Mechanochemistry: an efficient and versatile toolbox for synthesis, transformation, and functionalization of porous metal–organic frameworks

Tomislav Stolar and Krunoslav Užarević*

Mechanochemistry is nowadays recognized as a green approach to chemical synthesis, but the full scope of the accompanying solid-state reactivity is just beginning to be unravelled. This is especially true for the preparation of porous metal–organic frameworks, whose synthesis by the use of mechanical force lagged behind that of other relevant classes of materials. Nevertheless, mechanochemical procedures have rapidly evolved from a mere synthetic curiosity towards efficient methods for obtaining high-quality MOFs on different scales. This Highlight is dedicated to the functional approach of using mechanochemistry for the preparation of catalytically active MOF composites and mixed-metal and mixed-ligand MOFs with synergistic properties as well as fine-tuning of the MOF performance via defect engineering and amorphization.

1 Introduction

Chemical reactivity induced by mechanical action, such as milling, shearing, grinding, scratching, etc., on bulk solids has become a well-recognized alternative to traditional solution synthesis methods.1-3 Mechanochemistry has been used for chemical extraction already in prehistoric times,4 and is widespread in the metallurgy and cement industry. However, despite being sporadically used in laboratories in the 20th century, the first systematic mechanochemical studies were carried out in the early eighties on supramolecular materials.5-7 Reports on mechanochemical

Tomislav Stolar is a PhD candidate at Ruder Bošković Institute in Zagreb, Croatia under the supervision of Dr. Krunoslav Užarević. He started his scientific career as an undergraduate volunteer at the same institution in 2013. His research interest spans solid-state chemistry, crystal engineering, prebiotic chemistry, mechanochemistry and MOFs.

Krunoslav Užarević graduated in 2009 at the University of Zagreb in the field of structural and inorganic chemistry. After a Marie-Curie Newfelpro Fellowship with Prof. Tomislav Friščić at McGill University in Montreal, he started working as a Head of Laboratory for Green Synthesis at Ruder Bošković Institute in Zagreb in 2016. His main scientific focus is on developing mechanochemical and solvent-free procedures for the synthesis and transformation of various classes of functional materials, from supramolecular receptors and organic compounds to porous metal–organic frameworks (MOFs). A particular part of his research involves designing new milling reactors and developing new methodologies for in situ monitoring of milling and aging reactions.
Highlight

The first reported synthesis of an extended coordination polymer by manual grinding likely dates to 1968, more than 20 years before Robson’s seminal work, and it probably represents also the first synthesis of a porous MOF material. Authors Musgrave and Mattson did not recognize at the time the potential of the prepared materials, which two decades later expanded to a field of porous MOFs. They did recognize, however, the coordination abilities of one of the most popular ligands for the preparation of MOFs nowadays, 4,4’-bipyridine (bipy), stating it to be “particularly interesting because its structure should preclude chelation and favor coordination of the nitrogen atoms to two different metal ions; i.e., it should coordinate so as to form polymeric complexes.” Mixing ethanol solutions of metal nitrates and bipy resulted in the rapid formation of 1D-coordination polymers with the general formula M(bipy)(NO3)2. However, grinding several metal nitrates (Ni, Co, and Cu) in a mortar with an excess of bipy (50–100 times) and a small amount of methanol afforded a new type of coordination polymers which differed in color from the M(bipy)(NO3)2 products (Fig. 1a). The authors concluded from their analytical data

Fig. 1 First MOFs prepared by grinding or milling procedures: (a) dissolving Cu(NO3)2 and bipy in EtOH results in the formation of a 1D-coordination compound whereas grinding them in the presence of MeOH results in a squarate coordination framework (1968); (b) HKUST-1 (CCDC FIIOGEN) from dry milling of copper acetate and BTC (2008), and (c) [Cu(ina)]2(H2O)2 (CCDC BAHGUN) from dry milling copper acetate and ina (2006).
that two bipy molecules coordinated to a single metal cation and that the new products are octahedral complexes of the general formula M(bipy)2(NO3)2. The molar ratio of bipy to metal cation and the presence of “entrapped” solvent molecules point to the formation of square networks characteristic of MOFs containing copper-, cobalt-, or nickel nitrates and bipy bridges (Fig. 1a). The following systematic study of the advantages of mechanochemical procedures over the conventional solution synthesis of squarates took more than 50 years, but the authors expanded their scope also to continuous mechanochemical procedures such as TSE.37

In 2006, the James group reported the first intentional mechanochemical synthesis of a porous MOF.32 This groundbreaking contribution was focused on the dry milling reaction between copper(n) acetate monohydrate and isonicotinic acid (ina). Milling for 10 minutes at a 25 Hz oscillation rate resulted in the quantitative formation of a single product of the reaction.44 The real change in the synthetic paradigm came in 2009 when Friščič and coworkers showed how metal oxides, precursors which are usually avoided in solution synthesis due to their low solubility, can be exploited as starting reagents for the rapid and clean synthesis of six different pillared Zn-MOFs. The developed LAG procedures are a combination of acid-base reactions and coordination-driven self-assembly and, importantly, produce water as the sole by-product of the reaction.44

The following studies also showed that the type of the MOF product could be governed by the choice of grinding liquid and ionic additives. During mechanochemical synthesis of pillared MOFs from ZnO, fumaric acid and 1,4-diazabicyclo[2.2.2]octane (dabco), it was discovered that the addition of an ionic salt (5 mol percent) in the ion-and-liquid assisted grinding (ILAG) would inadvertently govern the reaction towards a specific topology, namely the tetragonal or hexagonal form of the [Zn(fum)(dabco)] MOF (Fig. 2a).45 These templating effects were further confirmed by 15N solid-state NMR and Fourier-transform infrared spectroscopy (FTIR) studies, which revealed that the ions were included in the pores of the product. A similar effect was also shown for Zn(2-ethylimidazolate)2 [Zn(Et-Im)2], a MOF belonging to the family of zeolitic imidazolate frameworks (ZIFs),46 where the ionic additives directed the mechanochemical formation towards three different topologies (Fig. 2b).47 The presented results provided the first indication of how templating and self-organization could affect the synthesis of extended coordination frameworks in the solid state. These early studies established a firm ground for the mechanochemical synthesis of MOFs to become a viable alternative to conventional solution synthesis and have, without doubt, inspired the rapid development of the field in the following years.

**3 Advances in mechanochemical synthesis of MOFs and in situ monitoring of ball-milling reactions**

After the initial reports on mechanochemical synthesis of MOFs, it was evident that ball-milling is contributing to reducing the amount of used solvents, energy requirements, and the duration of the synthetic processes while at the same time offering high-quality MOFs. However, the mechanisms...
monitoring, it was revealed that the ionic additive in the mixtures (Fig. 4a). On the other hand, two different reaction mechanisms. On the one hand, LAG synthesis to 4 minutes by milling. The technique relies on high-energy synchrotron X-rays which pass through the walls of the reaction vessel, interact with the milled sample and can be detected on a high-resolution 2D detector (Fig. 3a). Highly crystalline ZIFs were ideal model compounds for the development of in situ diffraction methods (Fig. 3b and c), showing dynamic changes of crystalline phases with time-resolution in seconds and consequently enabling the optimization of milling reactions. The technique was also extended to other relevant MOF materials, and some results will be presented throughout this Highlight.

In the first contribution describing the in situ PXRD monitoring, it was revealed that the ionic additive in the milling of 2-methylimidazole and ZnO indeed had a tremendous accelerating effect on the product formation rate. Monitoring the change in the intensity of the characteristic (211) reflection of ZIF-8 showed a sigmoidal pattern characteristic of nucleation and growth of a crystal phase in both the LAG and ILAG procedures (Fig. 3d–f). The monitoring thus proved that the ILAG, besides being an atom and energy economical process, also results in a significant shortening of the reaction, from 29 hours by solvothermal synthesis to 4 minutes by milling.

The influence of liquid additives on the mechanochemical synthesis of HKUST-1 was also studied by in situ methods. It was shown that LAG additives direct the mechanochemistry of HKUST-1 via completely different reaction mechanisms. On the one hand, LAG using MeOH or similar short-chained additives resulted in the direct formation of HKUST-1 from the reactant mixtures (Fig. 4a). On the other hand, two different discrete intermediates (INT1 and INT2) containing a mononuclear copper core, and with the general formula [Cu(H$_2$BTC)$_2$(solvent)$_2$]$_n$ were isolated when the milling process was interrupted (INT1), or when the additives contained longer aliphatic chains (INT2). The study also showed how mechanochemistry allows for the use of the weakly soluble precursor Cu(OH)$_2$, yielding water as the only by-product of the reaction.

Julien et al. have shown how Zn-MOF-74 can be synthesized from ZnO and 2,5-dihydroxyterephthalic acid (H$_2$-DHTA) by milling under one hour under room temperature conditions, using water as the liquid additive. The structure of MOF-74, also known as CPO-27, is characterized by honeycomb channels, and belongs to a particularly interesting family of MOFs, widely investigated for adsorption and catalysis applications due to their open metal-sites and large surface areas. In situ monitoring of the mechanochemistry revealed that the reaction proceeds in two steps, first yielding a non-porous 2-D coordination polymer [Zn(H$_2$DHTA)(H$_2$O)$_2$] which then reacts with another equivalent of ZnO to form a porous [Zn$_2$(DHTA)(H$_2$O)$_2$] (solvent)$_n$ MOF-74 framework in 45–90 minutes of milling (Fig. 4b). Interestingly, water or methanol additives proved to be much more suitable for the mechanochemical preparation of Zn-MOF-74 than the conventional dimethylformamide (DMF), for which the milling was longer and involved two different unknown types of 1:1 (Zn:DHTA) intermediates. This step-wise synthesis was later used for the controllable preparation of a series of bimetallic MOF-74 materials (section 6).

Looking from a synthetic perspective, more complex groups of MOFs are those based on discrete metal cluster nodes since the assembly of a cluster is a necessary precondition for the formation of MOFs. In 2015, the Lewinski group reported the successful ball-milling synthesis of one of the most famous MOFs, MOF-5 (IRMOF-1), by using the “SMART” strategy (SBU-based Mechanochemical Approach for Precursor Transformation). MOF-5, which is based on [Zn$_2$O] cluster nodes, was not accessible by milling of the simple zinc precursors and terephthalic linker. The authors switched to discrete zinc precursors bearing a similar [Zn$_n$O]$_n$ core, such as the benzolate [Zn$_n$(O$_2$C$_2$Ph)$_n$] derivative or more basic benzamidate [Zn$_n$(NHOC$_2$Ph)$_n$] derivative (Fig. 4c). The SMART strategy proved to be a smart choice as it resulted in crystalline and high-quality MOF-5 after a mere 60 minutes of LAG at room temperature, strongly contrasting the harsh solution approaches needed for the preparation of this archetypal MOF. The basicity of the precursor was shown to be particularly important for the milling reaction, and the benzamidate precursor yielded crystalline MOF-5 even after 30 minutes of dry milling. Solid amide, which is the only by-product of synthesis, could be recycled and used for generation of new cluster precursors. The SMART approach was later used for the preparation of other IRMOFs, such as IRMOF-3, IRMOF-10, and MOF-177.
Soon to follow, in 2016, another large and important family of MOFs with discrete oxocluster nodes have been successfully synthesized. MOFs based on bridging carboxylate ligands and zirconium oxocluster nodes attracted attention immediately upon their discovery in 2008, since they offered unprecedented stability under atmospheric conditions and in a wide range of pH. This, together with a high density of metal cations in \([\text{Zr}_6\text{O}_4(\text{OH})_4]^{12+}\) nodes, motivated a large number of studies that established numerous new topologies of this exciting family of MOFs. The solution syntheses involved the extensive use of formamide solvents and acidic or corrosive reactants. The first mechanochemical synthesis of UiO-66 and UiO-66-NH\(_2\) from preorganized Zr\(_6\)-oxoclusters allowed for the use of “greener” liquid additives. Switching to preorganized benzoate \([\text{Zr}_6\text{O}_4(\text{OH})_4(\text{C}_6\text{H}_4\text{COO})_{12}]\) or methacrylate \([\text{Zr}_6\text{O}_4(\text{OH})_4(\text{C}_6\text{H}_4\text{COO})_{12}]\) clusters yielded highly crystalline, active, and porous products by LAG (MeOH) or accelerated aging processes on a gram-scale. The curiosity in these syntheses was that methanol and ethanol yielded much more crystalline UiO-products than formamide additives.

The UiO-66-F\(_4\) derivative, with a fluorinated terephthalic acid linker, was accessible from the methacrylate Zr\(_6\) cluster by LAG with a water additive and in several minutes, thus avoiding the need for organic solvents in the preparation and purification of the product. Unfortunately, the same methodology was not applicable for other, more conventional UiO-66 derivatives. To try to amend this, authors switched to the new dodecanuclear
acetate cluster $[\text{Zr}_{12}\text{O}_{8}(\text{OH})_8(\text{CH}_3\text{COO})_{24}]$ with more basic and mobile acetate ancillary ligands. This strategy was successful; pure, highly porous, and crystalline UiO-67 and NU-901 were synthesized. The measured porosity of the UiO-67 material was 2250 m$^2$ g$^{-1}$, establishing a new benchmark for the porosity of the material prepared by ball-milling.65

In situ monitoring has also shown how solid-state reactivity can be profoundly different compared to that in solution, gaining solid phases not accessible by any other synthetic procedures (Fig. 5a).66 Milling of ZnO and 2-methylimidazole with a small amount of diluted acetic acid afforded ZIF-8 almost instantaneously, which was followed by its amorphization after 20 minutes of milling. Unexpectedly, the continuation of milling resulted in the recrystallization of the amorphous matrix into a new topological polymorph of ZIF-8 named katsenite (kat). The kat polymorph was reported the amorphous matrix into a new topological polymorph of its amorphization after 20 minutes of milling. Unexpectedly, afforded ZIF-8 almost instantaneously, which was followed by porosity of the material prepared by ball-milling.

4 Topology transformations by ball-milling

The above-described synthesis of the kat polymorph of ZIF-8,66 which proceeds in the order ZIF-8-amorph-kat-dia, is also a nice example of MOF topology transformation by ball-milling. Akimbekov et al. provided the first combined experimental and theoretical evaluation of this reaction, showing how the differences in ligand structure and framework topology affect the relative stability of iso-compositional ZIFs.68 The results show that the observed mechanochemical synthesis and transformations of polymorphs of ZIF-8 (ref. 66) are consistent with Ostwald’s rule of stages69 and proceed toward increasingly thermodynamically stable and denser phases (Fig. 5b).

The Zn(η-Im)$_2$ phases displayed similar behavior. Besides the ammonium salts as ionic additives, which directed the formation of the RHO, ANA, or qtz topology in the Zn(η-Im)$_2$ ZIF, the volume of added liquid additives was shown to play an essential role in their mutual transformations.48,49 In situ PXRD data revealed that during the ball-milling, different topologies of Zn(η-Im)$_2$ occur in the reaction vessel, and the occurrence and life-span of the respective form is directly linked to the amount of the liquid additive in the reaction mixture.48 By prolonged milling, the polymorphs of Zn(η-Im)$_2$ transform in the sequence RHO–ANA–qtz, from the most porous one (and thermodynamically least stable) to the least porous one (and thermodynamically most stable phase),70 thus following Ostwald’s rule of stages (Fig. 5c). Very recently, the Friščič group reported the phenomenon of “disappearing” polymorphism in mercury(II)-ZIFs.71 In their attempt to prepare a known dia-phase of the ZIF, the authors synthesized a new layered phase with the sqI-topology. The diamondoid phase became elusive; it was detected as a short intermediate in the milling process, whereas the solution procedures showed no evidence of it. This ZIF system thus shows behavior that is opposite to that of the known Zn-ZIFs described above, achieving a less stable phase by milling. The theoretical studies rationalized this behavior as to stem from the weak interactions stabilizing the layered sqI-phase, indicating that the non-covalent interactions can also play a role in the mechanochemical control over the MOF polymorphs.

Topology transformation by milling is not limited to ZIFs; very recently, mechanochemical procedures were used for rapid synthesis of phase-pure products and topology
transformation in the 12-coordinated porphyrinic zirconium MOF polymorphic pair, MOF-525 and PCN-223. MOFs based on the tetrakis(4-carboxyphenyl)porphyrin (TCPP) ligand and zirconium oxoclusters represent a particularly interesting subclass of zirconium carboxylate MOFs due to their occurrence in several different topologies, while the vast majority of known zirconium MOFs have been isolated and reported as one sole crystalline phase. Mechanochemical procedures were shown to be very suitable for the green and rapid production of MOF-525 and PCN-223 polymorphs, gaining pure phases in 25–60 minutes of ball-milling, and mending the problematic solution procedures which often yielded mixed phases. The resolution between the polymorphic phases in LAG processes was directed by liquid additives and the type of preorganized zirconium clusters. Moreover, when using zirconium dodecanuclear acetate cluster \([\text{Zr}_{12} \text{O}_8 \text{(OH)}_8 \text{(CH}_3\text{COO})_{24}]^{65-}\) and a MeOH additive, \textit{in situ} PXRD monitoring revealed that MOF-525 formed rapidly and then transformed into a pure PCN-223 form in a mere 30 minutes of milling (Fig. 6). This transformation that occurs during the \textit{in situ} formation of MOF-525 is in strong contrast with long solution or slurry procedures, pointing towards the importance of plastic deformations, defects, and flexibility of partially coordinated zirconium clusters that form during the mechanochemical nucleation and growth of a MOF phase. A similar phenomenon was also observed for the mechanochemical synthesis of UiO-66 from preorganized zirconium clusters, where the unit cell parameters change during the mechanochemical nucleation and growth of MOF particles.

### 5 MOF composites

Utilizing tunable and flexible MOFs as solid substrates for functional heterogeneous catalysis is an important direction of research, although it is still in its early stage. Some of the benefits that MOF catalysts offer are a high density of catalytic sites, post-synthetic modifications, and pore confinement. On the other hand, benchmark industrial catalysts have been developed for decades and offer high mechanical, chemical, and thermal stability. Therefore, high product selectivity for the synthesis of fine chemicals is a prerequisite for the industrial application of functional MOF catalysts. MOF composites, from controllable integration of MOFs and other materials, mitigate disadvantages that MOFs might have and can lead to synergistic performances.

Wei et al. have shown how mechanochemical milling can be used to prepare MOF composites consisting of enzymes as biocatalysts and MOFs. Several enzymes, including β-glucosidase, invertase, β-galactosidase, and catalase have been encapsulated into ZIF-8, UiO-66-NH$_2$, or Zn-MOF-74 during solid-state synthesis (Fig. 7), using the advantages of rapid mechanochemical reactions to minimize damage to enzyme catalytic activity. MOFs not only served as hosts but boosted the resistance to proteases and stability under acidic conditions (Fig. 7). This work has shown how solvent-free ball milling can be utilized as a tool for making MOF bio-composites that can be of great interest in different industrial processes.

Loading of catalytically active metals into a MOF support proved to be highly effective for the preparation of potent MOF catalysts. Jiang et al. directly deposited Au nanoparticles (NPs) onto ZIF-8 by solid grinding with a volatile organogold complex and without using organic solvents (Fig. 8a). Au@ZIF-8 samples have shown high catalytic activity in gas phase CO oxidation after thermal
activation at around 300 °C, enabled by the high thermal stability of the ZIF-8 support. It is expected that this approach can be extended to loading of other noble metal NPs into MOF supports.86,87

Furthermore, Bhattacharyya et al. used ball-milling to prepare perovskite quantum dot (PQD) MOF-composites.88 Solvent-free synthesis of a PQD@MOF composite was achieved using the metallated anionic AMOF-1 \([\text{(NH}_2\text{Me})_2\text{Zn}_3\text{(L)}_2\text{]}\cdot\text{9H}_2\text{O}\) (\(L = 5,5′-(1,4\text{-phenylenebis(methylene)})\text{bis(oxy)}\text{-disopthalate})\) as the template. The procedure includes an exchange of the organic cations with \(\text{Pb}^{II}\), followed by grinding of \(\text{Pb}^{II}@\text{AMOF-1}\) with \(\text{CsX}\) (\(X = \text{Cl}, \text{Br}, \text{and I}\)) for 15–20 min (Fig. 8b). The \textit{in situ} formation of PQDs was evidenced by characteristic perovskite emission using a UV lamp. CsPbX_3 PQD nanocrystals are formed on the surface of AMOF-1 with size dependence on AMOF-1, thus showing a quantum confinement effect. The authors have shown that the CsPbX_3@AMOF-1 samples have good stability in several solvents and can be easily processed as a colour-tuned ink.

The SMART approach was also used for loading of ibuprofen into a HKUST-1 network, where the authors managed to efficiently encapsulate ibuprofen into the MOF by a one-pot mechanochemical procedure involving a pre-assembled \([\text{Cu}_3\text{I}2\text{ibuprofen}]\) cluster.89 The \textit{in situ} loading during the mechanoanalysis enabled room-temperature synthesis of drug-loaded MOF composites for slow release of ibuprofen in buffered solutions.

6 Mixed-metal and mixed-ligand MOFs

Panda et al. reported a mechanical alloying method for the preparation of mixed-metal MOFs,90 which was first demonstrated on two isostructural MOFs with a dicarboxylic acid linker, \([\text{Al(OH)}(1,4\text{-naphthalenedicarboxylate})] (\text{Al-ndc})\) and \([\text{Ga(OH)}(1,4\text{-naphthalenedicarboxylate})] (\text{Ga-ndc})\). The
methodology involves dry milling of both MOFs under an argon atmosphere, which was shown to induce amorphization of the reaction mixture. The mechanical alloying methodology allowed for different ratios of two MOFs to be mixed, each resulting in crystalline and porous MOFs after the accelerated aging\(^2\) in a humid atmosphere (3 days in a 95% RH atmosphere at 25°C). X-ray and STEM-EDX studies revealed that mechanical milling promotes high diffusivity of each metal ion in an amorphous solid matrix, allowing for the preparation of mixed-metal MOFs with a homogeneous distribution of metal centers, at least at the resolution offered by STEM-EDX (Fig. 9a). The methodology was also applied to ZIF-8 and MOF-74 to show the generality of the principle, and the results indicated that the success of the method depends on various parameters, such as ionic radii, valence states, coordination preferences, the electronegativity of metal ions, and the MOF topology.\(^9\)

Lee et al. showed that mechanical alloying of isolated \([\text{Fe(1,2,3-triazolate)},_\text{II}],\) with isostructural \([\text{Cu(1,2,3-triazolate)},_\text{II}],\) results in a bimetallic MOF with a homogeneous distribution of the two metal centers. This hybrid material, when pyrolyzed, retains the bimetallic homogeneity and can be used as an oxygen reduction reaction (ORR) catalyst.\(^93\) The two metals, included in the MOF structure, work in synergy, and show exceptional ORR performance, outperforming the benchmark Pt/C. This behavior was attributed to the homogeneous distribution and control of the Fe\(^{2+}\) and Cu\(^{2+}\) composition within the MOF crystals, which cannot be obtained by solution-based synthesis. The findings of this study showed that MOFs can be alloyed together by the application of mechanochemical techniques and that these new materials may show synergistic properties that outperform the individual components.

Ball-milling was successfully applied for the synthesis of a ZIF-8 material composed of five divalent metal cations, Zn(II), Ni(II), Cd(II), Cu(I), and Co(II), dispersed randomly throughout the 3D-network in the sod topology of the MOF (Fig. 9b).\(^9\) The authors named the new multi-metal ZIF-8 “high-entropy zeolitic imidazolate framework, HE-ZIF”, inspired by high-entropy alloys, where five or more metal species are incorporated deliberately into a single lattice with random occupancy. The distribution of specific metals was established by EDS microscopy, and inductively coupled plasma atomic emission spectrometry (ICP-AES) showed that HE-ZIF contains all five metals in much higher content than those assembled from solution, in which zinc was the principal constituent. HE-ZIF was highly porous and showed enhanced catalytic activity compared with ZIF-8, which the authors presumed to be a consequence of the synergistic effect of the five metal-constituents.\(^9\) The results of this study showed how mechanochemistry can be used as a powerful tool for the preparation of multimetallic MOFs, but control of the spatial distribution of heterometallic centers remained a challenge.

Ayoub et al. demonstrated how the nature of the ligand could be exploited for targeted, rapid, and controllable mechanochemical synthesis of bimetallic MOF-74 materials (formula \([\text{M1M2(DHTA)}_n(solvent)])\) with a homogeneous distribution of metal centers and controlled 1:1 stoichiometric composition of heterometallic nodes.\(^5\) The authors used the ditopic nature of the DHTA ligand to control the metal positioning in the MOF; the first metal (M1) reacts with the carboxylic functionalities of H\(_2\)DHTA, forming nonporous 1:1 M1(H\(_2\)DHTA) solid coordination complexes of Zn(II), Mg(II), Ni(II), and Co(II) in the first synthetic step (Fig. 10a). These coordination polymers then react in the second step with an equimolar amount of the second metal (M2), and the prolonged LAG (alcohols) resulted in open and crystalline MOF-74. This approach results in the assembly of various mixed-metal MOF-74 materials composed of pairs of d-block or main group metals in a predetermined 1:1 stoichiometric ratio, including ZnMg-, ZnCo-, ZnCu-, MgZn-, MgCo-, NiZn-, NiMg-, NiCo-, CoZn-, CoMg-, CoCu-, and MgCa-MOF-74. Similar attempts in solution failed, and control of the metal distribution was not achievable by conventional methods.

One of the first MOF families prepared by milling, pillared Zn-MOFs\(^4\) which are discussed in more detail above, are built by the bridging carboxylate and the dabcycl linkers, thus also presenting an example of mixed ligand MOFs. Roztocki et al. have shown how MOFs with more complex mixed linkers can be obtained quantitatively in a mechanochemical reaction.\(^9\) The authors were studying the Zn-MOFs built from 5-substituted isophthalic acids (Xiso) and 4-pyridinecarbaldehyde isonicotinoyl hydrazone (pih), containing N and O donors. These MOFs, with the general...
7 Amorphous and defective MOFs

Although the vast majority of the discovered MOFs are crystalline solids, amorphous MOFs are an emerging area of MOF research. Amorphization is a process where long-range order is lost and replaced by the local ordering of the solid. It is accompanied by the loss of porosity due to the collapse of the structure. This methodology can be used to entrap dangerous chemicals like radioactive iodine, encapsulate drug molecules, or produce gas separation membranes. On the other hand, with thousands of MOF compounds being known, there is a growing interest in modifying the chemical and physical properties of the already synthesized MOFs. Indeed, the introduction of defects by either de novo synthesis or post-synthetic modification offers the possibility of tailoring MOF properties, for example in heterogeneous catalysis.

Having already been known that mechanochemical ball-milling is a fast and an efficient technique for obtaining highly crystalline ZIFs, Bennet et al. showed that amorphous ZIFs (am-ZIFs) could also be obtained in bulk by mechanosynthesis. Starting from evacuated ZIF-4, am-ZIF-4 is obtained after only 30 min of milling at room temperature and without crystalline impurities. The amorphous phase obtained by ball-milling is indistinguishable from the one obtained by thermal treatment for 5 hours at 300 °C.

Orellana-Tavra et al. developed a drug delivery system (DDS) based on the amorphous UiO-66 framework. Hydrophilic and fluorescent model drug calcein (cal) was loaded into UiO-66 by soaking it in a calcein solution. cal@UiO-66 was subsequently ball-milled, and the process resulted in the encapsulation of calcein due to the structural collapse of the framework. By doing this, the authors were able to significantly increase drug release times from 2 to up to 30 days in a DDS with a particle size of 272 ± 157 nm (Fig. 11b). Furthermore, as evidenced by confocal microscopy, both cal@UiO-66 and cal@am-ZIF-66 were successfully incorporated into HeLa cells with the slower release of the drug from the amorphous material. This showed that the kinetic characteristic of the delivery was preserved for both the crystalline and amorphous MOF-based DDSs.

Ye et al. reported the de novo synthesis of UiO-66 with increasing defects and without the addition of a monocarboxylic acid or solvent. The procedure included milling ZrOCl2·8H2O and 1,4-benzenedicarboxylic acid (BDC) using a mortar and pestle. Such a pre-milled reaction mixture was then transferred to an autoclave and crystallized at a certain temperature and for a certain time. After optimizing the reaction conditions, the maximum number of missing linkers per Zr6O4(OH)4BDC reached 2.16, much higher than that in UiO-66 prepared by a solvothermal method. The role of defects was verified by studying the oxidative desulfurization (ODS) reactions of dibenzothiophene (DBT) and 4,6-dimethyldibenzothiophene (4,6-DMDDBT) as well as the oxidation of benzyl alcohol. It was shown how the introduction of defects enhanced the catalytic performance when compared to defect-free UiO-66.

Ogiwara et al. have shown how amorphization can be used to modify the molecular motion of 2-methylimidazolate (Me-
Im) linkers in ZIF-8. The authors have taken advantage of solid-state 2H NMR spectroscopy where 2H line shape, spin–lattice and spin–spin relaxation ($T_1$ and $T_2$) are defined by intramolecular quadrupole interaction, making them consequently sensitive to the type and the rate of the molecular motion. Firstly, the authors deuterated Me–Im linkers and used them to synthesize ZIF-8 crystals. Secondly, deuterated ZIF-8 was evacuated, and the amorphization was performed by ball-milling. Solid-state 2H NMR studies have revealed that amorphization significantly affected the mobility of the Me–Im linkers, including the rotational angle and speed. Surprisingly, even a new librational mode appeared in $\alpha_{m}$ZIF-8.

### 8 Industrial potential of large-scale mechanochemical synthesis

In the 21st century and after the development of green chemistry concepts, sustainable and scalable synthesis of MOFs is one of the requirements for their successful industrial application. Generally, the majority of laboratory-scale synthesis of MOFs is done by a solvothermal approach using high-boiling and hazardous organic solvents that will have to be washed away during later stages of MOF activation. When thinking on the chemical design level, any volume reduction of organic solvent usage, or the usage of water instead, will have both environmental and economical benefits in the long run. Mechanochemical synthesis of MOFs also requires the input of solvents/liquids by either the LAG or ILAG methods; however, they are added only in catalytic amounts. As an example, for the synthesis of 500 mg of a MOF product, approximately 200 $\mu$L should be added and often simple alcohols (MeOH and EtOH) or water can be used as the liquid additive.

Very important economic analysis of the large-scale industrial synthesis of MOFs was performed by DeSantis et al. It was shown that for the solvothermal synthesis method, a large percentage of the overall costs is attributed to the precipitation step (manufacturing cost) and solvent used (material cost). As a consequence and in direct comparison, a detailed cost breakdown for the synthesis of Mg-MOF-74 has yielded $48.52 per kg for the solvothermal synthesis method, $17.96 per kg for the aqueous synthesis method and $11.88 per kg for the LAG mechanochemical synthesis method. As a conclusion, the authors reported that the potential costs for the LAG method are projected at $8.23 per kg which is below the $10 per kg set by the US Department of Energy (DOE) as a technical target for the industrial application of MOFs.
Often overlooked, mechanochemical milling is also a scalable synthesis method. Planetary ball-milling offers the possibility of synthesis on a tens-of-grams scale, whereas extrusion, in particular TSE, shows potential for industrial-scale output. A TSE is a device with a barrel having two intermeshing rotating screws that transport the reaction mixture along the barrel. The mixture is transported to the kneading segment, a distinct part of the screws where the material is subjected to mechanochemical treatment by shearing and kneading. The kneaded mixture is then transported further, either to the end of the barrel or to the next kneading section, until it reaches the end of the barrel and exits into a container. The separate segments in the barrel can be heated, and additives can be added to the reaction mixture at different points of the process, thus providing many possibilities to alter and influence the TSE process. While a TSE was mainly used in the reactive extrusion of polymers and organic materials, a real breakthrough in the synthesis of MOFs was made in 2015 by the James group. The authors have shown how TSE can be used for the synthesis of HKUST-1, ZIF-8 and Al(fumarate)(OH) with a kg h⁻¹ product output rate, amounting to a space time yield (STY) of 144,000 kg m⁻³ d⁻¹ for HKUST-1 and even higher STYs for the other tested MOFs (Fig. 12a). Recently, Karadeniz et al. managed to scale-up the synthesis of several zirconium-based MOFs which are characterized by high chemical stability and catalytic activity for the degradation of chemical warfare agents. MOF-801, MOF-804, UiO-66 and UiO-66-NH₂ were synthesized on a 500 mg scale using water as the liquid additive. In the case of UiO-66-NH₂, its synthesis was achieved by TSE using MeOH as the liquid additive with a 1.4 kg h⁻¹ output rate (Fig. 12b). Importantly, the adsorption and catalytic properties of the mechanochemically synthesized MOFs were validated and are similar to their solvothermally synthesized MOF counterparts. This showed that continuous-flow extrusion reactors, which are being used in many industrial processes, can be readily applied for large-scale production of important MOFs.

9 Summary and outlook

As can be seen from this short overview, mechanochemistry and MOFs have, despite the relatively late start, become rapidly intertwined in many new and exciting areas of materials science. Ball-milling is not only being used for a greener and high-yielding approach towards relevant MOFs, but also offers a platform for the preparation of non-conventional MOFs and solid-phases not available by any other synthetic methods. Unlike those for other material classes, the mechanisms of the synthetic grinding processes for MOFs have been relatively well characterized thanks to in situ monitoring methods. The knowledge about the factors governing the reactions towards specific phases can be utilized in the scale-up of the syntheses. On the one hand, two important examples in the literature have shown how TSE is a cost-effective method that minimizes the requirements for costly soluble metal precursors, organic solvents, and energy in the process while affording high-quality MOFs in kg per hour output rates. We expect that these studies will greatly contribute to achieving continuous manufacturing of MOFs on industrial scales in a sustainable manner. On the other hand, we feel that the full potential of mechanochemical techniques is still not achieved, and the rising number of articles describing the use of mechanochemistry for the preparation of MOF hybrid materials, polymorph control, and transformation of MOFs into new phases promises the field to expand further, for mechanochemistry to become more present in synthetic laboratories and chemical industries focused on MOF chemistry.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors are thankful to Dr. Stipe Lukin for critically reading the manuscript. The work has been supported in part by the “Research Cooperability” Program of the Croatian Science Foundation funded by the European Union from the European Social Fund under the Operational Programme Efficient Human Resources 2014-2020, through grant PZS-2019-02-4129.

References

Highlight


The text continues with more references.


