

Clean and Efficient Synthesis Using Mechanochemistry: Coordination Polymers, Metal-Organic Frameworks and Metallodrugs

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Abstract. This review briefly discusses recent advances and future prospects in the mechanochemical synthesis of coordination compounds by ball milling and grinding, and highlights our contributions to the mechanosynthesis of porous metal-organic frameworks (MOFs) and zeolitic imidazolate frameworks (ZIFs), metal-organic pharmaceutical derivatives and metallodrugs using the recently developed mechanochemical methods of liquid-assisted grinding (LAG) and ion- and liquid-assisted grinding (ILAG). The role of mechanochemistry in the development of a solvent-free laboratory, cocrystal synthesis and new materials for luminescence and gas absorption is also highlighted. (doi: 10.5562/cca2014)

Keywords: mechanochemistry, solid-state chemistry, X-ray diffraction, green chemistry, metal-organic frameworks, metallodrugs

INTRODUCTION

Mechanosynthesis in Organic Synthesis and Cocrystallization

A principal challenge of modern chemistry is to develop new energy-, solvent- and atom-efficient approaches to chemical synthesis¹ in order to aid the chemical industry in managing the global problems of pollution, growing energy demand and a shortage of raw materials.² Chemical synthesis using mechanical force, also known as mechanochemistry,³ is a well-established field of organic synthesis.⁴ In the context of organic synthesis, mechanochemistry has been demonstrated to provide a solvent-free path to a plethora of transformations, including oxidations,⁵ reductions,⁶ Wittig condensations,⁷ palladium-catalyzed Sonogashira⁸ and Suzuki couplings.⁹ Recently, different research groups including Ondruschka and co-workers¹⁰ and Bolm and co-workers,¹¹ have demonstrated that besides allowing solvent-free reactivity mechanochemical synthesis in a planetary mill allows substantial improvements in energy efficiency, compared to conventional solution-based or microwave-assisted synthesis.

However, the most rapid developments in the area of mechanochemistry¹² have occurred in the areas of molecular cocrystals and metal-organic materials. The introduction of pharmaceutical cocrystals¹³ based on hydrogen bonds has inspired the rapid development of efficient methods for their screening. This effort, greatly supported by the pharmaceutical industries, has led to the development of liquid-assisted grinding (LAG) which has been recognized as a highly efficient and rapid method for cocrystal screening.¹⁴ LAG uses sub-stoichiometric amounts of a liquid phase to enable,¹⁵ accelerate^{15,16} and template¹⁷ self-assembly reactions involving solid, liquid or gaseous reactants.^{18,19} The techniques of LAG and of neat grinding have also recently been adapted into continuous screw-extrusion processes compatible with industrial scale-up.²⁰ Although the detailed mechanisms¹⁷ underlying LAG cocrystallization, and especially control of polymorphism²¹ and templating of open molecular framework,¹⁸ are not known, simple explanations for the efficiency and speed of LAG have recently been proposed. In particular, it was proposed by several research groups^{22,23} that the speed of reactions conducted by

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LAG (which is also known as solvent-drop grinding (SDG)²⁴ and has been developed from the kneading²⁵ technique inaugurated by Braga and co-workers) is the result of molecular diffusion enhanced by sub-stoichiometric amounts of the added liquid. The liquid additive is, however, present in sufficiently small amounts for the system to thermodynamically behave as if it were solvent-free.²⁶ Consequently, LAG reactions are not affected by limitations of solubility that plague solution-phase reactivity²⁷ and mechanochemical screening can rapidly provide cocrystals based on starting materials that are too soluble for efficient cocrystallization from solution, or cocrystals of composition that is difficult to obtain by solution growth. The ability to efficiently conduct reactions in stoichiometric compositions that are not effective in solution has also been observed in organic mechanosynthesis. Aakeröy²⁸ has recently reported the complete oxime functionalization of the external rim of a calix-[4]-arene using only a stoichiometric amount of the reagents, whereas solution synthesis even in large excesses of hydroxylamine yields only partially functionalized products.

Mechanosynthesis and Metal-Organic Materials

The evident benefits of mechanochemistry and mechanochemical screening using either neat grinding or LAG have inspired our work in another field that has experienced unparalleled growth in the past decade: synthesis of metal-organic compounds based on coordination bonds. The rapid development of mechanochemical coordination chemistry started around 2002, when parallel communications from Otera's²⁹ and Steed's³⁰ groups reported the efficient synthesis of molecular squares and of a coordination polymer, respectively (Figure 1).

Since then, the area of mechanochemical transformations involving coordination bonds³¹ has blossomed to include a variety of coordination polymers,³² clusters,³³ solid solutions of coordination polymers,³⁴ luminescent materials³⁵ and derivatives of pharmaceutical molecules.³⁶ This area of mechanochemical research has recently been reviewed,³⁷ as has the application of reactive milling with metals for environmentally benign production.³⁸

Our engagement in metal-organic mechano-synthesis follows in two directions. One the one hand, we are combining efficient mechanochemical synthesis with modern methods of solid-state analysis, to create a "solvent-free" synthetic laboratory in which the entire synthesis-analysis sequence is conducted without using bulk solvents. At the same time we are developing mechanochemical approaches to activate metal oxides and sulfides, whose low solubility hinders their use as reactants in conventional chemical synthesis, for the room-temperature synthesis of advanced metal-organic

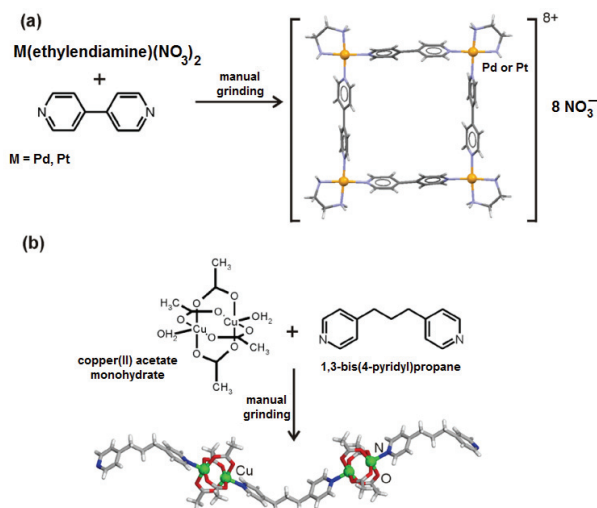


Figure 1. The mechanochemical syntheses of: (a) molecular square reported by Otera²⁹ and (b) coordination polymer reported by Steed.³⁰

materials. The development of such oxide-based chemistry at room temperature will provide a low-solvent and low-energy routes to advanced metal-organic materials directly from the most readily available and inexpensive precursors, and help industry avoid large energy and materials expenses associated with transformations of oxide-based metal minerals.

Developing a Solvent-Free Research Laboratory

The development of laboratory instrumentation and software tools has made high-quality solid-state instrumental analysis techniques, such as powder X-ray diffraction (PXRD),³⁹ solid-state NMR (SSNMR)⁴⁰ and solid-state infrared attenuated total reflection spectroscopies (FTIR-ATR) commonplace in many chemistry departments and laboratories. Particularly impressive developments have been made in algorithms and software for structure determination from PXRD data.^{39,41} Consequently, it is likely that the further development of efficient mechanochemical synthetic methods, combined with existing methodologies of solid-state structural characterization, will provide a means to conduct the majority of conventional laboratory procedures of synthesis and analysis in the absence of bulk solvents.

Indeed, a notable example of a solid-state mechanochemical synthesis of a molecular materials coupled with structure determination from PXRD data was reported in 2003 by Cheung *et al.*⁴² who described the formation and characterization of a three-component cocrystal of benzoquinone, anthracene, and racemic bis- β -naphthol obtained by manual grinding of the three components. The report by Karki *et al.*⁴³ demonstrated the mechanochemical ball-milling synthesis of two model organic pharmaceutical cocrystals, followed by structural characterization using PXRD data and

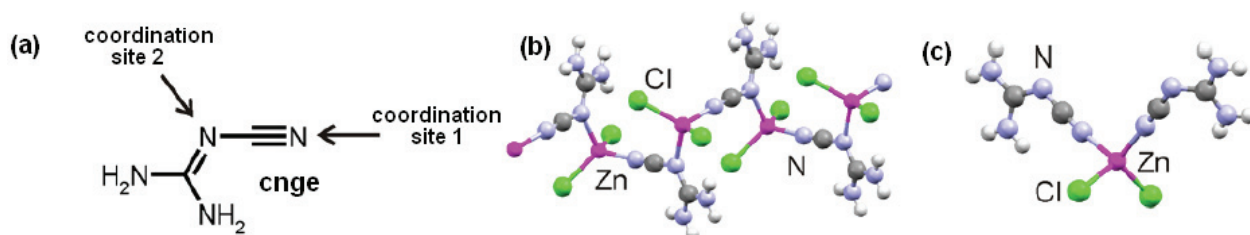


Figure 2. (a) Diagram of the ditopic cyanoguanidine (cnge) ligand and fragments of crystal structures; (b) polymeric $\text{Zn}(\text{cnge})_2\text{Cl}_2$ (CCDC code PEYGAC) and (c) monomeric $\text{Zn}(\text{cnge})_2\text{Cl}_2$ (CCDC code ZIYYEL).⁴⁵

thermogravimetric analysis. The synthesis, characterization and structural determination were all performed in less than one day. In order to verify whether such a combination of rapid and solvent-free solid-state synthesis and analysis is also possible for coordination compounds, we have explored the coordination complexes of a simple and rigid ligand cyanoguanidine (cnge, Figure 2a) with metal chlorides ZnCl_2 and CdCl_2 . The ligand cnge is heteroditopic, *i.e.* it provides two different metal binding sites. Such ligand structure enables the formation of at least two stoichiometrically different cnge complexes. In one case, the ligand acts as a bridging unit, utilizing both metal coordination sites, while in the other it takes a role of a terminal ligand, binding to the metal using only the site with the strongest metal binding affinity. The availability of two different coordination modes enables the synthesis of metal-organic materials with different topologies using the same building blocks. Indeed, solution crystallization has previously provided two different cnge and ZnCl_2 complexes, with compositions $\text{Zn}(\text{cnge})\text{Cl}_2$ (CCDC code PEYGAC, Figure 2b) and $\text{Zn}(\text{cnge})_2\text{Cl}_2$ (CCDC code ZIYYEL, Figure 2c).⁴⁴

As our first entry⁴⁵ into the development of the solvent-free laboratory concept, we attempted the mechanochemical synthesis of $\text{Zn}(\text{cnge})\text{Cl}_2$ and $\text{Zn}(\text{cnge})_2\text{Cl}_2$. Ball milling of ZnCl_2 with cnge in 1:1 and 1:2 ratios yielded sticky and hygroscopic solids. However, repeating the experiments with a catalytic amount of a liquid phase gave white crystalline powders which were identified by PXRD to be $\text{Zn}(\text{cnge})\text{Cl}_2$ and $\text{Zn}(\text{cnge})_2\text{Cl}_2$, as expected.

This confirmed the potential of mechanochemistry as a simple approach to control the stoichiometric composition of coordination complexes, as $\text{Zn}(\text{cnge})_2\text{Cl}_2$ was previously obtained from solutions containing ZnCl_2 and cnge in 1:1 stoichiometric ratio by varying solvent composition and/or pH.⁴⁴ Such potential has also been demonstrated by Bowmaker and co-workers⁴⁶ in the mechanochemical synthesis of ethylenethiourea silver halide complexes. The solution reaction of AgCl and ethylenethiourea yields a single product, $\text{AgCl}(\text{ethylenethiourea})_{1.5}$, composed of 1-D polymeric cationic tapes $[\text{ClAg}_4(\text{ethylenethiourea})_6]^{3+}$ surrounded by Cl^- anions (Figure 3). However, neat grinding with further 1.5 equivalents of ethylenethiourea partially transforms this cationic polymer into a new material $\text{AgCl}(\text{ethylenethiourea})_3$ (Figure 3). LAG using a small amount of water quantitatively yielded $\text{AgCl}(\text{ethylenethiourea})_3$ within one minute.⁴⁶

As the next step in developing a solvent-free research laboratory, we undertook the synthesis of analogous complexes with CdCl_2 .⁴⁵ Neither $\text{Cd}(\text{cnge})\text{Cl}_2$ nor $\text{Cd}(\text{cnge})_2\text{Cl}_2$ had been reported previously, which provided suitable models for our study. In contrast to ZnCl_2 , standard neat ball milling of CdCl_2 with cnge in either 1:1 and 1:2 produced only the $\text{Cd}(\text{cnge})\text{Cl}_2$ complex. With a 1:1 stoichiometric ratio of starting materials pure $\text{Cd}(\text{cnge})\text{Cl}_2$ was obtained and was successfully characterized through FTIR-ATR, ^{13}C , ^{15}N and ^{113}Cd SSNMR spectroscopy. However, ball milling of CdCl_2 and cnge in a 1:2 stoichiometric ratio under slightly harsher conditions, achieved by using grinding balls of a larger diameter (10 mm instead of

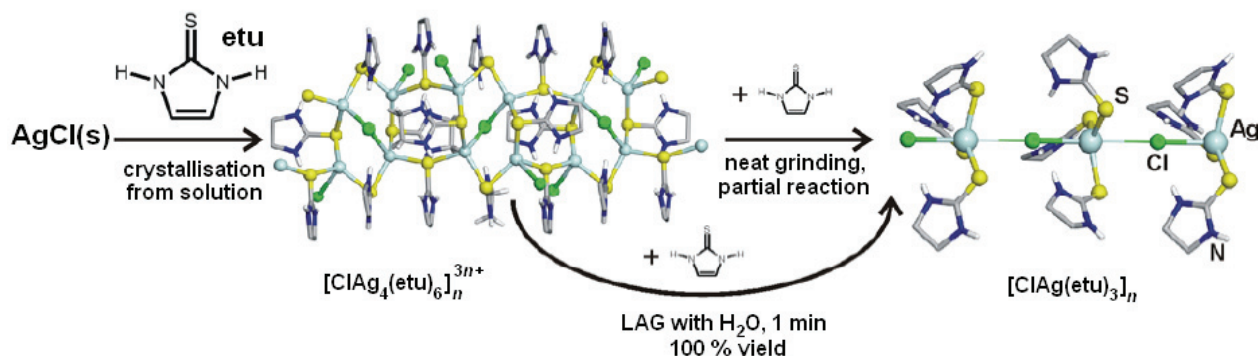


Figure 3. Mechanochemical transformation of the $[\text{ClAg}_4(\text{ethylenethiourea})_6]^{3+}$ coordination polymer into $\text{AgCl}(\text{ethylenethiourea})_3$.⁴⁶

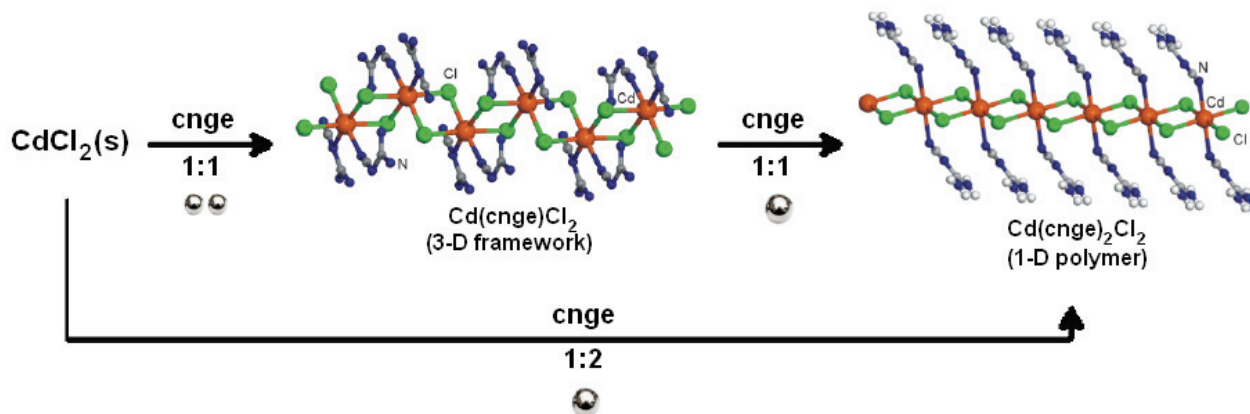


Figure 4. Mechanochemical synthesis of coordination polymers from CdCl_2 and the cnge ligand provides the $\text{Cd}(\text{cnge})\text{Cl}_2$ three-dimensional polymer upon mild ball milling (two stainless steel balls with 7 mm diameter) which, upon harsher treatment (one 10 mm diameter grinding ball) can be quantitatively converted into the one-dimensional polymer $\text{Cd}(\text{cnge})_2\text{Cl}_2$.⁴⁵

standard 7 mm), quantitatively provided the desired $\text{Cd}(\text{cnge})_2\text{Cl}_2$. Controlled experiments demonstrated that the synthesis of $\text{Cd}(\text{cnge})_2\text{Cl}_2$ involves the intermediate $\text{Cd}(\text{cnge})\text{Cl}_2$ in a process that requires both the mechanical and autogenous thermal effects of harsher milling conditions. This mechanism was rationalized by examining crystal structures of $\text{Cd}(\text{cnge})\text{Cl}_2$ and $\text{Cd}(\text{cnge})_2\text{Cl}_2$ determined from PXRD data. As expected, $\text{Cd}(\text{cnge})\text{Cl}_2$ was found to be a material of higher dimensionality than $\text{Cd}(\text{cnge})_2\text{Cl}_2$. In contrast to ZnCl_2 analogues, $\text{Cd}(\text{cnge})\text{Cl}_2$ is a three-dimensional (3-D) coordination polymer with a structure sustained by $\text{Cd}\cdots\text{N}$ and $\text{Cd}\cdots\text{Cl}$ bonds, whereas $\text{Cd}(\text{cnge})_2\text{Cl}_2$ is a one-dimensional (1-D) tape polymer held together by $\text{Cd}\cdots\text{Cl}$ bonds with terminal cnge ligands held by $\text{Cd}\cdots\text{N}$ bonds (Figure 4). Presumably, the high connectivity of 3-D $\text{Cd}(\text{cnge})\text{Cl}_2$ provides a kinetic barrier for the synthesis of less interconnected 1-D material $\text{Cd}(\text{cnge})_2\text{Cl}_2$ (Figure 4). This rationalization was further supported by the mechanochemical synthesis of $\text{Cd}(\text{cnge})_2\text{I}_2$ from CdI_2 which required harsh milling, consistent with a kinetic barrier in the transformation of higher connectivity two-dimensional (2-D) CdI_2 into discrete 0-dimensional (0-D) complex $\text{Cd}(\text{cnge})_2\text{I}_2$.⁴⁵

Overcoming Solubility Limitations: Reactions of Metal Oxides

A particularly attractive aspect of mechanochemical synthesis is the ability to conduct chemical reactions with materials that are only slightly soluble and, consequently, cannot be used as reagents in conventional solution-based procedures. Much pioneering research into mechanochemical transformations of slightly soluble metal carbonates into coordination polymers has been conducted by Adams and co-workers.⁴⁷ Our group has focused on the mechanochemical reactivity of metal oxides which are attractive as precursors because they are readily available, inexpensive and generate water as the only reaction byproduct.⁴⁸

Using fumaric acid (H_2fum) as a simple model ligand bearing a chemical functionality (double bond), we demonstrated⁴⁸ that a brief LAG procedure involving zinc oxide can provide different zinc fumarate polymers in quantitative yields (Figure 5a). Without adding the liquid phase, no reaction was observed by milling ZnO and H_2fum . Product formation was found to be readily controllable by varying the composition and the quantity of the grinding liquid, enabling the quantitative and selective synthesis of materials of composition $\text{Zn}(\text{fum})$, $\text{Zn}(\text{fum})\cdot 2\text{H}_2\text{O}$, $\text{Zn}(\text{fum})\cdot 4\text{H}_2\text{O}$ and $\text{Zn}(\text{fum})\cdot 5\text{H}_2\text{O}$. Whereas $\text{Zn}(\text{fum})\cdot 4\text{H}_2\text{O}$ and $\text{Zn}(\text{fum})\cdot 5\text{H}_2\text{O}$ had been previously reported and structurally characterized through single crystal X-ray diffraction, the synthesis of pure $\text{Zn}(\text{fum})$, $\text{Zn}(\text{fum})\cdot 2\text{H}_2\text{O}$ had never been reported.⁴⁹ The quantitative reaction yields enabled the collection of high-quality PXRD data, suitable for the structural characterization of these previously not known materials.⁴⁸

The formation of different zinc fumarate coordination polymers by grinding with a different liquid phase was subsequently rationalized⁵⁰ in a study using different mixtures of alcohols and water as grinding liquids. The composition of the product was found to be strongly correlated to the activity of water in the grinding liquid, pointing towards a rational strategy to mechanochemically screen for hydrated coordination polymers by varying the activity of water in the grinding liquid. We have subsequently exploited this in the pharmaceutical context, as a strategy to explore the phase space of hydrated magnesium complexes⁵¹ of the drug molecule naproxen (Figure 5b). The formation of solid hydrates is of particular importance in developing pharmaceutical formulations and new solid forms of pharmaceuticals. By controlling the water activity in the grinding liquid, we have generated four different magnesium derivatives of naproxen, simply by liquid-assisted grinding of MgO and the drug. Structures of two thus generated materials have been obtained by

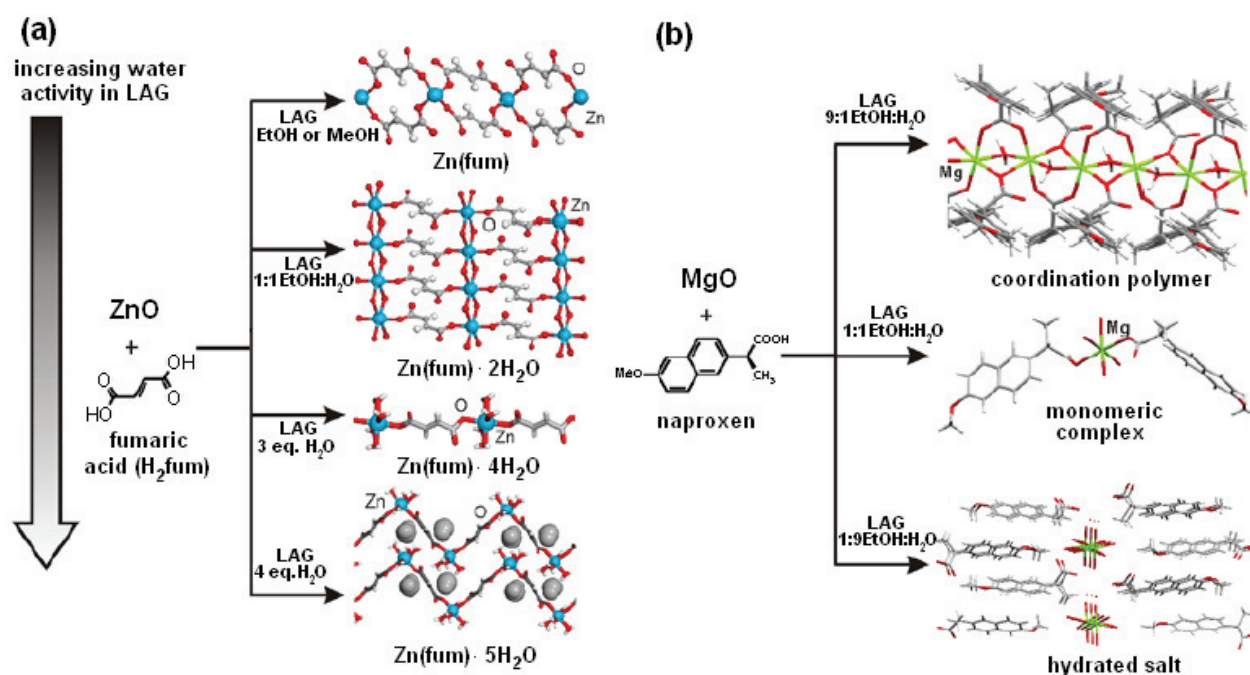


Figure 5. Mechanochemical screening for: (a) zinc fumarate coordination polymers⁴⁸ and (b) magnesium naproxen complexes, by varying the activity of water in the grinding liquid.⁵¹

re-crystallization and single crystal X-ray diffraction, and by structure determination from PXRD data obtained directly from the material obtained by mechanochemical screening.

Interrupting the mechanochemical formation of Zn(fum)·4H₂O revealed that the reaction involves the more hydrated Zn(fum)·5H₂O as an intermediate (Figure 6a).⁵⁰ This observation suggests a mass-action effect in LAG synthesis of coordination polymers, in which the relatively large amount of a liquid phase early in the reaction leads to the formation of a highly solvated product. Subsequently, this intermediate transforms into a final product whose composition is dictated by the stoichiometric composition of the reaction

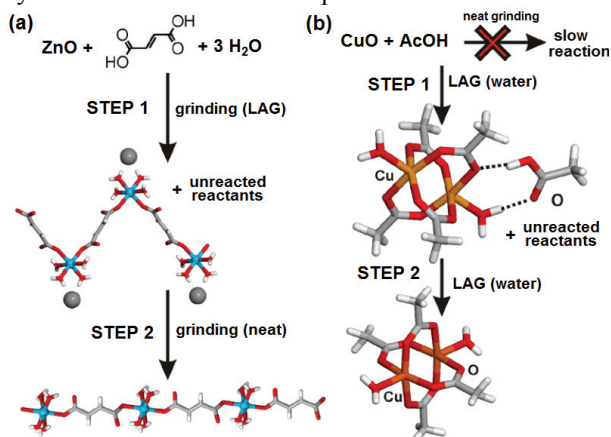


Figure 6. Stepwise reaction mechanisms in the oxide-based mechanosynthesis of: (a) zinc fumarate tetrahydrate and (b) copper(II) acetate monohydrate.⁵⁰

mixture. In support of this hypothesis, we also explored the water catalyzed reaction of copper(II) oxide, CuO, with acetic acid (AcOH) at short reaction times.⁵⁰ In accordance with the proposed stepwise mechanism the reaction was found to proceed *via* an acetic acid solvate of the copper(II) acetate⁵² paddlewheel dimer which subsequently transformed into the final product copper(II) acetate hydrate (Figure 6b).

Porous Metal-Organic Frameworks

Porous metal-organic frameworks (MOFs) have garnered immense attention of materials science researchers. Although MOFs were originally developed for reversible storage of fuel gases, such as hydrogen and methane,⁵³ their modular nature and robust design have led to numerous applications, including carbon dioxide sequestration,⁵⁴ catalysis,⁵⁵ sensing,⁵⁶ biomolecular sensing,⁵⁷ luminescent displays,⁵⁸ light harvesting⁵⁹ or synthesis of nano- and microstructures.⁶⁰ The wide range of MOF application and designs is contrasted by the energy and solvent-intensive methods for their solvothermal synthesis.⁶¹ The first solvent-free synthesis of a porous MOF was described by Pichon *et al.*^{62a} who synthesized the open framework of copper(II) isonicotinate in a ball-milling reaction of copper(II) acetate with isonicotinic acid (Figure 7a). This methodology was readily extended to the synthesis of the technologically important porous framework HKUST-1, by grinding copper(II) acetate with 1,3,5-benzenetricarboxylic acid.^{62b}

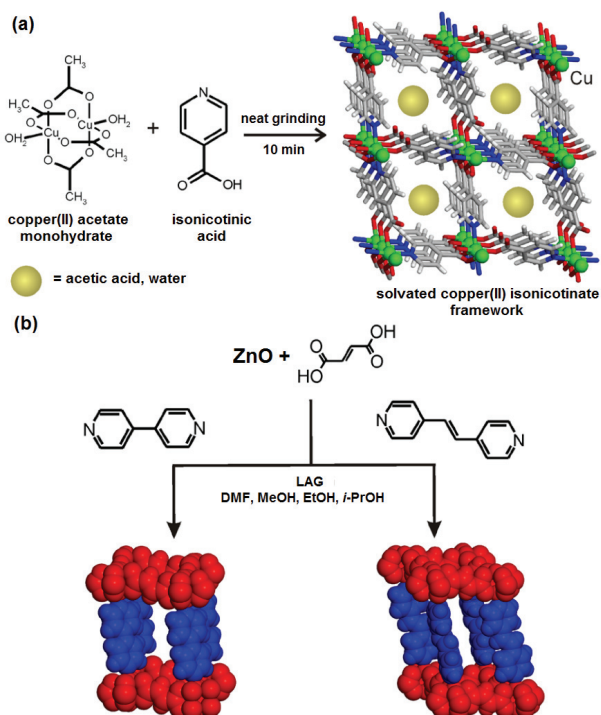


Figure 7. Mechanochemical approaches to the synthesis of porous MOFs: (a) neat grinding of copper(II) acetate with a carboxylic acid ligand yields copper carboxylate MOFs^{62a,b} and (b) LAG synthesis starting from a metal oxide yields pillared MOFs through four-component assembly which includes a liquid template.⁴⁸

Our entry into the mechanochemical synthesis of porous MOFs followed from our studies of reactions of ZnO and H₂fum.⁴⁸ Such reactions were found to proceed with the incorporation of water ligands onto the zinc fumarate framework (Figure 5a) and we explored the possibility of conducting analogous reactions in the presence of ditopic nitrogen ligand, such as 4,4'-dipyridyl (bipy) or *trans*-1,2-bis(4-pyridyl)ethylene (bpe), which we anticipated would bridge zinc fumarate polymers to form pillared MOFs designed by Hupp.⁶³ Indeed, ball milling of ZnO and H₂fum with either bipy or bpe in the presence of a space-filling liquid agent (*N,N*-dimethylformamide, DMF) provided the anticipated pillared MOFs (Figure 7b). The reaction yield was dependent on the amount of the space-filling liquid, leading to quantitative yields in the presence of sufficient DMF to fill the pores of the open framework. The mechanochemical synthesis of porous MOFs could also be conducted with other space-filling liquids, including environmentally more acceptable methanol, ethanol or 2-propanol.⁴⁸

However, attempts to mechanochemically synthesize pillared MOFs based on zinc terephthalate and diazabicyclo[2.2.2]octane (dabco) as a pillaring ligand in analogous way, *i.e.* by milling zinc oxide, terephthalic acid, dabco and a space-filling agent, have not been successful. Instead, the addition of small amounts of ionic salts was needed to enable the quantitative formation of the desired frameworks.⁶⁴ Moreover, whereas the use of nitrate salt additives (*e.g.* NaNO₃, KNO₃, NH₄NO₃) led to the formation of the porous

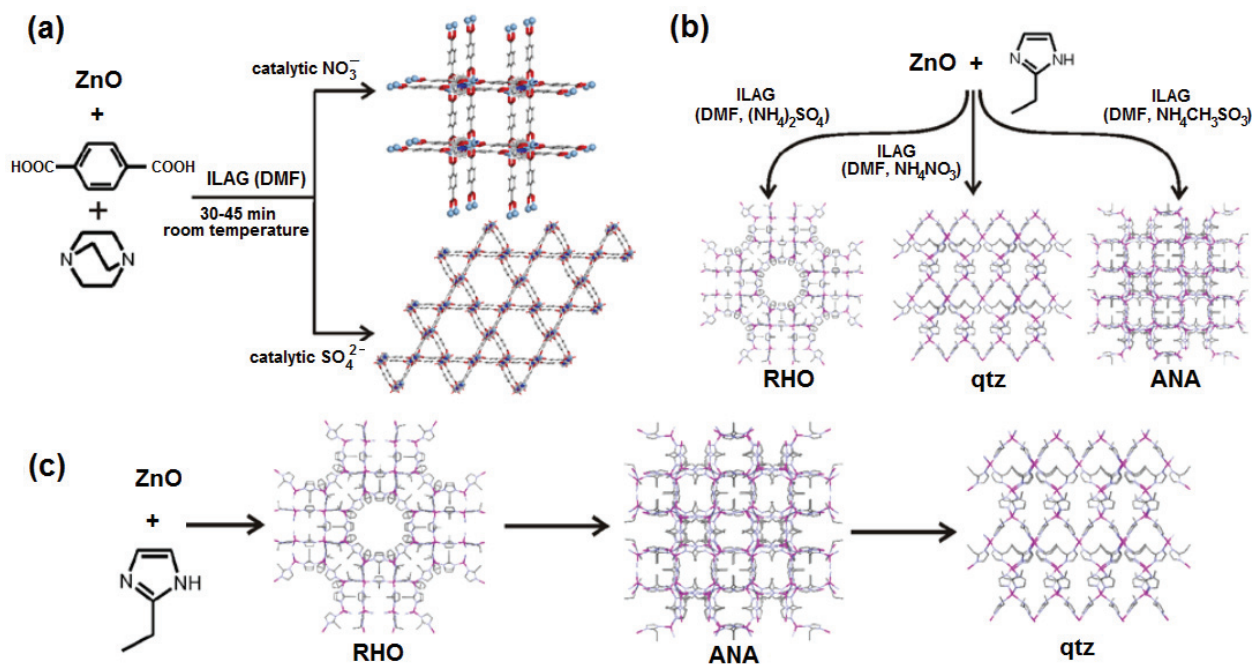


Figure 8. Mechanochemical oxide-based synthesis of MOFs⁶⁴ and ZIFs^{69a} using ILAG: (a) the synthesis of pillared MOFs directed by catalytic amounts of nitrate or sulfate ions; (b) the synthesis of ZIFs directed by ionic additives and (c) the stepwise mechanism of ZIF formation leading from a highly porous framework (zeolite RHO topology).

Table 1. ZIF topologies obtained in mechanochemical screening^{69a}

Ligand	Liquid	Salt			
		none	NH ₄ NO ₃	NH ₄ MeSO ₃	(NH ₄) ₂ SO ₄
HIm	none	mixture ^b	zni	zni	mixture ^b
HIm	DMF	cag	cag	cag	cag
HIm	DEF ^c	- ^d	nog	unknown ^e	unknown ^e
HIm	ethanol	zni	zni	zni	zni
HMeIm	none	-	SOD	SOD	-
HMeIm	DMF	SOD	SOD	SOD	SOD
HMeIm	DEF ^c	SOD	SOD	SOD	SOD
HMeIm	ethanol	SOD	SOD	SOD	SOD
HEtIm	none	-	qtz	RHO ^f	-
HEtIm	DMF	-	qtz	ANA	RHO
HEtIm	DEF ^c	-	qtz	ANA	RHO
HEtIm	ethanol	-	qtz	qtz	RHO

(^a) Each product was obtained by grinding for 30 min and '-' indicates no reaction.

(^b) Mixture of starting materials, zni-type ZIF and a yet unidentified crystalline material.

(^c) *N,N*-diethylformamide.

(^d) No reaction is initially evident, but aging yields cag- or nog-type ZIFs.

(^e) Initial product is a yet unidentified material which transforms into the nog-type ZIF upon aging.

(^f) Transforms into the qtz-topology ZIF upon aging.

framework based on square-grid zinc terephthalate sheets reported by Kim's group,⁶⁵ sulfate ion additives led to the formation of supramolecular isomer⁶⁶ of this pillared MOF based on hexagonal Kagome topology zinc terephthalate sheets (Figure 8a).⁶⁷ These unexpected structure-directing effects were tentatively explained by the inclusion of salts in the MOF porous structure suggested by solid-state NMR and Fourier-transform infrared (FTIR) spectroscopy.

We have given the name ILAG (ion- and liquid-assisted grinding) to this highly promising method of directing the structure by grinding starting materials with a small amount of an ionic salt additive. The ILAG methodology appears to be applicable beyond reactions of zinc oxide, as demonstrated by its recent use to enable the mechanochemical oxidation of cobalt and ruthenium complexes.⁶⁸ We have expanded the use of ILAG for the synthesis of zeolitic imidazolate frameworks (ZIFs),^{69a} a family of porous MOFs which exploit a combination of tetrahedral metal ions (*e.g.* Zn²⁺, Co²⁺)⁷⁰ and azolate anions⁷¹ to obtain porous metal-organic topologies analogous to those of zeolites.

Our study focused on imidazole (HIm), 2-methylimidazole (HMeIm) and 2-ethylimidazole (HEtIm) as ligands.^{69a} The mechanosynthesis of ZIFs by conventional liquid-assisted grinding of zinc oxide and imidazole ligands in the presence of a space-filling liquid was only partially successful (Table 1), yielding the non-porous zinc imidazolate (zni) and open cag topology frameworks with imidazole, and the open sodalite (SOD) topology framework based on MeIm, in partial

yields. However the application of ILAG using ammonium nitrate, methanesulfonate or sulfate led to the quantitative formation of a variety of ZIFs whose topology could be controlled either by the choice of the salt additive or the grinding liquid (Table 1). The rapid (30 min) ILAG reaction of HEtIm in the presence of different salts led to the formation of the open structure ZIFs with zeolite rho (RHO) and analcime (ANA) topologies, and the new non-porous material with α -quartz (qtz) topology (Figure 8b). However, ILAG at different grinding times revealed that the mechanochemical reactions in each case proceeded through a stepwise mechanism involving the interconversion of RHO, ANA and qtz topologies. Consequently, the structure-determining role of the ionic additive in ILAG synthesis of ZIFs was found to be not related to thermodynamic templating, but to controlling the rate of the RHO→ANA→qtz framework transformation. (Figure 8c). In addition to the synthesis of crystalline ZIF frameworks, mechanochemical treatment was recently used to synthesize amorphous forms of ZIFs, by ball milling of ZIF nanoparticles prepared by solution methods.^{69b}

Pharmaceutical Derivatives and Metallodrugs

The synthesis of salt and cocrystals of active pharmaceutical ingredients (APIs), closely related to the pioneering work of Etter⁷² and of Caira,⁷³ is a major application of mechanosynthesis. This application was expanded to the synthesis of API metal complexes by

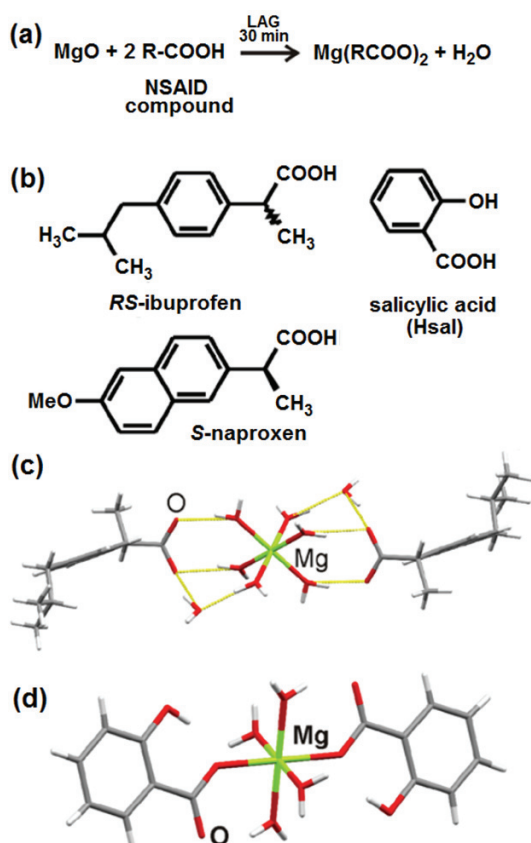


Figure 9. (a) Mechanochemical synthesis of magnesium derivatives of NSAID molecules;⁷⁶ (b) NSAID molecules explored in described work;^{51,76} (c) fragment of the crystal structure of magnesium ibuprofen hydrated salt (CCDC codes FUYCOS and FUYCOS01)⁷⁶ obtained by LAG and (d) an isolated molecule in the crystal structure of magnesium salicylate tetrahydrate complex obtained by LAG (CCDC codes VAXHUX and VAXHUX01).⁷⁷

Braga and co-workers who explored the complexation of zinc, copper(II) and silver(I) with drug molecules such as gabapentin and 4-aminosalicylic acid.^{36,74} The solid-state reactivity of metal oxides to yield derivatives of pharmaceuticals was extensively studied and described by Byrn and co-workers⁷⁵ who observed the slow reaction of magnesium oxide and non-steroidal anti-inflammatory drug (NSAID) pharmaceuticals upon exposure of solid-state mixtures to moisture at room temperature. We have explored the same type of oxide-based reactivity in the mechanochemical environment, by liquid-assisted grinding together of MgO with NSAIDs ibuprofen (*S*- and *RS*-forms),⁷⁶ salicylic acid and naproxen in a 1:2 stoichiometric ratio using water as the grinding liquid (Figure 9a).⁵¹ Such LAG experiments led to the quantitative formation of well-defined hydrated compounds characterized with a combination of solid-state spectroscopy and diffraction techniques. The reactions with either chiral or racemic forms of

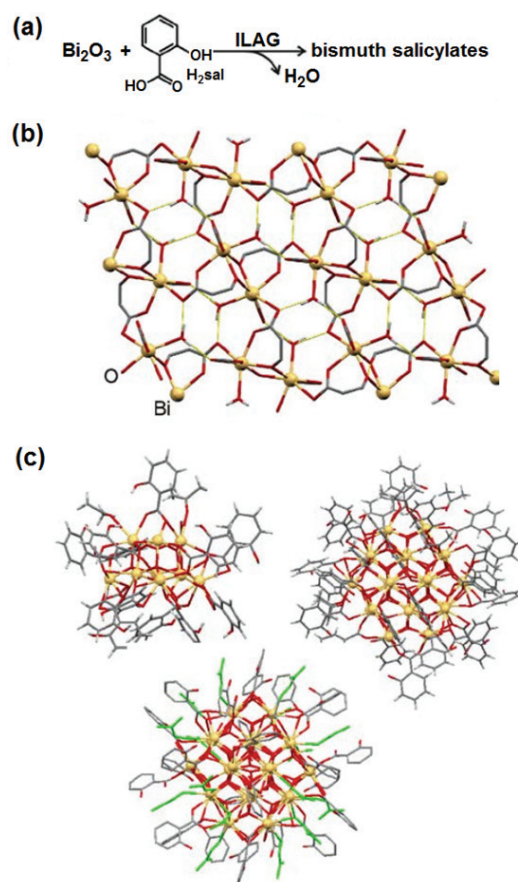


Figure 10. (a) Mechanochemical ILAG synthesis⁷⁸ of bismuth salicylate materials from Bi_2O_3 , (b) fragment of the crystal structure of bismuth disalicylate hydrate obtained by structure determination from powder X-ray diffraction data and (c) bismuth salicylate clusters previously obtained by hydrolysis of bismuth salicylate in acetone solution⁸¹ (top, CCDC codes CEMBEC, CEMBAY) and hydrolysis of bismuth disalicylate hydrate in DMF solution⁷⁸ (bottom, CCDC code IYSEL). For clarity, DMF molecules coordinated to bismuth ions on the surface of the cluster are shown in green.

ibuprofen produced an octahydrate salt which exhibited enhanced solubility in the water-ethanol solvent system (Figure 9b), providing a tentative explanation for the enhancement of the dissolution rate of ibuprofen when formulated with MgO. In the case of naproxen, systematic LAG screening using water-alcohol mixtures exhibiting different water activities revealed at least five different hydrated forms of a magnesium naproxen, including a coordination polymer, a discrete complex and a tentative highly hydrated salt.⁵¹

ILAG also enabled a rapid and environmentally-friendly synthesis of the metallodrug bismuth subsalicylate, the active component of the popular gastrointestinal drug Pepto-Bismol,⁷⁸ as well as of two further bismuth salicylates directly from Bi_2O_3 (Figure 10a). The outcome of the mechanochemical reactions, which

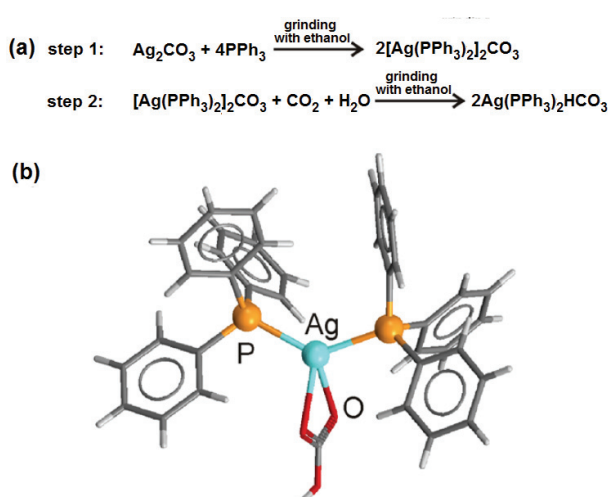


Figure 11. (a) The proposed two-step mechanism for the absorption of carbon dioxide by liquid-assisted grinding of silver(I) carbonate and triphenylphosphine and (b) a molecule in the crystal structure of the final reaction product, bis(triphenylphosphino)silver(I) hydrogencarbonate (CCDC code OTAHUN).⁸²

are performed by ball milling in the presence of water and ammonium nitrate, was determined by the stoichiometric ratio of bismuth and salicylic acid in the reaction mixture. The quantitative reaction yields also facilitated the structural characterization of mechanochemical products using powder X-ray diffraction data, leading to the structural characterization of bismuth disalicylate monohydrate, an outstanding target from the 2002 Second Structure Determination by Powder Diffractometry Round Robin challenge (SDPDRR-2).⁷⁹ The crystal structure revealed a two-dimensional hybrid inorganic-organic material and corrected the previously proposed composition⁸⁰ involving hydroxide ligands (Figure 10b). The structure of bismuth disalicylate hydrate is currently the only known crystal structure for a bismuth salicylate complex without auxiliary organic ligands. As a potential model for the bismuth subsalicylate active drug ingredient, it is in striking contrast to previously proposed⁸¹ model discrete oxo-cluster structures involving additional acetone ligands, which were obtained by hydrolysis of bismuth salicylate in acetone solution. Recrystallization of bismuth disalicylate hydrate from a DMF solution, however, leads to the formation of analogous clusters but decorated with DMF ligands (Figure 10c).

Future Applications: Luminescent Materials and Carbon Dioxide Binding

This highlight is focused on our recent contributions to the development and applications of mechanochemistry to metal-organic materials synthesis, but the rapid development of the field would be difficult to illustrate

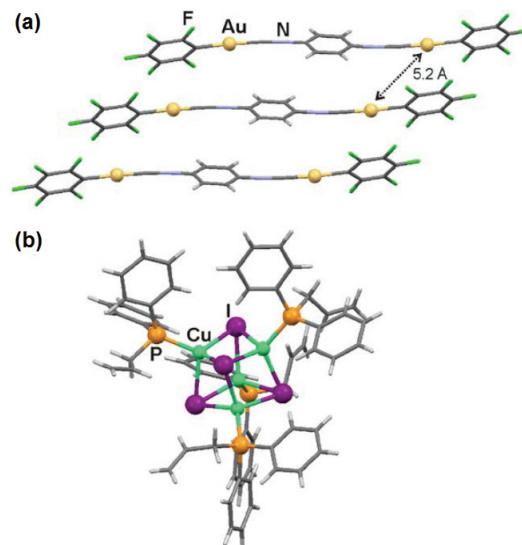


Figure 12. Fragments of crystal structures of: (a) $(\text{C}_6\text{F}_5\text{Au})_2(\mu\text{-}1,4\text{-diisocyanobenzene})$, displaying the long $\text{Au}\cdots\text{Au}$ interactions between discrete linear units⁸³ and (b) tetrakis[di(phenyl)allylphosphino]copper(I) iodide, displaying the luminescent Cu_4I_4 cage cluster with pendant phosphine ligands.⁸⁴

without bringing forward some of the highly exciting recent additions to the field. These include the recent reports on the gas carbon dioxide uptake by mechanochemical treatment of metal-organic silver(I)-phosphine complexes,⁸² as well as on the reversible mechanochromism and mechanoluminescence in metal-organic materials.^{83,84}

In particular, Bowmaker and co-workers⁸¹ have reported that manual grinding of solid silver carbonate, Ag_2CO_3 with triphenylphosphine (PPh_3) in air and in the presence of liquid ethanol leads to the absorption of one equivalent of water (present in the form of air moisture) and one equivalent of CO_2 gas to yield bis(triphenylphosphino)silver(I) hydrogencarbonate (CCDC code OTAHUN) which can again release CO_2 upon thermal treatment. Monitoring of the reaction through solid-state infrared spectroscopy suggests a two-step mechanism involving the formation of the solid tetrakis(triphenylphosphino)silver(I) carbonate as the intermediate (Figure 11). As sequestration of waste carbon dioxide is one of the leading problems of modern industry, it is likely that the study of such systems could lead to further applications for mechanochemistry in the context of environmentally-friendly technologies and sustainability.

Gentle manual grinding of the gold(I) complex $(\text{C}_6\text{F}_5\text{Au})_2(\mu\text{-}1,4\text{-diisocyanobenzene})$ ⁸² (Figure 12a) results in a stark change in fluorescence observed upon exposure to ultraviolet (UV) light. The initial blue fluorescence of the materials is converted to bright yellow upon grinding, and can be converted back to the original

blue either by recrystallization or by exposure of the ground solid to vapors of different organic solvents (for example dichloromethane). Thermal and powder X-ray diffraction analysis of the starting and ground materials indicated that the fluorescence change is a result of structural distortion by grinding, tentatively related to the shortening of long Au...Au interactions to form aurophilic interactions and not to a bulk formation of a new polymorph or a solvate. The observed fluorescence switching exhibits valuable potential for molecular sensing, detection or even information storage and is not limited to this particular example. Notably, Perruchas and co-workers⁸³ reported similar behavior for a copper(I) iodide complex of di(phenyl)allylphosphine, based on the well-known luminescent Cu₄I₄ cubane core (Figure 12b). Grinding of the complex leads to a notable shift in UV-induced fluorescence from the weak green emission at 530 nm to a bright yellow luminescence at 580 nm. Again, the reversible fluorescence shift could not be assigned to solvation or polymorphic transitions, but to the distortion of the Cu₄I₄ core upon grinding to provide a system with shorter Cu...Cu intra-cage distances.

CONCLUSION AND OUTLOOK

We have provided a brief overview of the recent developments of mechanochemical methods in our, as well as other research groups. The illustrated examples represent only a fraction of new applications of mechanochemistry, indicating that mechanosynthesis by grinding, in its different modalities (neat grinding, LAG, ILAG), is becoming an attractive efficient and environmentally-friendly alternative to conventional solution-based synthesis. We anticipate that this potential of grinding mechanochemistry will be further augmented by exciting recent developments in the areas of solid-state chemistry and analysis. Whereas crystal structure determination from X-ray powder diffraction data is now becoming a reliable method for solvent-free structural characterization of mechanochemically synthesized materials,^{43,85} the applicability and understanding of mechanochemical grinding synthesis will benefit from the development of cutting edge techniques including NMR crystallography,⁸⁶ crystal structure prediction⁸⁷ and terahertz (or phonon) spectroscopy.^{16,88} These advanced instrumental and computational techniques, we expect, will complement the ongoing systematic studies⁸⁹ of mechanochemical reactivity of molecular materials⁹⁰ and inorganic substances⁹¹ and in that way accelerate the unraveling of molecular-level mechanisms underlying grinding mechanosynthesis. This, in turn, should facilitate the greater implementation of mechanochemistry for solvent-free and energy-efficient industrial applications.⁹²

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