the enantioselectivities were lower (up to 64%). The higher temperatures in the ball mill might account for this difference. However, ball milling was beneficial in that no solvent was required almost equimolar amounts of starting materials could be used (a 3-fold excess of the nucleophile is common in solution reactions).

Proline-catalyzed aldol reactions are the most-studied organocatalytic asymmetric C-C-bond forming reaction.[229] They proceed *via* enamine intermediates generated *in situ* from one of the carbonyl components and the catalyst. Commonly, highly polar solvents such as DMSO, DMF or water are applied, which are difficult to remove after the reaction. Solvent-free reactions of this type under ball milling conditions were first performed by Bolm *et al.*.[230] Using 10 mol% of proline and nearly equimolar amounts of starting materials excellent yields (mostly >90%) of the *anti*-aldol products were obtained and both diastereo- and enantioselectivity were high (up to 99% *ee*) (Scheme 23).



up to 99% *ee*

Scheme 23 Proline-catalyzed asymmetric aldol reaction.

Various factors affecting yield and stereochemistry were studied,[231] and ball milling was superiorior to conventional stirring. In a similar approach Guillena and Nájera studied direct aldol reactions between ketones and aldehydes under solvent-free conditions.[232] A combination of BINAM-prolinamide (5-10 mol%, Figure 11) and benzoic acid (10-20 mol%) was used. The aldol products had up to 98% *ee* and were obtained in up to 90% yield.

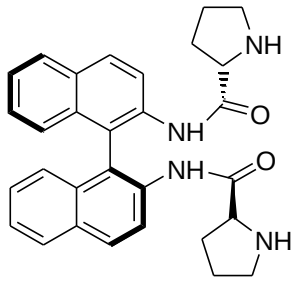


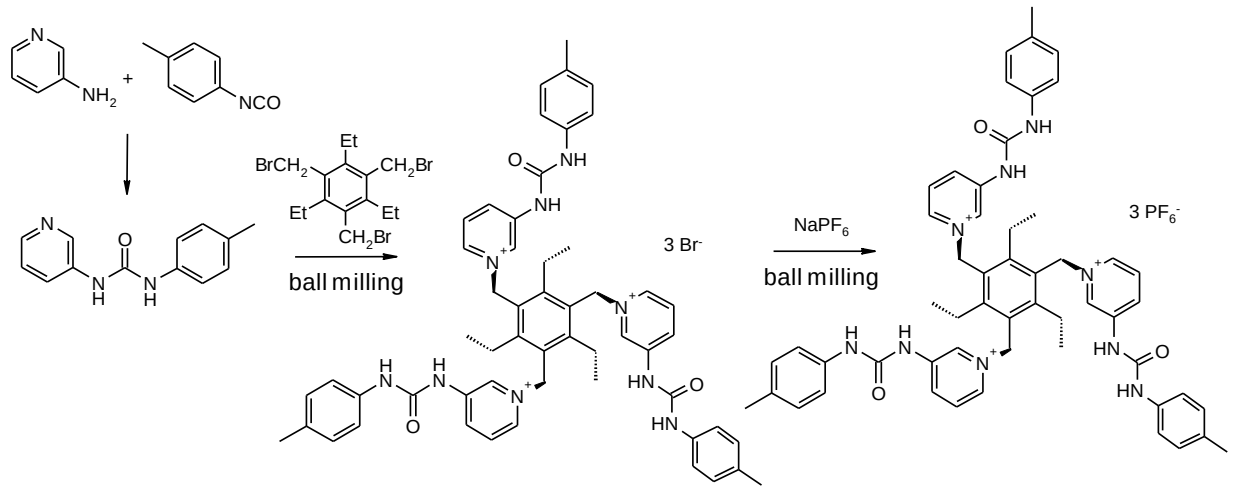
Figure 11 Binam-prolinamide organocatalyst applied in asymmetric aldol reactions.

Recently, Bolm *et al.* studied the phase behaviour of the proline-catalyzed aldol reactions between solid substrates under solvent-free conditions.[233] A significant nonlinear relationship between the *ee* of the catalyst (proline) and that of the aldol product was found, which was suggested to originate from the ternary phase behaviour of scalemic proline. Subsequent studies led to the discovery of an enantioenrichment by iterative retro-aldol/aldol reaction catalyzed by an achiral or racemic base.[234]

6.5 Synthesis of ligands and hosts

Organic synthesis in balls mills has been applied in a number of cases to ligands and hosts. In the early 2000s Raston and Scott.[18, 235] developed mechanochemical syntheses based on aldol condensation, Baeyer-Villiger oxidation, azomethine synthesis, aromatic bromination, alcohol etherification and benzyl alcohol oligomerization.[18] Also reported was a route to Kröhnke type pyridines (Scheme 24).[235c] The mechanochemical approach involved solventless aldol condensation followed by Michael addition with a second ketone. It gave unsymmetrical compounds in excellent yield, some of which are inaccessible using conventional methods.

Swinburne and Steed used LAG reactions of pyridine derivatives with benzylbromide derivatives to give tripodal pyridinium anion binding hosts. There are no byproducts and no purification was required. This S_N2 substitution, leaving a bromide counter anion is, however, just part of the overall scheme which starts by reaction of 3-aminopyridine with an isocyanate to give a pyridyl urea (Scheme 24). An additional post-reaction step involves metathesis of the bromide counter ion to the less coordinating PF_6^-. In fact this entire sequence lends itself to mechanochemical synthesis and the combined molecular and supramolecular steps in the sequence were all carried out on the solid product using either neat reagents or LAG in yields generally comparable to the solution based alternatives. While overall the method proved versatile, clean and convenient, some pyridine derivatives did not react at all and in other cases yields were low for reasons that are unclear but which may relate to the sterically hindered nature of the system.[237]

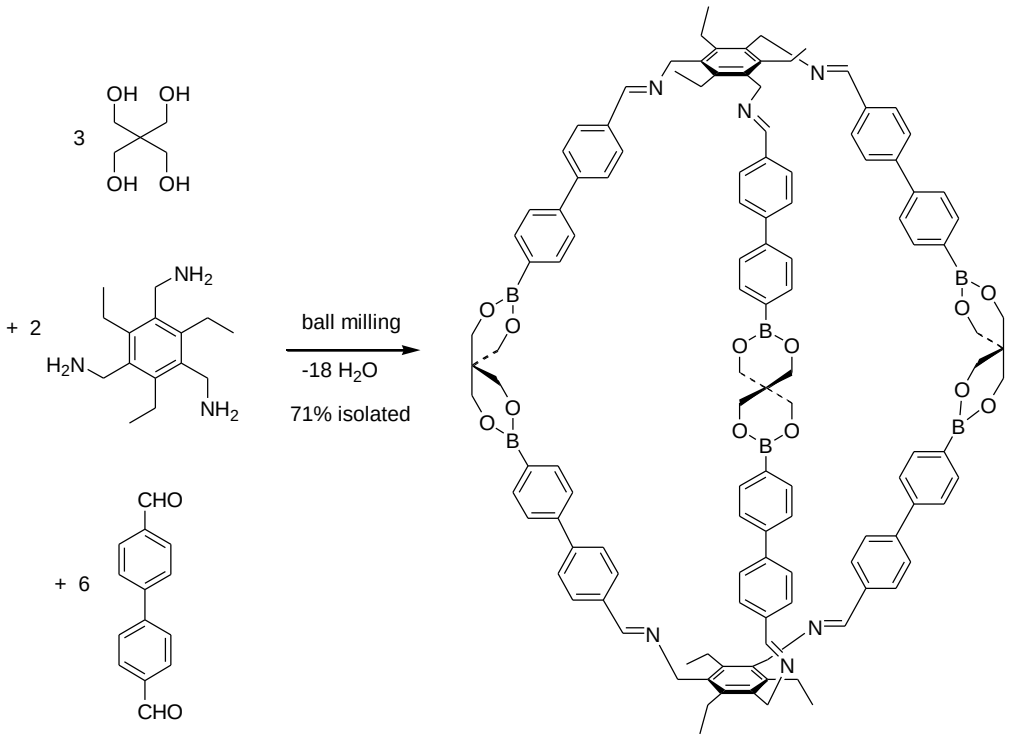


Scheme 24 Combined neat or liquid assisted grinding synthesis of a supramolecular anion host.[237]

Mechanochemical methods have also been investigated in the context of macrocyclic hosts, specifically unusual calix[*n*]arene (*n* = 5 or 7), [4]resorcarene and cyclotriveratrylene (CTV) derivatives, and, recently, covalent organic cages. A mixture containing *p*-benzylcalix[5]arene (10-15% when isolated) and *p*-benzylcalix[7]arene (5-10% when isolated) is produced from ball milling a mixture of the *p*-benzylcalix[6 or 8]arenes in the presence of KOH and formaldehyde. Dehydration was achieved with sacrificial molecular sieves. Similar conversions were seen in refluxing diphenyl ether solutions. An interesting byproduct was the very unusual *p*-benzylcalix[10]arene.[238] *Tris*-(*O*-allyl)cyclotriveratrylene is formed after manual grinding of solid benzyl alcohol monomers with a suitable solid acid (the mixture becomes a viscous liquid) and leaving to stand for 10 days. After solvent-base work-up 35% of the product was isolated.[239] Related calix[4]resorcinarenes cab be obtained in 80-96% yield by manual grinding of resorcinol and benzaldehyde derivatives with *p*-toluene sulfonic acid as catalyst at ambient temperature.[240] The mixture becomes a viscous liquid and then solidifies. Isolation involves washing with water and recrystallization from methanol. Yields are comparable to the solution-mediated routes and the process is convenient. [4]resorcarenes have a tendency to self assemble into giant hydrogen bonded capsules. This tendency is shared by the closely related [4]pyrogallolarenes derived from 1,2,3-trihydroxybenzene (pyrogallol). Reaction of liquid isovaleraldehyde with a fine dispersion of pyrogallol and a catalytic amount of solid *p*-toluenesulfonic acid with grinding milling using a mortar and pestle results in a condensation reaction to give a brittle white solid within two minutes. This solid is milled to a fine, yellow powder which whose solid state ^{13}C NMR spectrum was consistent with a hexameric hydrogen-bonded capsule.[241]

Severin *et al.* found that very large covalent organic cages could be assembled by solvent-free ball milling without solvent. Remarkably, the reaction involves formation of 18 boronate ester and imine linkages between eleven components and was significantly higher-yielding than in solution, although solvent

(toluene) was still required for purification.[242] Mechanochemistry enabled the synthesis and isolation of the large cage shown in Scheme 25 (71% isolated yield). A smaller version of this cage was obtained in 94% yield by the mechanochemical method, compared to only 24% from solution synthesis.



Scheme 25 Solventless ball milling synthesis of a large organic cage from ref.[242]

Examples described in this subsection show that macrocyclization and cage formation can be remarkably effective under solventless ball milling conditions, and even more favoured than in solution. This is intriguing given the very high concentrations present and the consequent expectation for larger oligomers or polymers (it seems to be the extreme opposite of traditional high-dilution approaches). Elucidating the underlying reasons for such product speciation would be of great interest.

6.6 Conclusions

Various bond-forming reactions can be accelerated under mechanochemical conditions compared to solution-based methods, and that the use of hazardous or otherwise undesirable solvents can simultaneously be minimized. It is also noteworthy that the energy demands of ball milling have begiun to

be evaluated in this context and can be low compared to other techniques such as microwave heating.[35] Furthermore, previously unknown molecular transformations have been reported, some of which have proved impossible in solution. As with solution-based methods, as the use of ball milling becomes more widely accepted, it would be encouraging to find replacements for palladium catalysts for coupling reactions with less expensive transition metals such as nickel and iron under these conditions.

7. Synthesis of discrete metal complexes

7.1 Introduction

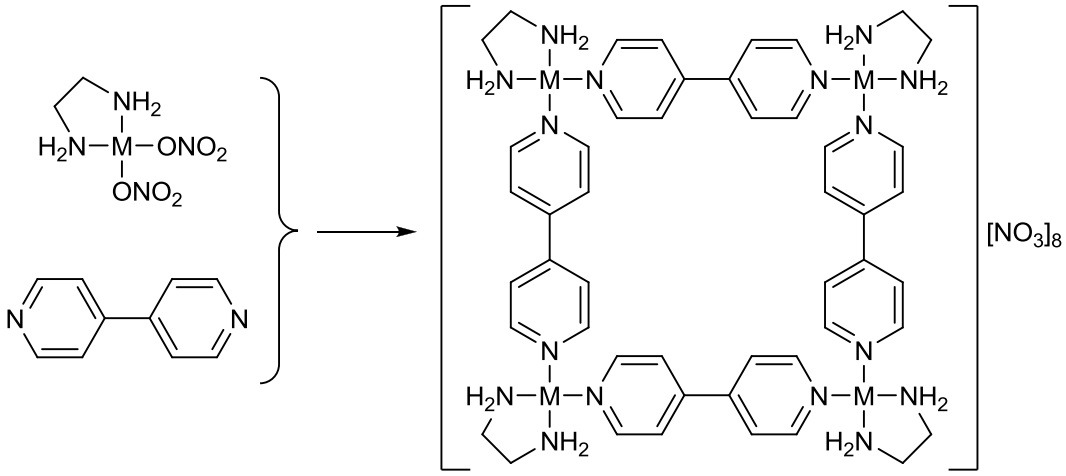
The complexation of metal ions is a fundamental and very diverse class of reaction, spanning great ranges of characteristics such as lability, and with applications from small (e.g. radiopharmaceuticals) to very large scales (e.g. metal extraction). As with organic synthesis, it has almost exclusively been developed as solution-state chemistry. However, a growing amount of literature suggests that solvent-free grinding and liquid assisted grinding (LAG) are effective for a wide range of metal complexation reactions. This section deals with discrete metal complexes (coordination polymers are dealt with in Section 8). It is organized by reaction type, specifically ligand additions, ligand additions with elimination, acid-base reactions and main group complexes.

7.1 Ligand addition reactions

Many coordination complexes can readily be formed by grinding simple transition metal starting materials with potential ligands. Thus, grinding $Ni(NO_3)_2{\cdot}6H_2O$ or $FeCl_2{\cdot}4H_2O$ with 1,10-phenanthroline gives $[Ni(phen)_3](NO_3)_2$ [243] or $[Fe(phen)_3]Cl_2$ [244] respectively, grinding $PtCl_2$ with triphenylphosphine gives $PtCl_2(PPh_3)_2$,[41] and grinding hydrated or unhydrated MCl_2 with imidazole gives $MCl_2(imidazole)_2$ (M = Co, Cu, Zn).[245] Grinding MCl_2 (M = Co, Ni, Cu) with ligands L (L = PPh_3, $OPPh_3$, $OAsPh_3$ [246] or toluidine[247]) gave the complexes MCl_2L_2, and in a more risky application of the methodology $Ni[ClO_4]_2$ was ground with $OPPh_3$ to give $[Ni(OPPh_3)_2(ClO_4)_2]$.[246] 2-aminopyrimidine (2-Apy) may be ground with either one or two equivalents of $CuCl_2$ to form the complexes $CuCl_2$(2-apy) and $CuCl_2(2\text{-apy})_2$ respectively,[248] and dimethylglyoxime (H_2dmg) will react with NiX_2 (X = Cl, NO_3) to form $[Ni(H_2dmg)_2]X_2$.[249] Grinding thiourea or a derivative with silver salts AgX (X = NO_3, SO_4, ClO_4) gave compounds with various silver:thiourea ratios depending upon the stoichiometry used,[250] and whilst grinding $PtCl_2$ with imidazole (Him) gave $[PtCl_2(Him)_2]$, the analogous reaction with $PdCl_2$ gave the salt $[Pd(Him)_4]Cl_2$.[251] More complicated ligands may also be used, such as the amino acid gabapentin which can be ground with MCl_2 (M = Cu, Zn) to form $MCl_2(gabapentin)_2$.[252] Simple metal *salts* may also be made in this way, as grinding two equivalents

of imidazolium chloride ([H_2im]Cl) with the metal chlorides MCl_2 (M = Co, Cu, Zn) gave the imidazolium tetrachlorometallates $[H_2im]_2[MCl_4]$.[245]

It is also possible to use more complicated metal precursors than simple salts; the iron(III) centre of the protoporphyrin complex hemin will coordinate two imidazole molecules[253] or two fluoride ions[254] upon co-grinding, and reaction of $M(en)(NO_3)_2$ (M = Pd, Pt; en = ethan-1,2-diamine) with 4,4′-bipyridine forms the tetranuclear square $[M(bipy)(en)]_4(NO_3)_8$ (Scheme 26).[255] This last reaction illustrates the benefits that solid-state reactions can have over the equivalent solution reactions – formation of the platinum complex takes 4 weeks at 100 ºC in solution, but is complete in 10 minutes by grinding.



Scheme 26 Formation of a tetranuclear square by grinding.[255]

7.2 Ligand addition reactions with elimination of a by-product

New complexes may also be formed by replacing a ligand at a metal centre and eliminating it as a by-product or part of a by-product; for example, reaction of $PtCl_2(PPh_3)_2$ with K_2CO_3 displaces the chloride ligands and forms $Pt(CO_3)(PPh_3)_2$ with elimination of KCl.[41] Various tris(pyrazolyl)borate complexes have been made by grinding thallium salts of the ligands with MCl_2 starting materials (M = Mn, Co, Ni), eliminating TlCl and forming the desired products with greater efficiency than the corresponding reactions in solution.[256] Grinding (in an inert atmosphere) thallium cyclopentadienylide with iron or nickel dichlorides gave ferrocene and nickelocene respectively in good yields; potassium and sodium cyclopentadienylide did not give such good yields, but milling $FeCl_2$ with sodium methylcyclopentadienylide gave 1,1′-dimethylferrocene with 90% conversion.[257]

Mechanochemistry may often prove useful in the conversion of inert and insoluble coordination polymers into more tractable molecules, by reaction with extra ligands that break up the polymeric structure. Thus the inert species $[Nb_2(E_2)_2Cl_4]_\infty$ (E = S, Se) react with anionic bidentate ligands LL, such as

dithiocarbamates, xanthates and oxalate salts, to form $[Nb_2(E_2)_2(LL)_4]$ with the elimination of chloride,[258] and $[M_3E_7Br_4]_\infty$ (M = Mo, W; E = S, Se) can be broken up with oxalate to give $[M_3E_7(ox)_3]^{2-}$ anions[259] or with bromide to make $[M_3E_7Br_4]^{2-}$.[260] Grinding polymeric VO(salen) is suggested to give monomers directly without added ligands.[261]

7.3 Acid-base reactions

A third method of synthesising coordination compounds by grinding involves acid – base reactions of three types. Type 1 is the reaction of a basic metal salt MX and a salt of a protonated ligand $[HL]^+$ to give the complex ML, illustrated by the reaction of imidazolium chloride ([Him]Cl) with cobalt hydroxide or carbonate to form the imidazole complex:[245]

$$2[Him]Cl + CoCO_3 \rightarrow CoCl_2(im)_2 + CO_2 + H_2O$$

$$2[Him]Cl + Co(OH)_2 \rightarrow CoCl_2(im)_2 + 2H_2O$$

Analogous reactions were also reported with basic zinc or copper carbonates[245] and palladium acetate.[251] A variant of this class involves a neutral pro-ligand HL, in which case the conjugate anion is incorporated into the product; for example the deprotonation of the amino acid glycine by copper(II) hydroxide to form $Cu(gly)_2$, or the reaction of 1,2,4,5-benzenetetracarboxylic acid (H_4btec) with $Mg(OH)_2$ to form bimetallic $Mg_2(btec)(H_2O)_{10}$.[262] Further use of the acetate ion as a base is illustrated by the reaction of copper acetate with alanine:[263]

$$Cu(OAc)_2{\cdot}H_2O + 2Hala \rightarrow Cu(ala)_2 + 2HOAc + H_2O$$

and the reaction of nickel acetate with dimethylglyoxime to form $[Ni(Hdmg)_2]$[249] or with nicotinic acid to form nickel bis(nicotinate)[264] (the same researchers have reported very similar results with Ca,[265] Zn,[266] Mn and Mg[267]). A number of metal compounds bearing substituted acac ligands are formed on grinding $M(OAc_2)$ (M = Mn, Cu, Zn) with the protonated proligand.[268] The use of a metal isopropoxide species was demonstrated in the reaction of $Al(O\textit{i}Pr)_3$ with ammonium fluoride:[269]

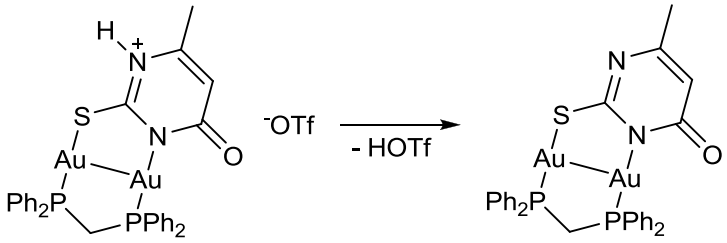
$$Al(O^{\textit{i}}Pr)_3 + 6NH_4F \rightarrow [NH_4]_3[AlF_6] + 3NH_3 + 3^{\textit{i}}PrOH$$

Type 2 acid – base reactions involve the addition of an external base to a metal salt of a protonated pro-ligand. This was reported in the reaction of the imidazolium salts $[Him]_2[MCl_4]$ (M = Co, Cu, Zn) with potassium hydroxide, generating a stoichiometric mixture of the desired coordination compound and potassium chloride:[245]

$$[Him]_2[MCl_4] + 2KOH \rightarrow MCl_2(im)_2 + 2KCl + H_2O$$

Similarly, pyrazolium tetrachloropalladate, $[H_2pz][PdCl_4]$, can be deprotonated with potassium *tert*-butoxide to form $[PdCl_2(Hpz)_2]$, whilst the analogous platinum system requires silver oxide to effect a clean reaction.[251]

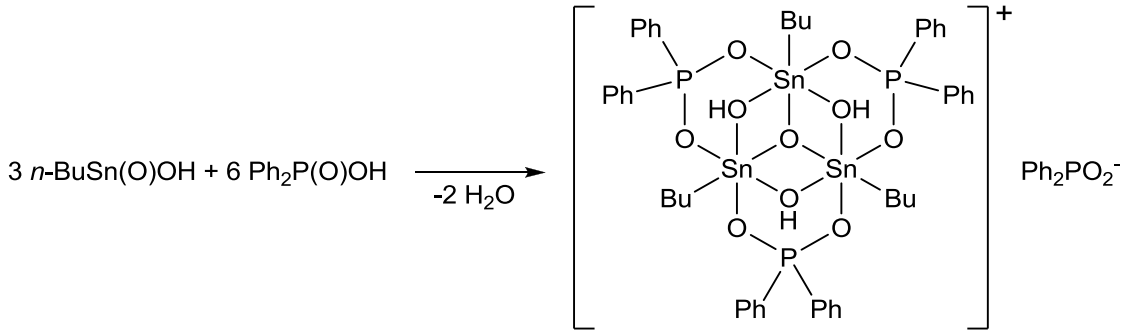
Type 3 acid - base reactions involve those compounds that release an acid without addition of a base. There are systems that will do this spontaneously, but the gold system reported by Eisenberg (Scheme 27) appears unique in that the acid vapour is only released when the crystals are crushed.[270] The change is accompanied by a dramatic change in the luminescence properties of the system, a phenomenon which has been named luminescence tribochromism.[271]



Scheme 27 Deprotonation by crushing of a digold(I) compound.[270]

7.4 Main-group compounds

Mechanochemistry has also been applied to the synthesis of molecular main-group compounds. A great deal of Russian work in this area was summarized by Volkov,[272] who reported syntheses of diborane through the reduction of MBH_4 (M = Li, Na, K) by a variety of reducing agents; if the hydrochloride of a nitrogen-donor Lewis-base is used as the reducing agent then the product obtained is the borane adduct. Reactions with larger clusters are also feasible, as the preparation of $SnB_9C_2H_{11}$ from $CsB_9C_2H_{12}$ demonstrated.[272] Another class of reaction summarized in the same work[272] is the formation of metal tetrahydridoborates through milling of metal chlorides MCl_x (M = Zn, Cd, Ti, Zr, Hf, U) with lithium, sodium and potassium borohydrides, which builds on work first reported in 1957.[273] In a similar vein, calcium and magnesium tetrahydridoaluminates can be made from appropriate combinations of $MAlH_4$ (M = Li, Na) and $M'Cl_2$ (M′ = Ca, Mg).[274] Some particularly elegant examples of acid-base reactions were reported by Chandresekar *et al.*, who reacted a range of organotin oxides and hydroxides with protic reagents such as carboxylic, suphonic or phosphinic acids. This produced in excellent yields a variety of organotin clusters and cages with complicated but well-defined architectures (Scheme 28).[275]



Scheme 28 A mechanochemical organotin reaction.[275]

7.5 Conclusions

Generally it appears that the formation of metal-ligand bonds in the solid-state can be a powerful and general alternative to solution-based techniques, although it can be noted that most studies so far have concentrated on the more labile metal ions. Mechanochemical methods have also yet to be widely applied to the large range of air-sensitive metal complexes such as those of low-valent platinum-group metals, organometallic compounds of electropositive metals etc., although ball milling is compatible with inert atmosphere techniques. Also with regard to this, some organic reactions catalysed by Pd complexes have been found to be more tolerant to air under ball milling than when done conventionally in solution (see Section 6.3) Therefore, avoidance of solutions might provide advantages in dealing with air-sensitive species.

8. Synthesis of coordination polymers (MOFs)

8.1 Introduction

Coordination polymers or metal organic frameworks (MOFs) have become one of the most intensely researched areas of materials chemistry. This section is organized by reaction type in a similar way to the previous section, specifically ligand addition, ligand exchange and acid-base reactions. These three reaction types have been investigated through different mechanochemical methodologies: neat grinding,[276] liquid-assisted grinding (LAG) or kneading[24] and grinding-annealing.[277] There are some analogies with cocrystals (Sections 4 and 5) in that the extended solid state packing is the key point of interest. Because of their growing technological importance, mechanosynthesis of porous MOFs is discussed separately.

8.2 Coordination polymers by ligand addition

The addition of neutral ligands to metal-containing building blocks has been extensively used for the construction of coordination polymers. In fact, possibly the first mechanochemical synthesis of a coordination polymer was a reaction of this type.[278] In particular, Bourne *et al.* found that the 1-D zig-zag polymer $ZnBr_2$(pyrazine) could be ground with a further equivalent of pyrazine in a small 'WIG-L-BUG' type shaker mill to give the 2-D square grid $ZnBr_2(pyrazine)_2$. In a further example, Pichon and James used neat grinding of copper(II) acetylacetonate $Cu(acac)_2$ or hexafluoroacetylacetonate $Cu(hfac)_2$ with 4,4'-bipyridyl (bipy) to give 1-D polymers held together by axial Cu-N bonds.[39] The grinding products $Cu(acac)_2(bipy)_n$ and $Cu(hfac)_2(bipy)_n$ were obtained quantitatively and identified through powder X-ray diffraction (PXRD) (Figure 12a).

As with mechanochemical cocrystallisation, stepwise mechanisms can occur in such reactions, as noted during neat grinding of anhydrous $ZnCl_2$ with the diamine [2.2.2]-diazabicyclooctane (dabco).[279] The first step is the formation of crystalline hydrate Zn Cl_2(dabco)·$4H_2O$, which upon heating or further grinding dehydrates to the 1-D zigzag polymer $ZnCl_2$ (dabco). The formation of an intermediate hydrate was ascribed to the hygroscopic nature of dabco, illustrating how the atmosphere can influence the course of a mechanochemical reaction. If the mechanosynthesis was conducted in dry air with dried reactants the non-hydrated polymer $ZnCl_2$(dabco) formed without observable intermediates.[279] With the less hygroscopic 4,4'-bipyridyl (bipy) an analogous zigzag 1-D polymer was formed in a single step.[280] In contrast, the construction of a 2-D sheet polymer $CoCl_2$(bipy) from anhydrous $CoCl_2$ and bipy was not possible by neat grinding. The polymer could, however, be obtained by neat grinding of $CoCl_2·6H_2O$ and bipy, suggesting that the water produced by desolvation of the reagents plays an important role in achieving mechanochemical reactivity (Figure 12c).[280] The construction of polymer $CoCl_2$(bipy) from anhydrous $CoCl_2$ was possible by LAG however.

An increased rate of reaction in LAG over neat grinding was also observed in the synthesis of ethylenethiourea (etu) adducts of silver halides.[250a] For example, while neat grinding of AgI and etu gave no reaction, LAG with a small amount of water quantitatively gave $AgI(etu)_2$. LAG was also applicable to the construction of coordination polymers based on other silver salts.[250b]

The addition of a liquid is not only a means to accelerate or enable a mechanochemical reaction, but also an opportunity for molecular inclusion in coordination polymer hosts. This was demonstrated by Braga *et al.*[281] with a versatile 1-D polymer host composed of copper(II) chloride and 1,4-diaminocyclohexane (dace). Although the polymer could not be obtained by neat grinding of $CuCl_2$ and dace, LAG of the two components with a small amount of DMSO gave the host polymer $CuCl_2$(dace) and inclusion of DMSO to form $CuCl_2$(dace)·*n*DMSO.

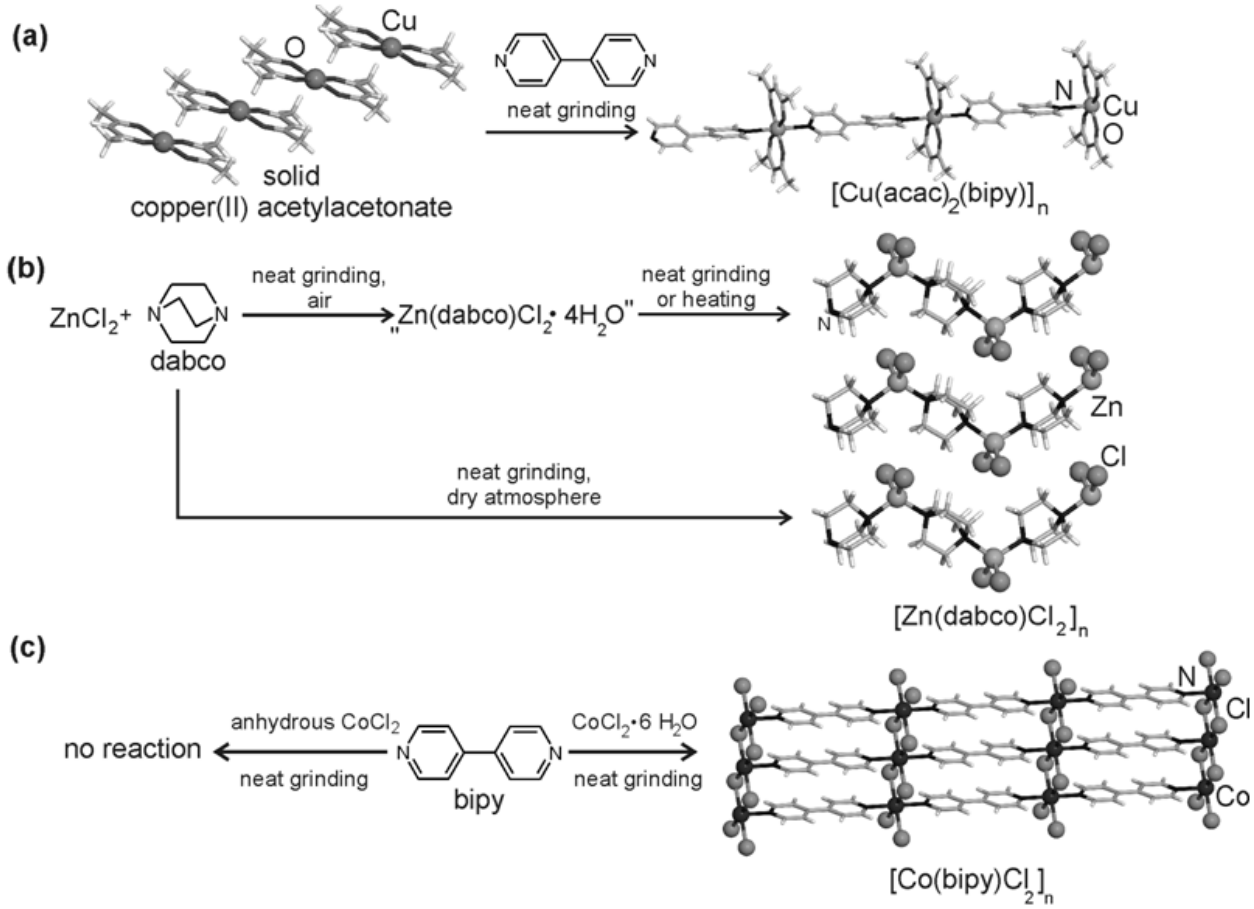


Figure 12 (a) Mechanochemical construction of a 1-D coordination polymer from copper(II) acetylacetonate and bipy;[39] (b) formation of the coordination polymer $ZnCl_2$(dabco) by manual grinding in air and grinding in a dry atmosphere;[279] and (c) difference in mechanochemical reactivity of bipy towards anhydrous $CoCl_2$ and $CoCl_2·6H_2O$.[280]

Similarly, LAG using water gave inclusion compound $CuCl_2(dace)\cdot nH_2O$ (dace = 1,4-diaminocyclohexane). Both structures are 'clay-like' with layers of $CuCl_2(dace)$ chains separated by layers of guests.[281] Thermal desolvation gave the non-solvated polymer $CuCl_2(dace)$ which reversibly included a variety of organic molecules upon kneading and suspension overnight.

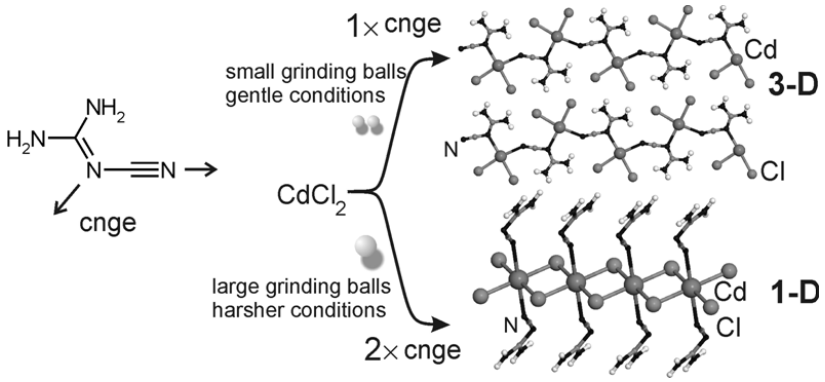


Figure 13 The ligand cnge with different metal binding sites indicated by arrows and its reactions with $CdCl_2$ upon neat grinding under various reaction conditions.

The ligand addition reactions of $ZnCl_2$ or $CdCl_2$ with cyanoguanidine (cnge, Figure 13) illustrate the effect of varying neat grinding conditions on coordination polymer mechanosynthesis.[282] The ligand has two different binding sites, enabling the formation of polymers with different metal:ligand ratios and, hence, dimensionality. Grinding $ZnCl_2$ with one or two equivalents of cnge provides the 1-D polymer $ZnCl_2(cnge)$ or the discrete complex $ZnCl_2(cnge)_2$, respectively. Neat grinding of $CdCl_2$ and cnge in a 1:1 ratio provides the 3-D coordination polymer $CdCl_2(cnge)$. The product was always obtained as a pure phase and was structurally characterised using powder XRD data. In contrast to $ZnCl_2$, neat grinding of $CdCl_2$ and cnge in the 1:2 stoichiometric ratio provided only a mixture of $CdCl_2(cnge)$ with excess ligand. The 1-D polymer $CdCl_2(cnge)_2$ could be obtained only through harsher grinding conditions, *i.e.* by employing heavier grinding balls (Figure 13). The difficulty to form 1-D $CdCl_2(cnge)_2$ was tentatively related to the higher dimensionality and, hence, kinetic stability of the 3-D $CdCl_2(cnge)$. Similar observations were also made for the reaction of CdI_2 and cnge.[282] The solid-state synthesis and analysis of $Cd(cnge)Cl_2$ and $CdCl_2(cnge)_2$ were used as a proof-of-principle of a solvent-free approach to laboratory research.

8.3 Coordination polymers by ligand exchange

Manual grinding of copper(II) acetate monohydrate with 1,3-bis(4-pyridyl)propane (pn) replaced the water molecules on the cluster with bridging pn ligands, producing a water inclusion compound of a zigzag 1-D polymer (Figure 14a).[283] The ^{13}C MAS-NMR spectrum was identical to that of the methanol solvate, excluding the resonances of guest methanol.[283] Manual grinding of silver acetate and dabco displaces

the acetate ligands by dabco and with simultaneous water absorption from the air gives $AgOAc(dabco)_2 \cdot 5H_2O$ (Figure 14b).[279] This illustrates how important the surrounding atmosphere can be in mechanosynthesis.[279] Inclusion of moisture was also observed in the mechanochemical reaction of AgOAc with dace.[284] Neat grinding gave a coordination polymer tentatively characterized as AgOAc (dace)$\cdot n H_2O$ whose crystal structure is not yet known although recrystallization from anhydrous methanol or by passing a stream of dry argon yields two structurally similar products: $AgOAc(dace) \cdot 3H_2O$ and $AgOAc(dace) \cdot H_2O_{0.5} \cdot CH_3OH$, respectively.

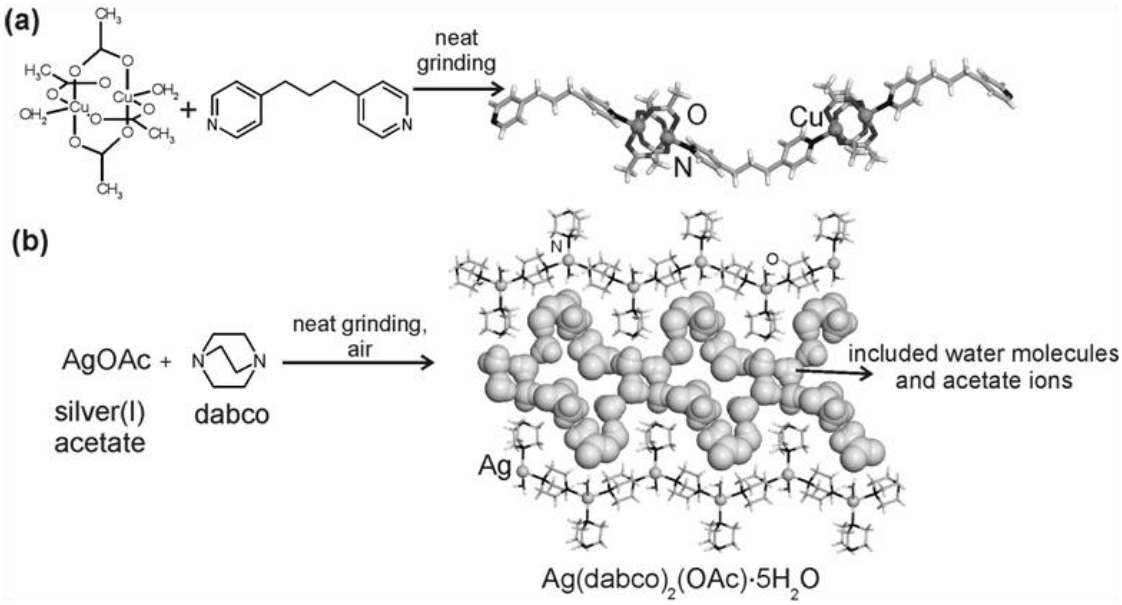


Figure 14 (a) Mechanochemical construction of a 1-D coordination polymer by ligand exchange on the copper(II) acetate paddlewheel complex;[283] (b) formation of a hydrated coordination polymer by neat manual grinding of silver(I) acetate and dabco in air. Water and acetate guests are shown using the space-filling model.[279]

8.4 Acid-base reactions

In this reaction class the combination of metal acetates with organic acids, accompanied by the release of acetic acid, is particularly noteworthy. For example hydrated nickel(II) acetate and acetylenedicarboxylic acid (H_2adc) react to form a hydrated 3-D coordination polymer $Ni(adc)(H_2O)_2$.[39, 285] Analogously zinc(II) acetate dihydrate gave a previously unknown 3-D polymer $Zn(adc)(H_2O)_2$, isostructural to the Ni(II) polymer.[39] Similarly Stein and Ruschewitz prepared coordination polymers based on alkaline earth metals, by grinding-annealing of magnesium or calcium acetates with H_2adc. The resulting materials Ca(adc) and $Mg(adc) \cdot 2H_2O$ were isostructural to Sr(adc) and $Mn(adc) \cdot 2H_2O$.[286] The acidic ligand in such reactions does not, however, need to be a carboxylic acid, as demonstrated by Yoshida *et al.*, who

conducted neat manual grinding of transition metal acetates with 3-cyanoacetylacetone (HCNacac).[268] For Fe(II), Co(II) and Ni(II) non-porous 3-D frameworks were obtained.[268] The formation of $[Ni(CNacac)_2]_n$ in pure form is noteworthy, as solution methods yield a product contaminated with $Na[Ni(CNacac)_3]$.[268, 277, 287] Reactions with other acetates gave previously unknown mononuclear complexes $Mn(CNacac)_2{\cdot}2H_2O$, $Cu(CNacac)_2{\cdot}H_2O$ and $Zn(CNacac)_2{\cdot}H_2O$. Upon heating to 100 ^oC, these complexes lose water to form coordination polymers, further illustrating the applicability of grinding followed by annealing in mechanosynthesis. Grinding-annealing is also effective for the thermal dehydrohalogenation of mutually isomorphous 4,4'-bipyridinium salts of $FeCl_4^{2-}$, $CoCl_4^{2-}$ and $ZnCl_4^{2-}$ anions, prepared by neat grinding of 4,4'-bipyridinium chloride with $FeCl_2{\cdot}4H_2O$, $CoCl_2$ (or $CoCl_2{\cdot}6H_2O$) and $ZnCl_2$, respectively. The heating step eliminates HCl gas to leave 1-D zigzag (with Zn) or 2-D sheet (with Fe and Co) polymers.[280, 288] The dehydrohalogenation could also be achieved through the addition of an external base, such as KOH, rather than heating leaving a product containing KCl byproduct.

The use of only slightly soluble carbonate or oxide reactants is also possible. Metal oxides are attractive precursors due to low cost, ready availability, and because the only byproduct is water. Mechanochemical reactivity of metal oxides with organic ligands was explored by Fernandez-Bertran,[289] who obtained known coordination polymers of Ag(I), Zn, Cd and Hg(II) by neat grinding of respective metal oxides and imidazole, although no reactions occurred with PbO or MgO. Adams *et al.* obtained the 2-D polymer $CoCl_2$(bipy) by LAG of cobalt(II) carbonate with bipyridinium chloride.[288] The product was identical to that obtained by LAG of $CoCl_2$ and bipy with water. LAG of basic zinc carbonate with bipyridinium chloride gave a mixture of two polymorphs of the polymer $Zn(bipy)Cl_2$. This contrasts with the neat grinding reaction of $ZnCl_2$ and bipy which yields only one polymorph (see above).

The reaction of ZnO with fumaric acid (H_2fma) was used to rapidly screen for reactions by LAG.[290] Different liquid additives resulted in different products. Anhydrous zinc fumarate and a previously unknown dihydrate were structurally characterized directly from PXRD data. Grinding with three or four equivalents of water gave selectively the zinc fumarate tetrahydrate and the pentahydrate respectively, which form as a mixture from solution.[291] Subsequent study revealed that the formation of different products can be correlated with the activity of water in the grinding liquid, and that LAG with pure water proceeds in a stepwise fashion.[292] A crystalline hydrate forms first, which depletes the free water in the mixture so as to change the liquid-assisted reaction into a neat grinding process (Figure 15). The latter is speculated to proceed through an amorphous intermediate, deduced by the spontaneous formation of different coordination polymers by ageing of the partially reacted reaction mixture (Figure 15). A stepwise mechanism was also observed in the reaction of CuO with acetic acid.[292]

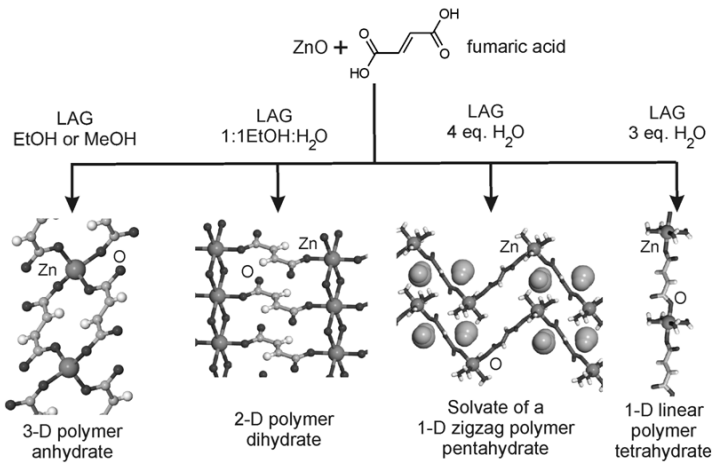


Figure 15 Screening for coordination polymers from ZnO using LAG.[290]

8.5 Porous MOFs by mechanochemistry

Porous metal-organic materials are an intensely researched area. Mechanochemical synthesis of such phases was demonstrated by James *et al.*,[40] by an acid-base reaction between copper acetate and isonicotinic acid (Hina) to give $Cu(ina)_2$. Neat grinding gave the porous framework quantitatively in a few minutes, with the acetic acid and water byproducts partially lost and partially included in the pores (Figure 16a). The latter could be completely removed by heating. A similar approach gave the industrially relevant open framework $Cu_3(btc)_2$ (btc = 1,3,5-benzenetricarboxylate) or HKUST-1 (pore diameter ca. 9 Å) by neat grinding of copper(II) acetate with trimesic acid (see below for the properties of the mechanochemically-prepared material).[293]

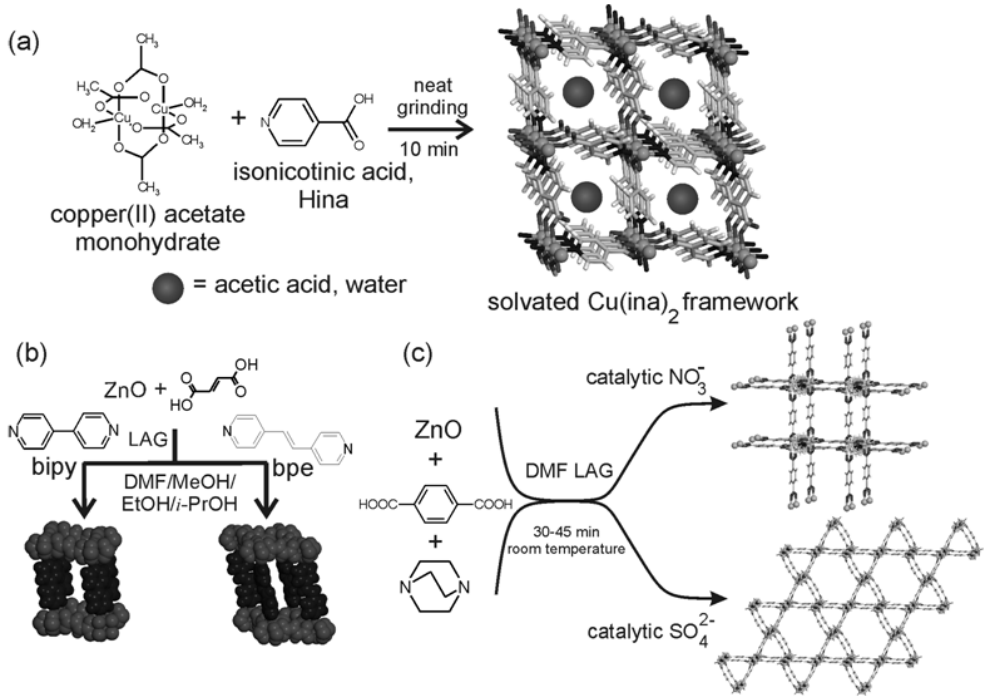


Figure 16 Mechanochemical synthesis of porous MOFs: (a) by neat grinding;[40] (b) by liquid-assisted grinding[294] and by ion- and liquid-assisted grinding, exploiting the catalytic effect of nitrates and sulfates.[295]

Liquid-assisted grinding of ZnO, H_2fma and the bridging ligand with DMF, methanol, ethanol or 2-propanol quantitatively yielded porous MOFs pillared by bipy or *trans*-1,2-bis(4-pyridyl)ethylene (bpe).[290] The latter, previously unknown, MOF was structurally characterized from powder diffraction data by Rietveld refinement to the known copper-analogue.

Mechanosynthesis of a pillared material with larger pores based on terephthalic acid and dabco proceeded very slowly and in low yield. However, the synthesis could be completed within 45 minutes by adding catalytic amounts of an alkali metal or ammonium nitrate salt (Figure 16c).[295] This ion- and liquid-assisted grinding (ILAG) gave a pillared framework based on square grid layers with ca. 15 Å pore diameter.[296] Replacing nitrate catalysts with sulfates gave the hexagonal isomer of this material framework within 30 minutes, with pores of ≈18Å diameter. Although the structural basis of such templating and catalytic effects are not yet known, solid-state NMR studies indicate that salt inclusion within the neutral MOF plays a significant role. In contrast, the analogous pillared framework involving bipy could be readily obtained by LAG.[37]

Synthesis from metal oxides can also give zeolitic imidazolate frameworks (ZIFs). Whereas neat grinding of ZnO with solid imidazole has limited scope in such synthesis, LAG or ILAG gave rapid and quantitative formation of a series of close-packed and open-frameworks. The grinding liquid and the ionic salt catalyst

enhance the reactivity and direct the final product topology. The reactions proceed by stepwise mechanisms in which the most porous structures are formed first and subsequently transform to more close-packed ones. This resembles an Ostwald staging process in which the less stable frameworks of low density (expressed as the ratio of tetrahedral sites (T) and the volume (V) of the unit cell) transform to more stable, denser structures (Figure 17b).

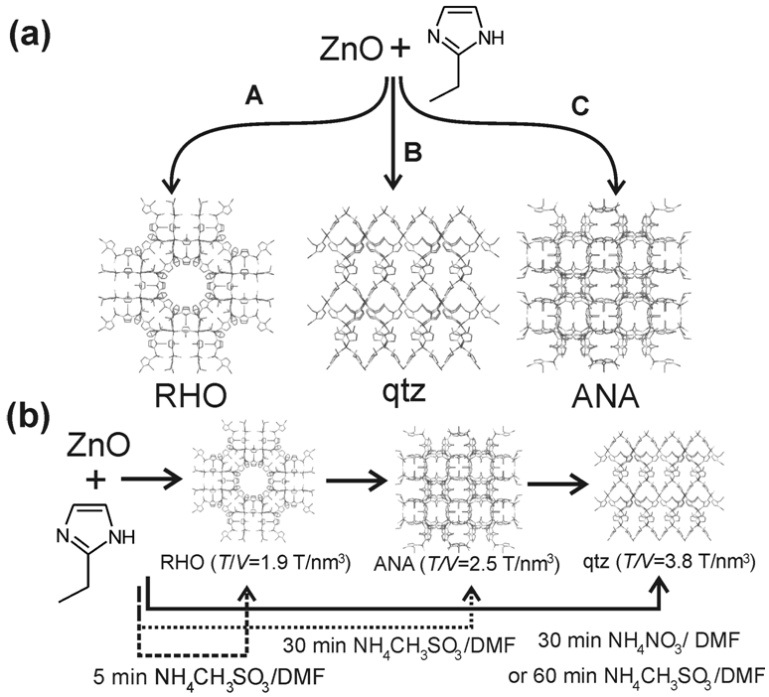


Figure 17 (a) Topologically specific mechanosynthesis of zeolitic imidazolate frameworks (ZIFs) directly from ZnO and 2-ethylimidazole using ILAG. Pathway A represents ILAG with $(NH_4)_2SO_4$; B is ILAG with NH_4NO_3 or $NH_4CH_3SO_3$ in the presence of EtOH and C is ILAG with $NH_4CH_3SO_3$ and DMF or DEF as the liquid phase; (b) time-dependent ZIF transformations under ILAG conditions, *T/V* is the number of tetrahedral sites (T) per nm^3.

While the synthesis of pillared MOFs using ILAG clearly reveals an anion-directing effect, ZIF synthesis strongly depends on the use of weakly acidic ammonium salts and appears to arise from their influence on the rate of interconversion between different structures, rather than from specific structure-templating effects.

A recently reported aspect of reactivity is the labile nature of MOFs under LAG.[37] Three different structural forms of Zn-bdc frameworks (bdc = benzenedicarboxylate) interconverted upon brief grinding with a suitable liquid (Figure 24b). This is probably effectively a grinding-assisted recrystallisation since the product was normally found to be the least soluble form in the liquid used for LAG. Pillared mixed-ligand structures could also be obtained by grinding these Zn-bdc phases with dabco or bipy.

Significantly, some of the mixed-ligand products could not be obtained as single step reactions showing that two-step strategies can be useful.[37, 297]

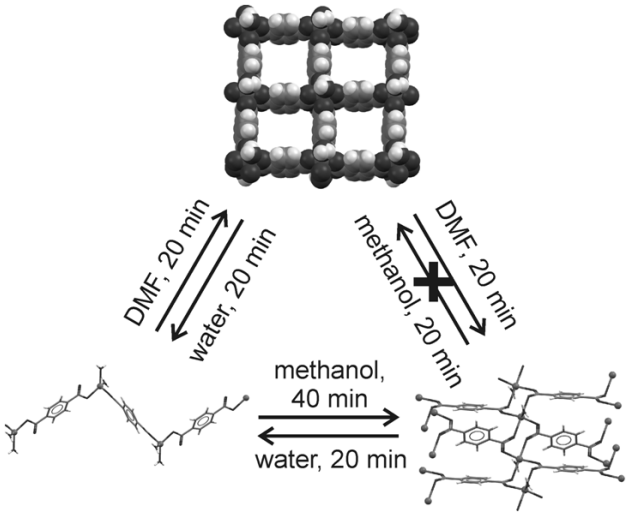


Figure 18 Mechanochemical interconversion of 1-D, 2-D and 3-D MOFs by LAG.[37]

The porosity of mechanochemically prepared MOFs has begun to be investigated. Yuan *et al.*,[297a] found that the Brunauer-Emmett-Teller (BET) surface area of $Cu_3(btc)_2$ (HKUST-1)[298] obtained by neat grinding or LAG of copper(II) acetate monohydrate with benzene-1,3,5-tricarboxylic acid was comparable to that of samples obtained by conventional solution-based routes. Another study by Schlesinger *et al.* [299]compared neat and liquid-assisted mechanosynthesis with a variety of other procedures, involving room-temperature and reflux solution synthesis, solvothermal reactions, microwave-assisted synthesis, sonochemical and electrochemical syntheses. The BET surface area and specific pore volume of HKUST-1 samples could be further increased if the reaction was conducted using LAG with DMF. The resulting surface area and pore volume were comparable to those for samples made solvothermally. Similar observations have been made by Emmerling *et al.* who also extended the synthesis to MOF-14 $Cu_3(btb)_2$ (btb is the larger tricarboxylate 4,4',4''-benzenetribenzoate). So far, in order to obtain high surface areas, immersion in bulk solvent has been required during the post-synthetic activation step for mechanochemically-synthesis MOFs.[300] It will be interesting to see with other examples or by adapting the reaction conditions whether this requirement can be avoided.

8.6. Solid solutions

Mechanochemical syntheses are interesting for the formation of solid solutions since they can circumvent troublesome solubility variations between different metal ions or ligands to give homogeneous products more readily than solution methods.**[301]** Formation of solid solutions of coordination polymers has been

demonstrated by James et al. LAG reactions of mixtures of different rare earth metal carbonates with 1,3,5-benzenetricarboxylic acid.[302][303] Mixed-lanthanide (Sm-Gd, Eu-Gd, Tb-Gd and Dy-Gd) 3-D open frameworks isostructural to those obtained from individual metal carbonate reactants were obtained. Notably, this work also shows the extension of mechanochemical MOF synthesis to trivalent metals. Adams *et al* [304] explored solid solutions for the synthesis of materials with systematically controllable lattice parameters and physical properties. LAG of anhydrous $CoCl_2$ or $CoBr_2$ with bipy gives the isostructural 2-D sheet coordination polymers $CoCl_2$(bipy) and $CoBr_2$(bipy) respectively. Correspondingly, LAG of mixtures of anhydrous $CoCl_2$ and $CoBr_2$ yields solid solutions of composition $CoBr_{2-x}Cl_x$(bipy) which were homogeneous at length scales detectable by powder X-ray diffraction. The solid solutions were isostructural to the single phases $CoCl_2$(bipy) and $CoBr_2$(bipy), but with lattice parameters which varied linearly with *x* over the range 0-2.

8.7 Conclusions

Mechanochemical synthesis in the burgeoning field of coordination polymers and MOFs is attractively fast and convenient, does not require additional heating, can sometimes be achieved starting from metal oxides, and avoids bulk solvent in the reaction step (although it may be needed for effective activation). The only waste product of the oxide-based reactions is water. As with cocrystals, there remain challenges in determining the structures of new phases since large single crystals are not obtained directly. However, products can be used to seed the formation of large crystals from solution and advances in structure solution from PXRD are making structure determination from these data more common (see Section 9). Again as with cocrystals, new phases different to those formed from solutions can be obtained, and it will be interesting to establish which generic differences may exist be between solventless mechanochemical and solution-based products.

9. Structural characterization of mechanochemically prepared materials

9.1 Introduction

Mechanochemistry is applicable to diverse types of synthesis, and in each case, the appropriate techniques for characterization of the product may differ. In some areas (particularly organic synthesis and with less-labile metal complexes), the normal methods of solution-state NMR or HPLC, etc, remain appropriate for monitoring reactions and for product identification, because of the inert nature of the products and the emphasis on molecular structure rather than crystal packing. However, in other areas (particularly cocrystals and coordination polymers, or MOFs), it is the crystal packing that is of key

interest. Also, labile molecular products may rearrange in solution. In such cases, it is clearly important to be able to characterize the mechanochemical product directly, without dissolution or solvent-based recrystallization. Such characterization is particularly important for previously unknown structures. However, because mechanochemical products are normally microcrystalline powders, single-crystal X-ray diffraction (XRD) usually cannot be applied. Instead, powder XRD (PXRD) is generally the main technique employed while other techniques (particularly solid-state NMR spectroscopy) can also yield valuable structural insights. Methods for structure determination from PXRD data have improved over recent years so that they can now be applied successfully to structures of moderate complexity, although it remains significantly more challenging than for structure determination from single-crystal XRD data. Due to its importance for gaining insights into mechanochemical reaction products, methods and illustrative examples are discussed in this Section.[305]

9.2 Assessing whether a mechanochemically prepared material is new

To determine if the crystal structure of a mechanochemical product is new, its experimental PXRD pattern must be compared with those of known materials (using either experimental data or data simulated from single crystal structures). Such comparison is commonly carried out "by eye" rather than subjecting the PXRD data to rigorous quantitative analysis. Unfortunately, this leaves considerable scope for misinterpretation. It is true that, in favourable cases, visual comparison may indeed provide unambiguous confirmation of whether the two patterns match or differ. However, as discussed below, experience shows that deeper scrutiny is frequently required.

PXRD patterns for the same material may actually appear significantly different as a result of instrumental factors, details of the data collection procedure and microstructural characteristics of the powder itself (e.g. the size, shape and orientational distribution of the crystallites). Therefore PXRD peak widths and intensities may vary significantly, which is especially important in regions of peak overlap. Even peak positions may differ due to instrumental factors or differences in the temperature at which data were collected (commonly single crystal data are obtained at low temperature and PXRD data at room temperature).

Conversely, small differences between PXRD patterns, which represent real structural differences in the samples, are often overlooked and materials are erroneously assumed to have the same crystal structure. Relevant issues here include differences in superstructures, crystal symmetry, occupancy of framework structures and degrees of disorder. An example, taken in part from ref.[306] is illustrated in Figure 19. Although very similar, detailed comparison reveals important differences (in this case at $2\theta \approx 29°$) which means the two materials cannot be identical (see Figure 21 for the actual structural differences).

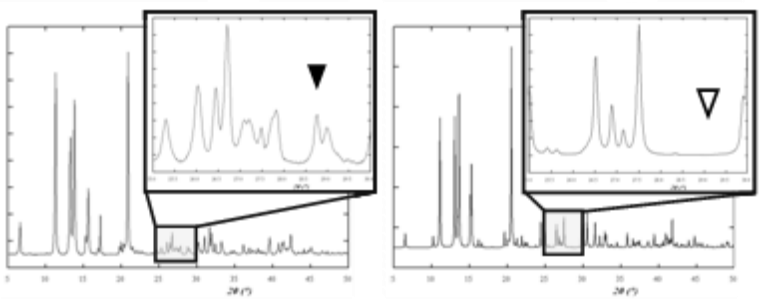


Figure 19 An example of comparison between the experimental powder XRD pattern of a material prepared by mechanochemical synthesis (left) with the simulated powder XRD pattern of a potential candidate of known structure prepared previously by a solvothermal route (right). Adapted from ref. 306, permission to be sought.

However, all of these factors can be taken into consideration by appropriate quantitative analysis. Thus, conducting a Rietveld refinement[307] using the experimental PXRD data with the crystal structure of the known material as the initial structural model is recommended.

9.3 Complete structure determination from powder XRD data

The recent upsurge in structure determination of molecular solids from powder XRD data has coincided with the development of the direct-space strategy. In this method trial structures are generated independently of the PXRD data, and then assessed against the PXRD data in an iterative process. This approach is particularly suited to materials constructed from well-defined modular building units (such as in metal-organic-frameworks). However, there have also been several reports of structure solution of molecular solids using traditional approaches such as the Patterson method, or the recently developed charge flipping algorithm.[308] These latter approaches are preferred when peak overlap is not severe and when there is less knowledge of the geometries of the molecules present.

The use of solid-state NMR in conjunction with XRD data serves as a particularly powerful combined experimental approach.[309][310] For example, solid state NMR can help to i. establish the composition, ii. identify tautomeric forms, iii. identify specific types of interactions (e.g. hydrogen bonding), iv. quantify inter-atomic distances, v. obtain *a priori* insights on the existence of disorder (including dynamic processes), and vi. assess whether the molecules occupy general positions or special positions. Such information can be important in setting up the correct structural model for use in structure solution calculations from powder XRD data, or for validation of results from Rietveld refinements.

The first [155] use of powder XRD to determine the structure of a mechanochemically prepared cocrystal was for the ternary structure (*bis*-β-naphthol)·(benzoquinone)·(anthracene)$_{0.5}$. Grinding a physical mixture of the three components gives a reddish purple polycrystalline powder with a different structure to the bluish-black cocrystals obtained from solution. Structure solution was carried out using the direct-space technique. The final crystal structure obtained following Rietveld refinement is shown in Figure 20, and may be rationalized on the basis of three different interaction motifs: edge-to-face interactions between benzoquinone (edge) and anthracene (face) molecules, face-to-face interactions between benzoquinone and *bis*-β-naphthol molecules, and chains of O–H···O hydrogen bonds involving *bis*-β-naphthol and benzoquinone molecules. This structure, with the naphthalene molecules lying on a two-fold rotation axis, was supported by the solid state ^{13}C NMR spectrum.

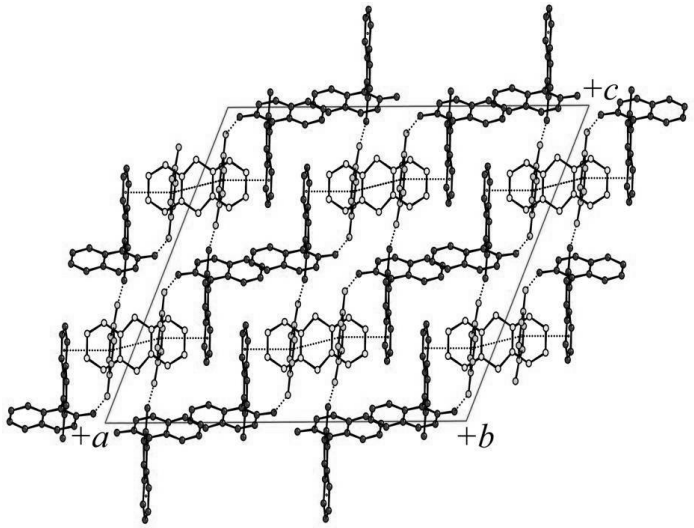


Figure 20 Crystal structure of the ternary cocrystal (*bis*-β-naphthol)·(benzoquinone)·(anthracene)$_{0.5}$. determined from PXRD data. Dotted lines indicate π-stacking interactions and hydrogen bonded chains. Reproduced from ref. 155, permission to be sought.

Another example concerns a porous interpenetrated mixed-ligand metal-organic-framework $Zn_2(fma)_2(bipy)$, prepared mechanochemically from $Zn(OAc)_2.2H_2O$, fumaric acid (H_2fma) and 4,4'-bipyridine (bipy).[306] As shown in Figure 21, its crystal structure bears some similarity to a previously reported DMF solvate material $Zn_2(fma)_2(bipy)\cdot(DMF)_{0.5}$ prepared by a solvothermal route, for which the crystal structure was determined from single-crystal XRD data.[294] Nevertheless, there are important structural differences between these materials, primarily concerning the fact that the bipy ligands in the DMF solvate are constrained to be planar (due to the mirror plane in the *C*2/*m* space group), whereas there is no such constraint in the structure of the mechanochemically prepared material (for which the space group is $P2_1/a$), and the dihedral angle between the two rings of the bipy ligand is 53.2° (see Figure 19 for a comparison of the PXRD data of the mechanochemical product and the simulated pattern for the

dmf solvate). Interestingly, desolvation of the DMF solvate material yields a material identical to that prepared by the mechanochemical synthesis.

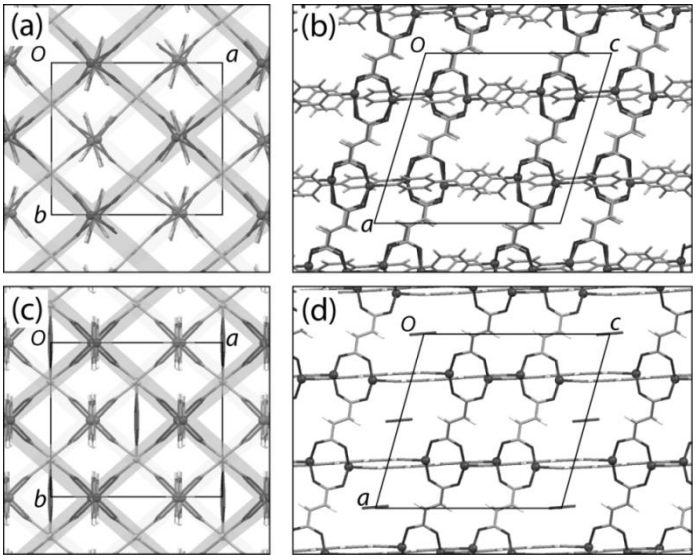


Figure 21 Crystal structure of a metal-organic framework material $Zn_2(fma)_2(bipy)$ prepared by mechanochemical synthesis, with structure determination carried out directly from powder XRD data,[306] viewed (a) along the *c*-axis and (b) along the *b*-axis. The two (identical) interpenetrated frameworks are indicated by yellow and purple shading. For comparison, (c) and (d) show the corresponding views of the structure of a DMF solvate material $Zn_2(fma)_2(bipy)\cdot(DMF)_{0.5}$ prepared by a solvothermal route.[294] Although there is some similarity between these structures, it is nevertheless clear that there are important structural differences. Reproduced from ref. 306, permission to be sought.

Other reports of crystal structures of materials prepared under mechanochemical conditions being determined directly from PXRD data include the metal-organic framework Co(dibenzoylmethanate)$_2$(nicotinamide)$_2$. This material was obtained by thermal desolvation of the corresponding acetone solvate, which was prepared by liquid-assisted grinding (LAG).[311] The structure comprises "wheel-and-axle" units of composition Co(dibenzoylmethanate)$_2$(nicotinamide)$_2$, which are assembled through hydrogen-bonded amide-amide interactions involving the nicotinamide molecules of neighbouring units, giving rise to anti-parallel chains of amide functionalities in a ladder-type motif. There are channels with approximately hexagonal cross-section running parallel to the hydrogen-bonded amide ladders (Figure 29).

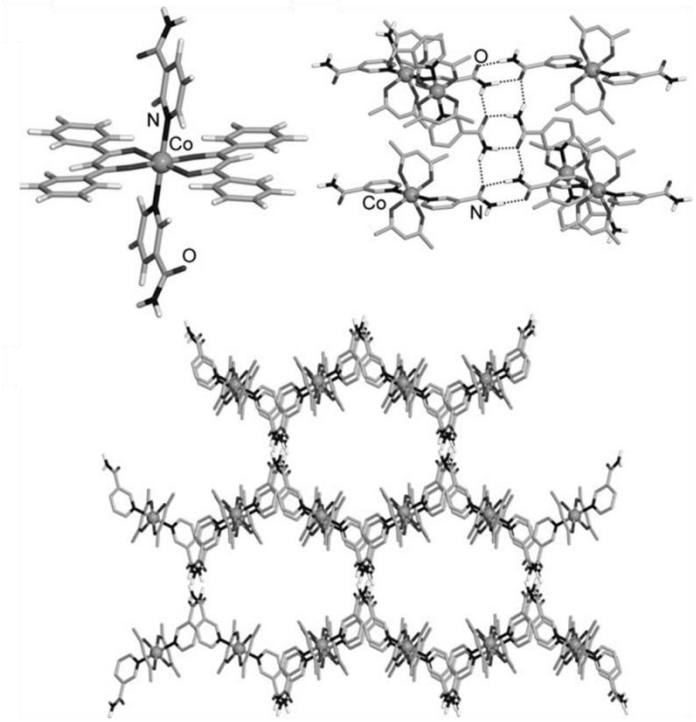


Figure 22 Structure of Co(dibenzoylmethanate)$_2$(nicotinamide)$_2$ determined directly from PXRD data

Further examples of organic materials include a hydrate cocrystal of 5-methyl-2-pyridone and trimesic acid, prepared by grinding a methanol solvate cocrystal of the same components under ambient atmospheric conditions,[312] and 1:1 cocrystals of theobromine with trifluoroacetic acid and theobromine with malonic acid, each prepared by LAG.[185]

9.4 Conclusion

As mechanochemistry becomes more widely used it is likely that structure solution from PXRD will become applied more extensively. It can be noted that this tool will be important toward understanding why the crystal structures of mechanochemical products often differ to those of materials crystallized from solution.

10. Obstacles and inherent limitations to the mainstream adoption of mechanochemistry

The previous sections show that mechanochemistry can clearly offer advantages as an alternative to traditional solvent-based synthesis, in that new or improved reactivity can be discovered and less (or

even no) solvent may be needed. However, some obstacles and limitations to the technique can be identified as follows.

Product purification: As mentioned in Section 1.3, even if a mechanochemical reaction step itself is solvent-free, solvents *may* still be needed for purification. Although many molecular mechanochemical reactions proceed to completion there will still be cases when non-volatile by-products and/or small traces of starting materials are present at some level, and can only practically be removed by solvent-based extraction or recrystallization. It is clearly unrealistic that mechanochemistry could make all of chemical synthesis completely solvent-free. Therefore it is important to try to identify the types of situations in which mechanochemistry *can* provide a clear advantage over conventional solvent-based approaches. These include: i. When, *overall*, it allows *less* solvents to be used, or if it avoids the use of particularly *undesirable* (toxic, carcinogenic etc.) solvents; ii. when it allows less energy to be used (see also '*Energy consumption*' below); iii. when it provides unique or improved reactivity, such as products not accessible through solution chemistry, faster rates, better selectivity etc. A subset of this situation is if it thereby enables fewer steps to be used; iv. when the product obtained mechanochemically is analytically pure and so requires no purification; v. when the product contains detectable impurities but which are acceptable for its intended use. A subset of this last situation is if a subsequent synthetic step (potentially solvent-based) removes the impurities.

A plausible holistic picture of the future involves use of mechanochemistry in these generic situations, with bulk solvents also being used as required but which are sustainably produced and *relatively* harmless.[313]

Scalability: Most of the synthesis described in the above sections has been done on laboratory scales ranging from a few hundred milligrams up to a few grams. Whilst milling equipment for much larger scale work is widely available and used in bulk scale materials *processing*,[6a] the issue of scalability in mechano*synthesis* has not yet been broadly addressed, and indeed a common perception is that there are difficulties in scaling up such mechanochemistry. Therefore, the clear recent demonstration of production-scale (20-50 kg) synthesis of drug/carrier composites by Vectorpharma Spa described in Section 2, for example,[51] is therefore very noteworthy and encouraging. In addition, the recent report of continuous flow mechanochemistry (a cocrystallization) in a twin-screw extruder[177] points to interesting new directions for scalable approaches, which do not necessarily have to based on ball milling.

Energy consumption: The energy consumption of grinding needs to be weighed up against alternative procedures, including energy-intensive ones such as solvent distillation,[2] which it can avoid. Typical laboratory-scale ball mills themselves are, perhaps surprisingly, *not* energy intensive.[297a, 314] For example, a laboratory shaker mill such as the Retsch MM400 consumes 100-150 W under typical reaction conditions,[297a, 314c] which is especially attractive when combined with the typically short or modest reaction times needed in mechanosynthesis (often less than one hour, and sometimes only a few

minutes). This energy consumption can also compare quite favourably with that of other methods such as microwave heating.[314] However, issues of scale will also need to be considered in the move towards larger scale applications.

Predictability and mechanistic understanding: It was noted in Section 1.4 that a comprehensive mechanistic understanding of mechanochemical reactions that can underpin a strongly predictive approach to this type of synthesis is still some way off, and consequently much mechanosynthesis is conducted initially on a trial-and-error basis. Despite this there are emerging some general pointers to conducting molecular mechanosynthesis successfully, such as employing, if feasible, lower-melting reactants,[19a, 39] considering the use of LAG[21] and generating internal solvent.[39] Also, the basic reactivity principles used for solution-based chemistry can also often be successfully applied to mechanochemistry. A simple but general example is in acid-base reactions; the stronger the acid and the base the more likely the reaction under mechanochemical conditions.[39]

The synthesis 'mind set': The usual question when planning synthesis is still 'which solvent should I use?' rather than 'do I need a solvent?' A change in this regard is needed for the wider acceptance of mechanochemistry, and this aspect may be as important as overcoming technical obstacles.

Mills for chemistry: The main intended application of ball mills is not for conducting chemical reactions, but for processing materials, such as in breaking them down to smaller particle sizes. Partly because of this, but also in some cases because of the inherent technical challenge, they are not equipped *as standard* with capabilities which synthetic chemists take for granted, such as temperature monitoring, temperature control[29] (although it should be noted that some such systems have been made and are even commercially available), or *in situ* monitoring by spectroscopy or diffraction techniques. The development of *in situ* analysis is likely to help gain mechanistic understanding, as well as to optimize and apply mechanochemical processes.

Full life cycle analyses: Above, some general consideration has been given to materials, time and energy usage. 'Curtate' life cycle analyses, i.e. limited-scale analyses which neglect upstream or downstream processes, have also begun to be made to compare the overall energy efficiency of ball milling versus other activation methods.[314a, 314b] Much further analysis of this type is needed, and full life-cycle analyses particularly are also required for mechanochemical processes.

11. General conclusion and outlook

It is clear that solventless (or minimal-solvent) mechanochemistry offers some advantages as an alternative approach to synthesis. These advantages can include greater efficiency with regard to time, materials and energy usage, as well as the discovery of new or improved reactivity and products. Its

usage therefore looks likely to continue to grow. We must bear in mind, however, that there are challenges and limitations to it becoming fully adopted as a mainstream technique, which we have attempted to identify in this review. Overall, though, optimism for its future does seem to be justified, since none of the challenges is inherently insurmountable (indeed some, such as scalability are presently being addressed with success), especially given the increasing effort devoted to the topic and the growing requirement to move over to more sustainable synthetic production methods. Mechanochemistry should feature strongly ‘in the mix’ of new and sustainable synthetic chemistry.

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